Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2571989 A1 2006/03/09

(21) 2 571 989

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2005/07/24
(87) Date publication PCT/PCT Publication Date: 2006/03/09
(85) Entrée phase nationale/National Entry: 2007/01/10
(86) N° demande PCT/PCT Application No.: US 2005/026353
(87) N° publication PCT/PCT Publication No.: 2006/025979
(30) Priorité/Priority: 2004/07/24 (US10/899,458)

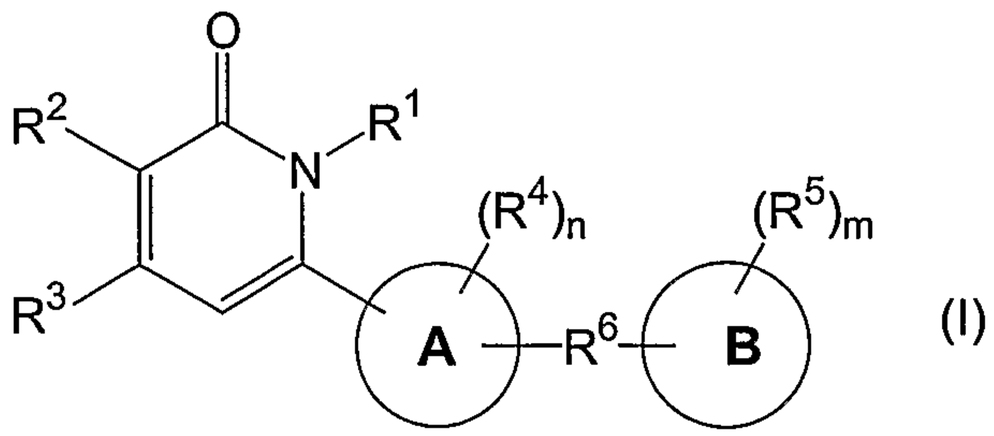
(51) Cl.Int./Int.Cl. *A61K 31/4439* (2006.01),
C07D 401/02 (2006.01)

(71) Demandeur/Applicant:
EXELIXIS, INC., US

(72) Inventeurs/Inventors:
BAYNE, CHRISTOPHER D., US;
JOHNSON, ALAN T., US;
LU, SHAO-PO, US;
MOHAN, RAJU, US;
NYMAN, MICHAEL C., US;
SCHWEIGER, EDWIN J., US;
STEVENS, WILLIAM C., JR., US;
...

(74) Agent: BENNETT JONES LLP

(54) Titre : MODULATEURS DE RECEPTEURS NUCLEAIRES
(54) Title: MODULATORS OF NUCLEAR RECEPTORS



(I)

(57) Abrégé/Abstract:
Compounds of the invention, such as compounds of formula (I), where n, m, A, R1, R2, R3, R4 and R5 are defined herein, are useful as modulators of the activity of liver X receptors. Pharmaceutical compositions containing the compounds and methods of using the compounds are also disclosed.

(21) 2 571 989

(13) A1

(72) **Inventeurs(suite)/Inventors(continued)**: WANG, HAIXIA, US; XIE, YINONG, US; BANNEN, LYNNE CANNE, US; CHAN, DIVA SZE-MING, US; HUANG, PING, US; JAMMALAMADAKA, VASU, US; KHOURY, RICHARD G., US; MAC, MORRISON B., US; PARKS, JASON JEVIOUS, US; WANG, YONG, US; XU, WEI, US

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 March 2006 (09.03.2006)

PCT

(10) International Publication Number
WO 2006/025979 A3

(51) International Patent Classification:
A61K 31/4439 (2006.01) *C07D 401/02* (2006.01)

(21) International Application Number:
PCT/US2005/026353

(22) International Filing Date: 24 July 2005 (24.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/899,458 24 July 2004 (24.07.2004) US

(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BAYNE, Christopher, D.** [US/US]; 3149 Clairemont Drive, Apartment 4, San Diego, CA 92117 (US). **JOHNSON, Alan, T.** [US/US]; 17058 Iron Mountain Drive, Poway, CA 92084 (US). **LU, Shao-Po** [CN/US]; 11693 Ramsdell Court, San Diego, CA 92131 (US). **MOHAN, Raju** [US/US]; 3125 Caminito Ricardo, Encinitas, CA 92024 (US). **NYMAN, Michael, C.** [US/US]; 4511 Rhode Island Drive, San Diego, CA 92116 (US). **SCHWEIGER, Edwin, J.** [US/US]; 4703 Vereda Luz Del Sol, San Diego, CA 92130 (US). **STEVENS, William, C., Jr.** [US/US]; 11632 Candy Rose Way, San Diego, CA 92131 (US). **WANG, Haixia** [CN/US]; 7375 Juncus Court, San Diego, CA 92129 (US). **XIE, Yinong** [US/US]; 9669 Gold Coast Drive #31, San Diego, CA 92126 (US). **BANNEN, Lynne, Canne** [US/US]; 1086 Rio Vista Drive, Pacificia, CA 94044 (US). **CHAN, Diva, Sze-Ming** [US/US]; 1775 46th Avenue, San Francisco, CA 94122 (US). **HUANG, Ping** [US/US]; 117 Whit's Road, Mountain View, CA 94040 (US). **JAMMALAMADAKA, Vasu** [US/US]; 2806 Maria Street, Pleasanton, CA 94588 (US). **KHOURY, Richard, G.** [US/US]; 225 Poseidon Lane, Redwood City, CA 94065 (US). **MAC, Morrison, B.** [US/US]; 2567 30th Avenue, San Francisco, CA 94116 (US). **PARKS, Jason, Jevious** [US/US]; 4005 Cowell Boulevard, Apartment 506, Davis, CA 95616 (US). **WANG, Yong** [CN/US]; 667 Catamaran Street, Apartment 4, Foster City, CA 94404 (US). **XU, Wei** [US/US]; 327 Glasgow Circle, Danville, CA 94526 (US).

(74) Agents: **EKSTROM, Carmen, P.** et al.; 170 Harbor Way, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

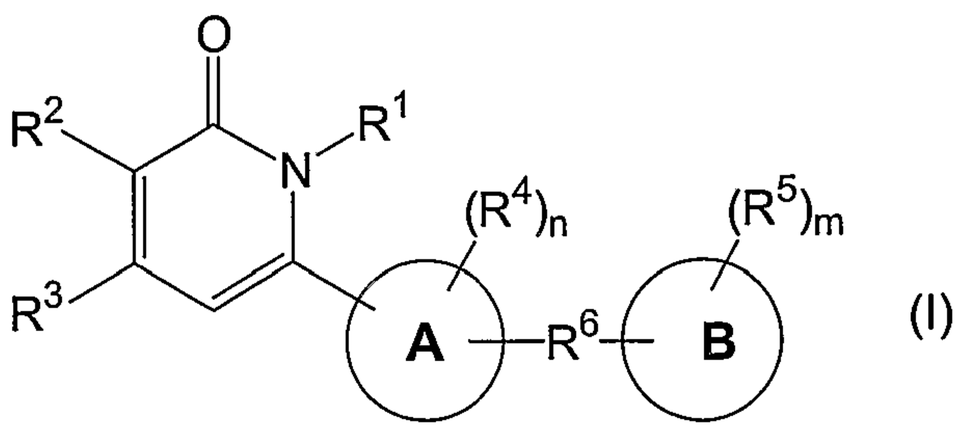
Published:
— *with international search report*

(88) Date of publication of the international search report:
28 September 2006

(15) Information about Correction:
Previous Correction:
see PCT Gazette No. 16/2006 of 20 April 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATORS OF NUCLEAR RECEPTORS



(I)

(57) Abstract: Compounds of the invention, such as compounds of formula (I), where n, m, A, R1, R2, R3, R4 and R5 are defined herein, are useful as modulators of the activity of liver X receptors. Pharmaceutical compositions containing the compounds and methods of using the compounds are also disclosed.

WO 2006/025979 A3

MODULATORS OF NUCLEAR RECEPTORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Application Serial No. 10/899,458 filed July 24, 2004 which claims priority to U.S. Patent Application Serial 10/327,813 filed December 20, 2002, which claims the benefit of priority to U.S. Provisional Patent Application Serial No. 60/342,707 filed December 21, 2001, the disclosures of which are incorporated herein in their entireties.

FIELD OF THE INVENTION

Compounds, compositions and methods for modulating the activity of nuclear receptors, particularly liver X receptors (LXRs) and farnesoid X receptor (FXR), are provided. In particular, pyridone derivatives are provided for modulating the activity of LXRs and FXR.

BACKGROUND OF THE INVENTION

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev. 15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptors or PPARs) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850).

The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression. There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), coding for RXRα, -β, and -γ, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-3020). In the adult liver, RXRα is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol. 20*:4436-4444.

Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for farnesoid X receptor (FXR).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science 189*:760-763 and O'Malley (1989) *Endocrinology 125*:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

LXRα and LXRβ

LXRα is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, *e.g.*, Willy, *et al.* (1995) *Gene Dev. 9(9)*:1033-1045). LXRβ is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, *e.g.*, Lehmann, *et al.* (1997) *J. Biol. Chem. 272(6)*:3137-3140). LXRα is activated by oxycholesterol and promotes cholesterol metabolism (Peet *et al.* (1998) *Cell 93*:693-

704). Thus, LXRs appear to play a role in, *e.g.*, cholesterol metabolism (see, *e.g.*, Janowski, *et al.* (1996) *Nature 383*:728-731).

Nuclear Receptors and Disease

Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), atherosclerosis and gallstones (see, *e.g.*, International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including LXRs, FXR and PPARs, and orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7α-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem. 275*:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317 and International Patent Application Publication No. WO 01/03705), and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1), as well as (ABCG1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

The nuclear receptors FXR and LXR are structurally and closely related receptors. Furthermore, FXR and LXR play critical and functionally distinct roles in coordinate control of bile acid, cholesterol, and triglyceride metabolism to maintain lipid homeostasis. Nuclear receptors and bile acid/oxysterol-regulated genes are potential targets for developing drug therapies for lowering serum cholesterol and triglycerides and treating cardiovascular and liver diseases. Compounds with dual activity for both LXF and FXR, then, can have profound effects on lipid homeostasis, and can more effectively control disease conditions implicating both FXR and LXR.

In addition to the anti-atherogenic effect of LXR agonists, studies in cell culture and animal model systems have demonstrated that LXR agonists increase the plasma triglyceride levels and promote the increased production of VLDL lipoprotein particles.

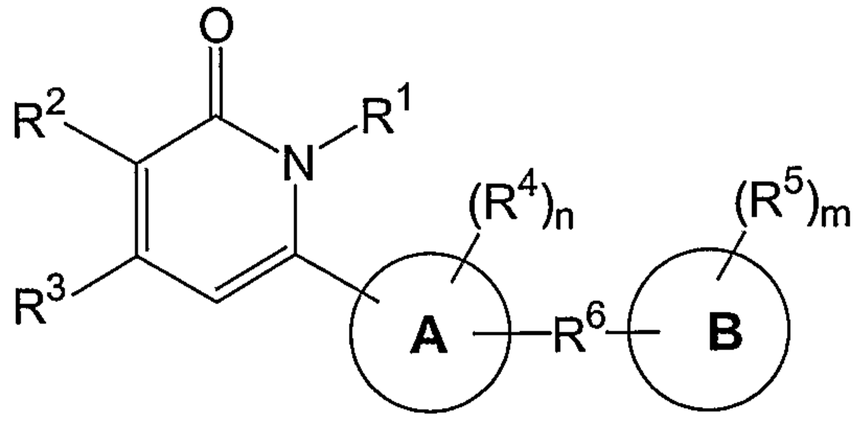
Schultz et al., Genes & Development 14:2831-2838 (2000); Repa et al., Genes & Development 14:2819-2830 (2000). In contrast, activation of FXR via FXR agonists decreases plasma triglyceride levels; Maloney et al., J. of Med. Chem. 43:2971-2974, (2000) and inhibits the production of VLDL lipoprotein particles. Hiorkane et al., J. Biol. Chem., 279:45685-45692 (2004); Sirvent et al., FEBS Lett. 566:173-177 (2004); Watanabe et al., J. Clin. Invest. 113:1408-1418 (2004); unpublished Exelixis data. A LXR/FXR dual agonist combining the agonist activity of both LXR and FXR in a single molecule should display anti-atherogenic activity while attenuating the unwanted side effects of hypertriglyceridemia and enhanced VLDL secretion.

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including LXRs, FXR, PPARs and orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

SUMMARY OF THE INVENTION

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating liver X receptors (LXRα and LXRβ), FXR, PPARs and/or orphan nuclear receptors are provided. In certain embodiments, the compounds are N-substituted pyridone compounds. In one embodiment, the compounds provided herein are agonists of LXR. In another embodiment, the compounds provided herein are antagonists of LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists. In one embodiment, the compounds provided herein are agonists of FXR. In another embodiment, the compounds provided herein are LXR/FXR dual agonists.

Accordingly, one aspect of this invention is directed to compounds of formula (I):

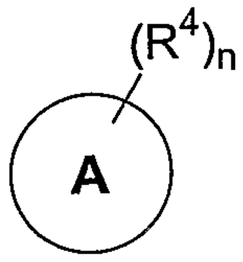


(I)

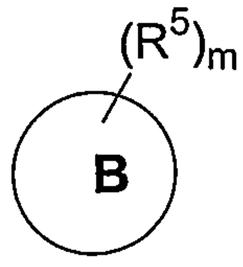
wherein:

n is 1 to 4;

m is 1 to 4;



is aryl or heteroaryl;



is aryl, heterocyclyl or heteroaryl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-C(O)OR^8$, $-R^7-N(R^8)_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^4 is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

Another aspect of this invention is directed to methods of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of modulating nuclear receptor activity, comprising contacting one or more nuclear receptors with a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of modulating cholesterol metabolism, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of treating, preventing or ameiliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of increasing cholesterol efflux from cells of a subject, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of increasing the expression of ATP-Binding Cassette (ABC1), as well as (ABCG1) in the cells of a subject, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to *in vitro* methods for altering nuclear receptor activity, comprising contacting the nuclear receptor with a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of formula (I) as set forth above, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of formula (I) as set forth above.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. For example, “a compound”

refers to one or more of such compounds, while "the enzyme" includes a particular enzyme as well as other family members and equivalents thereof as known to those skilled in the art.

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like. Unless stated otherwise specifically in the specification, the alkyl radical may be optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^8$, $-N(R^8)_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-N(R^8)C(O)OR^{10}$, $-N(R^8)C(O)R^8$, $-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-S(O)_pOR^8$ (where p is 1 to 2), $-S(O)_tR^8$ (where t is 0 to 2), and $-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8 and R^{10} is as defined above in the Summary of the Invention. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkyl group that the substitution can occur on any carbon of the alkyl group.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to eight carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, the alkenyl radical may be optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^8$, $-N(R^8)_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-N(R^8)C(O)OR^{10}$, $-N(R^8)C(O)R^8$, $-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-S(O)_pOR^8$ (where p is 1 to 2), $-S(O)_tR^8$ (where t is 0 to 2), and $-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8 and R^{10} is as defined above in the Summary of the Invention. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkenyl group that the substitution can occur on any carbon of the alkenyl group.

"Aryl" refers to refers to aromatic monocyclic or multicyclic ring system containing from 6 to 19 carbon atoms, where the ring system may be partially or fully saturated. Aryl groups include, but are not limited to groups such as fluorenyl, phenyl and naphthyl.. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally

substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-R^7-OR^8$, $-R^7-N(R^8)_2$, $-R^7-C(O)R^8$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-R^7-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-R^7-S(O)_pOR^8$ (where p is 1 to 2), $-R^7-S(O)_tR^8$ (where t is 0 to 2), and $-R^7-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8, R^7 and R^{10} is as defined above in the Summary of the Invention.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is one or more aryl radicals as defined above, *e.g.*, benzyl, diphenylmethyl and the like. The aryl radical(s) and the alkyl radical may be optionally substituted as described above.

"Alkylene" and "alkylene chain" refer to a straight or branched divalent hydrocarbon chain, linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, preferably having from one to eight carbons, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain may be attached to the rest of the molecule and to the radical group through one carbon within the chain or through any two carbons within the chain. The alkylene chain may be optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heteroaryl, heterocyclyl, $-OR^8$, $-N(R^8)_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-N(R^8)C(O)OR^{10}$, $-N(R^8)C(O)R^8$, $-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-S(O)_pOR^8$ (where p is 1 to 2), $-S(O)_tR^8$ (where t is 0 to 2), and $-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8 and R^{10} is as defined above in the Summary of the Invention. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

"Alkenylene" and "alkenylene chain" refer to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, *e.g.*, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. The alkenylene chain may be optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heteroaryl, heterocyclyl, $-OR^8$, $-N(R^8)_2$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$, $-N(R^8)C(O)OR^{10}$, $-N(R^8)C(O)R^8$, $-N[S(O)_tR^8]_2$ (where t is 0 to 2),

-$N(R^8)S(O)_tR^8$ (where t is 0 to 2), -$S(O)_pOR^8$ (where p is 1 to 2), -$S(O)_tR^8$ (where t is 0 to 2), and -$S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8 and R^{10} is as defined above in the Summary of the Invention.

"Alkynylene" and "alkynylene chain" refer to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to twelve carbon atoms, *e.g.*, ethynylene, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a triple bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. The alkynylene chain may be optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heteroaryl, heterocyclyl, -OR^8, -$N(R^8)_2$, -$C(O)R^8$, -$C(O)OR^8$, -$C(O)N(R^8)_2$, -$N(R^8)C(O)OR^{10}$, -$N(R^8)C(O)R^8$, -$N[S(O)_tR^8]_2$ (where t is 0 to 2), -$N(R^8)S(O)_tR^8$ (where t is 0 to 2), -$S(O)_pOR^8$ (where p is 1 to 2), -$S(O)_tR^8$ (where t is 0 to 2), and -$S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8 and R^{10} is as defined above in the Summary of the Invention.

"Cycloalkyl" refers to a stable monovalent monocyclic or bicyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, -R^7-OR^8, -R^7-$N(R^8)_2$, -R^7-$C(O)R^8$, -R^7-$C(O)OR^8$, -R^7-$C(O)N(R^8)_2$, -R^7-$N(R^8)C(O)OR^{10}$, -R^7-$N(R^8)C(O)R^8$, -R^7-$N[S(O)_tR^8]_2$ (where t is 0 to 2), -R^7-$N(R^8)S(O)_tR^8$ (where t is 0 to 2), -R^7-$S(O)_pOR^8$ (where p is 1 to 2), and -R^7-$S(O)_tR^8$ (where t is 0 to 2), -R^7-$S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8, R^7 and R^{10} is as defined above in the Summary of the Invention.

"Cycloalkylalkyl" refers to a radical of the formula -R_aR_d where R_a is an alkyl radical as defined above and R_d is a cycloalkyl radical as defined above. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl,

trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 2-bromoethenyl, 3-bromoprop-1-enyl, and the like.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^7-OR^8$, $-R^7-N(R^8)_2$, $-R^7-CN$, $-R^7-C(O)R^8$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-R^7-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-R^7-S(O)_pOR^8$ (where p is 1 to 2), $-R^7-S(O)_tR^8$ (where t is 0 to 2), and $-R^7-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8, R^7 and R^{10} is as defined above in the Summary of the Invention. For purposes of this invention, the tem "*N*-heterocyclyl" refers to heterocyclyl radicals as defined above containing at least one nitrogen atom in ring.

"Heterocyclylalkyl" refers to a radical of the formula $-R_aR_e$ where R_a is an alkyl radical as defined above and R_e is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. The heterocyclyl radical and the alkyl radical may be optionally substituted as defined above.

"Heteroaryl" refers to a 3- to 18-membered aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group

consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, phthalimidyl pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^7-OR^8$, $-R^7-N(R^8)_2$, $-R^7-CN$, $-R^7-C(O)R^8$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N[S(O)_tR^8]_2$ (where t is 0 to 2), $-R^7-N(R^8)S(O)_tR^8$ (where t is 0 to 2), $-R^7-S(O)_pOR^8$ (where p is 1 to 2), $-R^7-S(O)_tR^8$ (where t is 0 to 2), and $-R^7-S(O)_pN(R^8)_2$ (where p is 1 to 2) where each R^8, R^7 and R^{10} is as defined above in the Summary of the Invention. For purposes of this invention, the tem "*N*-heteroaryl" refers to heteroaryl radicals as defined above containing at least one nitrogen atom in ring.

"Heteroarylalkyl" refers to a radical of the formula $-R_aR_f$ where R_a is an alkyl radical as defined above and R_f is a heteroaryl radical as defined above, and if the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkyl radical at the nitrogen atom. The heteroaryl radical and the alkyl radical may be optionally substituted as defined above.

"Hydroxyalkyl" and "hydroxyalkenyl" refers to an alkyl and an alkenyl radical, as defined above, which are substituted by one or more hydroxy (-OH) groups. The alkyl and the alkenyl radical may be optionally substituted as defined above.

As used herein, compounds which are "commercially available" may be obtained from standard commercial sources including Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI, including Sigma Chemical and Fluka), Apin Chemicals

Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester NY), Fisher Scientific Co. (Pittsburgh PA), Fisons Chemicals (Leicestershire UK), Frontier Scientific (Logan UT), ICN Biomedicals, Inc. (Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG (Hannover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), and Wako Chemicals USA, Inc. (Richmond VA).

As used herein, "suitable conditions" for carrying out a synthetic step are explicitly provided herein or may be discerned by reference to publications directed to methods used in synthetic organic chemistry. The reference books and treatise set forth above that detail the synthesis of reactants useful in the preparation of compounds of the present invention, will also provide suitable conditions for carrying out a synthetic step according to the present invention.

As used herein, "methods known to one of ordinary skill in the art" may be identified though various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds of the present invention, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler *et al.*, "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, “Heterocyclic Chemistry”, 2nd Ed., John Wiley & Sons, New York, 1992; J. March, “Advanced Organic Chemistry: Reactions, Mechanisms and Structure”, 4th Ed., Wiley-Interscience, New York, 1992. Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C. may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services.

"Prodrugs" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the

invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed in vivo to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

The term "prodrug" is also meant to include any covalently bonded carriers which release the active compound of the invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and domestic animals, such as cats, dogs, swine, cattle, sheep, goats, horses, rabbits, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals as defined herein and aryl radicals having no substitution.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Pharmaceutically acceptable derivative" refers to pharmaceutically acceptable salts as defined herein and also includes esters, prodrugs, solvates and polymorphs of the compounds of the invention.

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, for a disease-state associated the nuclear receptor activity. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Modulating" or "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function or condition. For example, the compounds of the present invention can modulate hyperlipidemia by lowering cholesterol in a human, thereby suppressing hyperlipidemia.

"Treating" or "treatment" as used herein covers the treatment of a disease or condition associated with the nuclear receptor activity as disclosed herein, in a mammal, preferably a human, and includes:

(i) preventing a disease or condition associated with the nuclear receptor activity from occurring in a mammal, in particular, when such mammal is predisposed to the disease or condition but has not yet been diagnosed as having it;

(ii) inhibiting a disease or condition associated with the nuclear receptor activity, *i.e.*, arresting its development; or

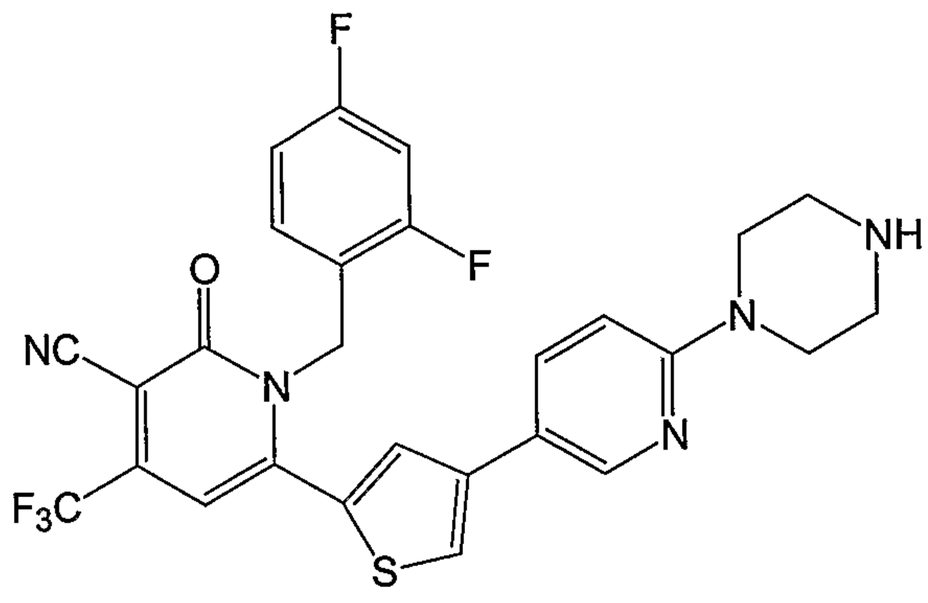
(iii) relieving a disease or condition associated with the nuclear receptor activity, *i.e.*, causing regression of the condition.

The compounds of formula (I), or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included.

The chemical naming protocol and structure diagrams used herein employ and rely on the chemical naming features as utilized by the ChemDraw program (available from Cambridgesoft Corp., Cambridge, MA). In particular, the compound

names were derived from the structures using the Autonom program as utilized by Chemdraw Ultra or ISIS base (MDL Corp.).

For example, a compound of formula (V) wherein n and m are each 1, Y is sulfur, R^1 is 2,4-difluorobenzyl, R^2 is cyano, R^3 is trifluoromethyl, R^4 is hydrogen, B is pyridin-3-yl, R^5 is piperazin-1-yl and R^6 is a direct bond, *i.e.*, a compound of the following formula:



is named herein as 1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(6-piperazin-1-yl-pyridin-3-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

The term "atherosclerosis" refers to process whereby atherosclerotic plaques form within the inner lining of the artery wall leading to atherosclerotic cardiovascular diseases. Atherosclerotic cardiovascular diseases can be recognized and understood by physicians practicing in the relevant fields of medicine, and include without limitation, restenosis, coronary heart disease (also known as coronary artery heart disease or ischemic heart disease), cerebrovascular disease including ischemic stroke, multi-infarct dementia, and peripheral vessel disease, including intermittent claudication, and erectile dysfunction.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of Low Density Lipoprotein, (LDL), Very Low Density Lipoprotein (VLDL) and depressed levels of High Density Lipoprotein (HDL) (less than 40 mg/dL)).

As used herein, "EC_{50}" refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated LDL cholesterol level (120 mg/dL and above); (2) hypertriglyceridemia, i.e., an elevated triglyceride level; (150 mg/dL and above) and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.

As used herein, "IC_{50}" refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of nuclear receptor, including the LXRα or LXRβ activity, in an assay that measures such response.

As used herein, "LXRα" (LXR alpha) refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative LXRα species include, without limitation the rat (Genbank Accession NM_031627), mouse (Genbank Accession BC012646), and human (GenBank Accession No. U22662) forms of the receptor.

As used herein, "LXRβ" (LXR beta) refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative LXRβ species include, without limitation the rat (GenBank Accession NM_031626), mouse (Genbank Accession NM_009473), and human (GenBank Accession No. U07132) forms of the receptor.

As used herein "LXR" or "LXRs" refers to both LXRα and LXRβ.

As used herein, farnesoid X receptor refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms (see, e.g. Huber *et al*, *Gene* (2002), Vol. 290, pp.:35-43). Representative farnesoid X receptor species include, without limitation the rat (GenBank Accession No. NM_021745), mouse (Genbank Accession No. NM_009108), and human (GenBank Accession No. NM_005123) forms of the receptor

The terms "obese" and "obesity" refers to a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/height (m^2).

Utility of the Compounds of the Invention

The compounds of the invention exhibit valuable pharmacological properties in mammals, and are particularly useful as selective LXR agonists, antagonists, inverse agonists, partial agonists and antagonists, as well as LXR/FXR dual agonists, for the treatment, or prevention of diseases associated with, or symptoms arising from the

complications of, altered cholesterol transport, cholesterol reverse transport, fatty acid metabolism, cholesterol absorption, cholesterol re-absorption, cholesterol secretion, cholesterol excretion, or cholesterol metabolism.

These diseases include, for example, hyperlipidemia, dyslipidemia, hypercholesterolemia, atherosclerosis, atherosclerotic cardiovascular diseases, hyperlipoproteinemia, (see, *e.g.*, Patent Application Publication Nos. WO 00/57915 and WO 00/37077), hyperglycemia, insulin resistance, diabetes, lipodystrophy, obesity, syndrome X (US Patent Application No. 20030073614, International Patent Application Publication No. WO 01/82917), excess lipid deposition in peripheral tissues such as skin (xanthomas) (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814), stroke, peripheral occlusive disease, memory loss (*Brain Research* (1997), Vol. 752, pp. 189-196), optic nerve and retinal pathologies (*i.e.*, macular degeneration, retintis pigmentosa), repair of traumatic damage to the central or peripheral nervous system (*Trends in Neurosciences* (1994), Vol. 17, pp. 525-530), prevention of the degenerative process due to aging (*American Journal of Pathology* (1997), Vol. 151, pp. 1371-1377), Parkinson's disease or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334; *Trends in Neurosciences* (1994), Vol. 17, pp. 525-530), prevention of degenerative neuropathies occurring in diseases such as diabetic neuropathies (see, *e.g.*, International Patent Application Publication No. WO 01/82917), multiple sclerosis (*Annals of Clinical Biochem.* (1996), Vol. 33, No. 2, pp. 148-150), and autoimmune diseases (*J. Lipid Res.* (1998), Vol. 39, pp. 1740-1743).

Also provided, are methods of increasing the expression of ATP-Binding Cassette (ABCA1), (see, *e.g.*, International Patent Application Publication No. WO 00/78972) thereby increasing reverse cholesterol transport in mammalian cells using the claimed compounds and compositions.

Accordingly in another aspect, the invention also includes methods to remove cholesterol from tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerosis or atherosclerotic cardiovascular disease manifest by clinical signs of such disease, wherein the methods comprise administering to the patient a therapeutically effective amount of a compound or composition of the present invention.

Additionally, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic cardiovascular disease event including ischemic heart disease, ischemic stroke, multi-infarct dementia, and intermittent claudication comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event. The patient may already have atherosclerotic cardiovascular disease at

the time of administration, or may be at risk for developing it. Risk factors for developing atherosclerotic cardiovascular disease events include increasing age (65 and over), male gender, a family history of atherosclerotic cardiovascular disease events, high blood cholesterol (especially LDL or "bad" cholesterol over 100 mg/dL), cigarette smoking and exposure to tobacco smoke, high blood pressure, diabetes, obesity and physical inactivity.

Also contemplated herein is the use of a compound of the invention, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following therapeutic agents in treating atherosclerosis: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives.

In one embodiment compounds of the invention are used in combination with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see,* U.S. Patent No. 4,231,938); simvastatin (ZOCOR®; *see,* U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see,* U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see,* U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see,* U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see*, U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in combination with the compounds of the invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry,* pp. 85-89 (5 February

1996). In presently preferred embodiments, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

The compounds of the present invention can also be used in methods for decreasing hyperglycemia and insulin resistance, *i.e.*, in methods for treating diabetes (International Patent Application Publication No. WO 01/82917), and in methods of treatment, prevention, or amelioration of disorders related to, or arising as complications of diabetes, hyperglycemia or insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" (See US Patent Application 20030073614) comprising the administration of a therapeutically effective amount of a compound or composition of the present invention to a patient in need of such treatment.

Additionally the instant invention also provides a method for preventing or reducing the risk of developing hyperglycemia, insulin resistance, diabetes or syndrome X in a patient, comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, e.g., LeRoith, D. *et al.*, (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for macrovascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDEM); and type 2 diabetes (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion

declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids, *e.g.*, cholesterol and triglyceride, in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, see, *e.g.*, Wilson, J. *et al.*, (ed.), Disorders of Lipid Metabolism, Chapter 23, *Textbook of Endocrinology*, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, *e.g.*, Joslin, *E. Ann. Chim. Med.* (1927), Vol. 5, pp. 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with non-diabetic subjects (see, *e.g.*, Garcia, M. J. *et al.*, *Diabetes* (1974), Vol. 23, pp. 105-11 (1974); and Laakso, M. and Lehto, S., *Diabetes Reviews* (1997), Vol. 5, No. 4, pp. 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., *et al.*, *Arteriosclerosis* (1978), Vol. 30, pp. 153-162).

The compounds of the invention can also be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, *e.g.*, Turner, N. *et al.*, *Prog. Drug Res.* (1998), Vol. 51, pp.33-94; Haffner, S.,

Diabetes Care (1998), Vol. 21, pp. 160-178; and DeFronzo, R. *et al.* (eds.), *Diabetes Reviews* (1997), Vol. 5, No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, *e.g.*, Mahler, R., *J. Clin. Endocrinol. Metab.* (1999), Vol. 84, pp. 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, *Diabetes Care* (1998), Vol. 21, pp. 87-92; Bardin, C. W.(ed.), *CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM*, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. *et al.*, *Ann. Intern. Med.* (1994), Vol. 121, pp. 928-935; Coniff, R. *et al.*, *Clin. Ther.* (1997), Vol.19, pp. 16-26; Coniff, R. *et al.*, *Am. J. Med.* (1995), Vol. 98, pp. 443-451; Iwamoto, Y. *et al.*, *Diabet. Med.* (1996), Vol. 13, pp. 365-370; Kwiterovich, P., *Am. J. Cardiol* (1998), Vol. 82 (12A), pp. 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

Accordingly, the compounds of the invention may be used in combination with one or more of the following therapeutic agents in treating diabetes: sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone), and related insulin sensitizers, such as selective and non-selective activators of PPARα, PPARβ and PPARγ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); antiglucocorticoids; TNFα inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the therapeutic agents discussed above for treating atherosclerosis.

Further provided by this invention are methods of using the compounds of the invention to treat obesity, as well as the complications of obesity. Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of type 2 diabetes (See, *e.g.*, Barrett-Conner, E., *Epidemol. Rev.* (1989), Vol. 11, pp. 172-181; and Knowler, *et al.*, *Am. J Clin. Nutr.* (1991), Vol. 53, pp. 1543-1551).

In addition, the compounds of the invention can be used in combination with agents used in treated obesity or obesity-related disorders. Such agents, include, but are not limited to, phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin,

cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptor modulators, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

Evaluation of the Utility of the Compounds of the Invention

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including the LXRs (LXRα and LXRβ) and FXR. Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see, generally, Glickman *et al.*, *J. Biomolecular Screening* (2002), Vol. 7, No. 1, pp. 3-10, as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays, (see, Lehmann. *et al., J. Biol Chem.* (1997), Vol. 272, No. 6, pp. 3137-3140.

High throughput screening systems are commercially available *(see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see, for example, Owicki, J., *Biomol. Screen* (2000 October), Vol. 5, No. 5, pp. 297), scintillation proximity assays (SPA) (see, for example, Carpenter *et al.*, *Methods Mol. Biol.* (2002), Vol 190, pp. 31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, *J. Steroid Biochem. Mol. Biol.* (2002 July); Vol. 81, No. 3, pp. 217-25; (Zhou *et al.*, *Mol. Endocrinol.* (1998 October), Vol. 12, No. 10, pp. 1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of LXRα, the LBD

comprises amino acids 188-447, for LXRβ the LDB comprises amino acids 198-461, and for FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound (for example, [^{3}H] 24,25 Epoxycholesterol) generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of LXR with RXRα can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to LXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXRα is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or

antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds of the present invention. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor (see, for example, US Patents Nos. 5,071,773; 5,298,429 and 6,416,957). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as the LXRs, as well as FXRs, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Typically, the expression plasmid comprises: (1) a promoter, such as an SV40 early region promoter, HSV tk promoter or phosphoglycerate kinase (pgk) promoter, CMV promoter, Srα promoter or other suitable control elements known in the art, (2) a cloned polynucleotide sequence, such as a cDNA encoding a receptor, co-factor, or fragment thereof, ligated to the promoter in sense orientation so that transcription from the promoter will produce a RNA that encodes a functional protein, and (3) a polyadenylation sequence. For example and not limitation, an expression cassette of the invention may comprise the cDNA expression cloning vectors, or other preferred expression vectors known and commercially available from vendors such as Invitrogen, (CA), Stratagene, (CA) or Clontech, (CA). Alternatively expression vectors developed by academic groups such as the pCMX vectors originally developed in the Evans lab (Willey et al. Genes & Development 9 1033-1045 (1995)) may also be used.

The transcriptional regulatory sequences in an expression cassette are selected by the practitioner based on the intended application; depending upon the specific use, transcription regulation can employ inducible, repressible, constitutive, cell-type specific, developmental stage-specific, sex-specific, or other desired type of promoter or control sequence.

Alternatively, the expression plasmid may comprise an activation sequence to activate or increase the expression of an endogenous chromosomal sequence. Such activation sequences include for example, a synthetic zinc finger motif (for example see US Patents 6,534,261 and 6,503,7171) or a strong promoter or enhancer sequence together with a targeting sequence to enable homologous or non-homologous recombination of the activating sequence upstream of the gene of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include human LXRα (accession U22662), human LXRβ (accession U07132), rat FXR (accession U18374), human FXR (accession NM_005123), human RXR α (accession NM_002957), human RXR β (accession XM_042579), human RXR.γ (accession XM_053680), human PPARα (accession X57638) and human PPAR δ

(accession U10375). All accession numbers in this application refer to GenBank accession numbers.

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase (typically with SV40 small t intron and poly-A tail, (de Wet *et al.*, (1987) *Mol. Cell. Biol.* 7 725-735) down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence, obtained for example, from the plasmid pBLCAT2 (Luckow & Schutz (1987) *Nucl. Acid. Res.*15 5490-5494)) which is linked in turn to the appropriate response element (RE).

The choice of hormone response element is dependent upon the type of assay to be used. In the case of the use of the full-length LXRα or LXRβ a reporter plasmid comprising a known LXR RE would typically be used, such as for example in a reporter plasmid such as LXREx1-tk-luciferase, (see U.S. patent No. 5,747,661, which is hereby incorporated by reference). In the case of a LXRα or LXRβ-LBD-Gal4 fusion, GAL4 Upstream Activating Sequences (UAS) would be used. Typically the GAL4 UAS would comprise the sequence 5'CGGRNNRCYNYNCNCCG-3', where Y = C or T, R =A or G, and N = A, C, T or G, and would be present as a tandem repeat of 4 copies.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase (see, Berger, J., *et al.*, *Gene* (1988), Vol. 66, pp. 1-10; and Kain, S.R., *Methods. Mol. Biol.* (1997), Vol. 63, pp. 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., *et al.*, *J. Chemilum. Biolum.* (1989), Vol. 4, pp. 99-111), chloramphenicol acetyltransferase (See, Gorman *et al.*, *Mol. Cell Biol.* (1982), Vol. 2, pp. 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; and 5,843,746) and naturally fluorescent proteins (Tsien, R.Y., *Annu. Rev. Biochem.* (1998), Vol. 67, pp. 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility

of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general, the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / Umud super families are used.

A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand (see, for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction significantly enhances the transcription of the reporter gene which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by

the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of LXRα, LXRβ or FXR may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally, the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by LXRα, LXRβ or FXR and other nuclear receptors *in vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by LXR target genes. Genes that are known to be regulated by the LXRs include the ATP binding cassette transporters ABCA1, ABCG1, ABCG5, ABCG8, the sterol response element binding protein 1c (SREBP1c) gene, stearoyl CoA desaturase 1 (SCD-1) and the apolipoprotein apoE gene (ApoE).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDR^{-/-}$) and atherosclerosis using both the Apo E($^{-/-}$) and LDL($^{-/-}$) mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally LXR or FXR animal models (e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (*see*, for example, Peet, *et al., Cell* (1998), Vol. 93, pp. 693-704, and Sinal, *et al., Cell* (2000), Vol. 102, pp. 731-744).

Administration of the Compounds of the Invention

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical

composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state associated with the activity of a nuclear receptor in accordance with the teachings of this invention.

A pharmaceutical composition of the invention may be in the form of a solid or liquid. In one aspect, the carrier(s) are particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup, injectable liquid or an aerosol, which is useful in, *e.g.*, inhalatory administration.

When intended for oral administration, the pharmaceutical composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the pharmaceutical composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following may be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch, lactose or dextrins,

disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent.

When the pharmaceutical composition is in the form of a capsule, *e.g.*, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or oil.

The pharmaceutical composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid pharmaceutical composition of the invention intended for either parenteral or oral administration should contain an amount of a compound of the invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral pharmaceutical compositions contain between about 4% and about 50% of the compound of the invention. Preferred pharmaceutical compositions and preparations according to the present invention are prepared so that a

parenteral dosage unit contains between 0.01 to 1% by weight of the compound of the invention.

The pharmaceutical composition of the invention may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of the invention from about 0.1 to about 10% w/v (weight per unit volume).

The pharmaceutical composition of the invention may be intended for rectal administration, in the form, *e.g.*, of a suppository, which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

The pharmaceutical composition of the invention may include various materials, which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials that form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule.

The pharmaceutical composition of the invention in solid or liquid form may include an agent that binds to the compound of the invention and thereby assists in the delivery of the compound. Suitable agents that may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One skilled in the art, without undue experimentation may determine preferred aerosols.

The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.1 mg to about 20 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.1 mg to about 10 mg/kg of body weight per day; and most preferably, from about 0.1 mg to about 7.5 mg/kg of body weight per day.

Compounds of the invention, or pharmaceutically acceptable derivatives thereof, may also be administered simultaneously with, prior to, or after administration of one or more of the therapeutic agents described above in the Utility of the Compounds of the Invention. Such combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of the invention and one or more additional active agents, as well as administration of the compound of the invention and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of the invention and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds of the invention and one or more additional active agents can be administered at essentially the same time, *i.e.*, concurrently, or at separately staggered times, *i.e.*, sequentially; combination therapy is understood to include all these regimens.

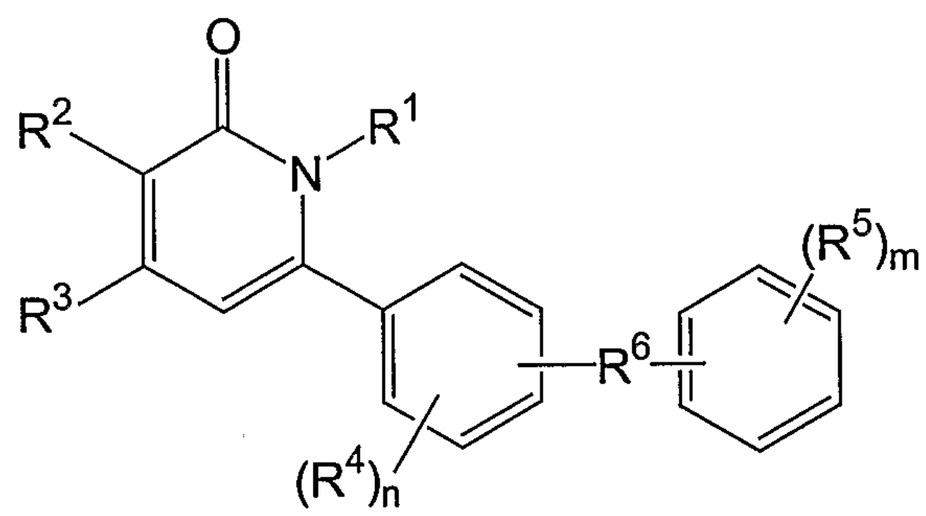
Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or

similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and, more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

Embodiments of the Invention

Of the various aspects of the invention as set forth above in the Summary of the Invention, certain embodiments are described herein. One embodiment are the compounds of formula (I) having the following formula (II):



(II)

wherein:

n is 1 to 4;

m is 1 to 4;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano or $-R^7-N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7$-CN, $-R^7$-OR^8, $-R^7$-O-R^9-$C(O)OR^8$, $-R^7$-$C(O)R^{11}$, $-R^7$-$C(O)OR^8$, $-R^7$-$C(O)OR^9$-$N(R^{11})_2$, $-R^7$-$C(O)N(R^8)OR^{11}$, $-R^7$-$C(O)OR^9$-OR^9-$N(R^{11})_2$, $-R^7$-$C(O)N(R^8)_2$, $-R^7$-$C(O)N(R^8)OR^8$, $-R^7$-$C(O)N(R^8)N(R^8)_2$, $-R^7$-$C(O)N(R^8)$-R^9-$C(O)OR^8$, $-R^7$-$C(O)N(R^8)$-R^9-OR^{11}, $-R^7$-$C(O)N(R^8)$-R^9-$N(R^{11})_2$, $-R^7$-$C(S)N(R^8)_2$, $-R^7$-$N(R^8)_2$, $-R^7$-$N(R^8)$-R^9-$C(O)OR^{10}$, $-R^7$-$N(R^8)C(O)R^8$, $-R^7$-$N(R^8)C(O)N(R^8)_2$, $-R^7$-$N(R^8)C(O)N(R^8)$-OR^{11}, $-R^7$-$N(R^8)C(O)N(R^8)$-R^9-OR^{11}, $-R^7$-$N(R^8)C(O)N(R^8)$-R^9-$N(R^{11})_2$, $-R^7$-$N(R^8)C(O)OR^{10}$, $-R^7$-$N(R^8)C(O)OR^9$-$N(R^{11})_2$, $-R^7$-$N(R^8)C(O)OR^9$-OR^9-$N(R^{11})_2$, $-R^7$-$N(R^8)C(O)OR^9$-OR^{11}, $-R^7$-$N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7$-$N(R^8)C(O)C(O)OR^{11}$, $-R^7$-$N(R^8)S(O)_2$-R^8, $-R^7$-$S(O)_tR^8$ (where t is 0 to 2) and $-R^7$-$S(O)_2N(R^8)_2$;

R^6 is $-OR^7$-, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of this embodiment, one further embodiment are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, haloalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted haloalkyl, optionally substituted haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^9 is a straight or branched alkylene chain optionally substituted by aryl or heteroaryl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein R^6 is $-OR^7-$.

Of this embodiment, a further embodiment are those compounds wherein R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $-NR^8C(O)OR^{10}$.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl, ethyl, 1-hydroxy-1-methylethyl, fluoromethyl, difluoromethyl, pentafluoroethyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl or haloalkyl.

Of this embodiment, a further embodiment are those compounds wherein each R^5 is independently selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, ethenyl or trifluoromethyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$ and $R^7-O-R^9-C(O)OR^8$

each R^7 is independently selected from a direct bond or methylene chain;

each R^8 is independently selected from hydrogen, alkyl, aryl and aralkyl; and

R^9 is a methylene chain.

Another embodiment of compound of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of heteroaryl, $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl or heterocyclyl optionally substituted with hydroxy;

R^9 is a straight or branched alkylene chain (optionally substituted by phenyl or imidazolyl); and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

m is 1 or 2;

each R^5 is independently selected from $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$ or $-R^7-C(O)N(R^8)N(R^8)_2$;

each R^7 is independently selected from a direct bond or methylene;

each R^8 is independently selected from hydrogen, methyl, ethyl, 1,1-dimethylethyl, benzyl, 2-phenylethyl, cyclohexyl or piperidinyl optionally substituted by hydroxy; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of heteroaryl, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen or alkyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl or heterocyclyl; and

R^9 is a straight or branched alkylene chain (optionally substituted by phenyl or imidazolyl).

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen or chloro;

R^5 is $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$;

R^7 is a direct bond;

each R^8 is independently hydrogen or alkyl; and

R^9 is a straight or branched alkylene chain optionally substituted by phenyl or imidazolyl.

Another embodiment of the compounds of formula(II) are those compounds wherein:

n is 1;

m is 1;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of phthalimidyl, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 or 2);

each R^7 is a direct bond; and

each R^8 is independently selected from hydrogen or alkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein R^1 is optionally substituted heteroarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted thiazol-5-ylmethyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl or haloalkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$ or $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl or heterocyclyl;

each R^9 is a straight or branched alkylene chain optionally substituted by aryl or heteroaryl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of alkyl, trifluoromethyl, $-R^7-OR^8$ and $R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

R^7 is a direct bond;

R^8 is hydrogen or alkyl; and

R^9 is a straight or branched alkylene chain.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of alkyl, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ or $-R^7-C(O)N(R^8)_2$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently hydrogen, alkyl, aryl or aralkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, pyrrolidinyl or piperidinyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, haloalkyl or $-R^7-OR^8$;

R^6 is a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

R^7 is a direct bond; and

R^8 is hydrogen or alkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of nitro, $-R^7-N(R^8)_2$, $-R^7-OR^8$ or $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen or alkyl; and

R^{10} is alkyl.

Another embodiment of the compound of formula (II) are those compounds wherein:

n is 1 or 2;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, or $R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl; and

R^9 is selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)_2$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$ and $-R^7-C(O)N(R^8)_2$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

R^9 is selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Another embodiment of the compounds of formula (II) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, and $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

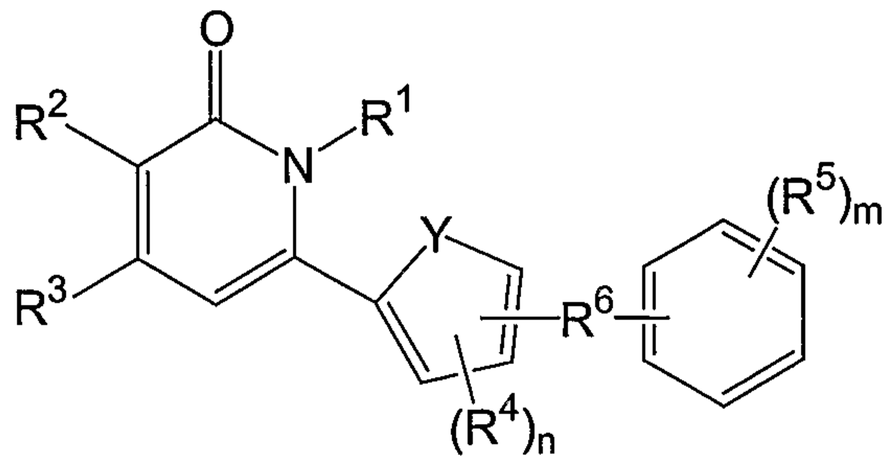
each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of the compounds of formula (I) as set forth above in the Summary of the Invention, another embodiment are those compounds having the following formula (III):



(III)

wherein:

Y is oxygen or sulfur;

n is 1 or 2;

m is 1 to 4;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, aryl, aralkyl, aralkenyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^{10} is independently selected from alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

Of this embodiment, a further embodiment are those compounds of formula (III) wherein:

Y is oxygen or sulfur;

n is 1 or 2;

m is 1 to 4;

R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$ or $-N(R^8)_2$;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

each R^9 is a straight or branched alkylene chain;

each R^{10} is independently selected from alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein Y is sulfur.

Of this embodiment, a further embodiment are those compounds wherein

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

each R^{10} is independently selected from alkyl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, $-R^7-OR^8$ and $-R^7-O-R^9-OR^8$;

R^6 is a direct bond, a straight or branched ethylene chain, a straight or branched ethenylene chain or a straight or branched ethynylene chain;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

each R^9 is a straight or branched ethylene chain.

Another embodiment of compounds of formula (III) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

when m is 1, R^5 is hydrogen or $-R^7-S(O)_tR^8$ (where t is 0 to 2); or

when m is 2, one R^5 is $-R^7-S(O)_tR^8$ (where t is 0 to 2) or $-R^7-S(O)_2N(R^8)_2$ and the other R^5 is independently selected from the group consisting of alkyl, halo, haloalkyl and $-R^7-OR^8$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl.

Another embodiment of compounds of formula (III) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ and $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is -N(H)- or a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Another embodiment of compounds of formula (III) are those compounds wherein Y is oxygen.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-OR^8$ and $-R^7-O-R^9-OR^8$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

each R^9 is a straight or branched ethylene chain.

Another embodiment of compounds of formula (III) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

when m is 1, R^5 is hydrogen or $-R^7-S(O)_tR^8$ (where t is 0 to 2); or

when m is 2, one R^5 is $-R^7-S(O)_tR^8$ (where t is 0 to 2) and the other R^5 is independently selected from the group consisting of halo, haloalkyl and $-R^7-OR^8$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl.

Another embodiment of compounds of formula (III) are those compounds wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ and $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

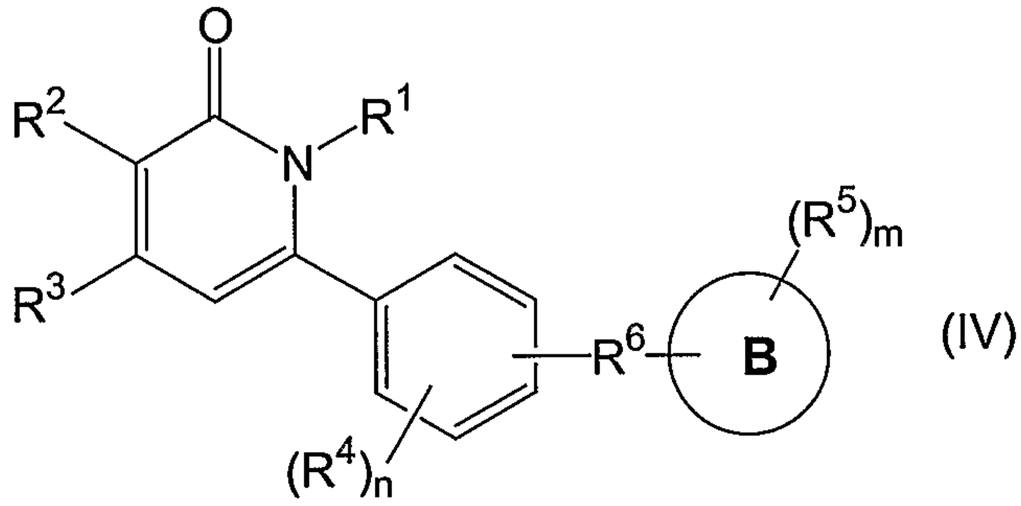
each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

Of the compounds of formula (I) as set forth above in the Summary of the Invention, another embodiment are those compounds having the following formula (IV):



(IV)

wherein:

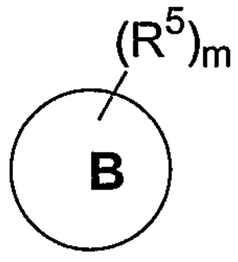
n is 1 to 4;

m is 1 to 4;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or $-R^7-N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl or heteroaryl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

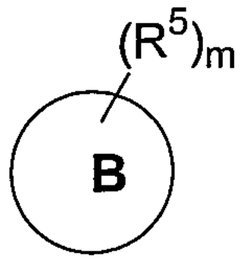
each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



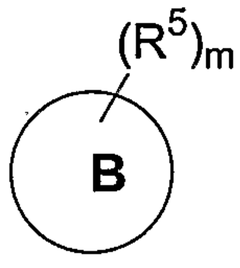
is a *N*-heteroaryl selected from the group consisting of indolyl and thiazolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7$-CN and $-R^7$-C(O)OR^8; and

R^6 is a direct bond.

Another embodiment of the compounds of formula (IV) are those compounds wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



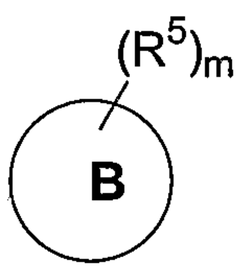
is *N*-heteroaryl selected from the group consisting of indolyl, pyrimidyl, pyrazinyl, pyridinyl and thiazolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7$-CN and $-R^7$-C(O)OR^8; and

R^6 is -O-.

Another embodiment of the compounds of formula (IV) are those compounds wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

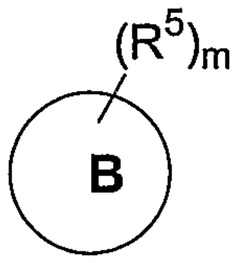


is *N*-heterocyclyl selected from the group consisting of piperidinyl and piperazinyl; and

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7$-CN and $-R^7$-C(O)OR^8.

Another embodiment of the compounds of formula (IV) are those compounds wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



is benzodioxolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7$-CN and $-R^7$-C(O)OR^8; and

R^6 is a direct bond.

Another embodiment of the compounds of formula (IV) are those compounds wherein:

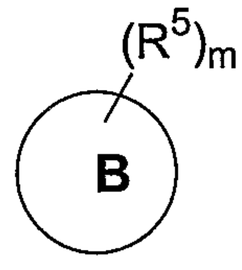
n is 1 to 4;

m is 1 to 4;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or $-R^7$-$N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl or heteroaryl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, optionally substituted aralkyl, $-R^7$-C(O)OR^8, $-R^7$-C(O)OR^9-$N(R^{11})_2$, $-R^7$-C(O)OR^9-OR^9-$N(R^{11})_2$, $-R^7$-C(O)$N(R^8)_2$, $-R^7$-C(O)N(R^8)-R^9-OR^{11}, $-R^7$-C(O)N(R^8)-R^9-$N(R^{11})_2$, $-R^7$-N(R^8)C(O)OR^{10}, $-R^7$-N(R^8)C(O)OR^9-OR^9-$N(R^{11})_2$, and $-R^7$-N(R^8)C(O)OR^9-OR^{11};

R^6 is $-OR^7$-, -N(R^8)- or a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of this embodiment, a further embodiment are those compounds wherein:

n is 1;

m is 1 or 2;

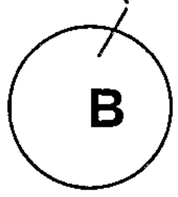
R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$, or $-N(R^8)C(O)OR^{10}$;

or R^1 is pyridinylalkyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$,$-N(R^8)_2$ and $-N(R^8)C(O)OR^{10}$;

R^2 is hydrogen, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or cyano;

R^3 is hydrogen, methyl, difluoromethyl or trifluoromethyl;

$(R^5)_m$



is indolyl, benzimidazolyl, pyrazolyl, or benzodioxinyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, optionally substituted aralkyl, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, and $-R^7-N(R^8)C(O)OR^9-OR^{11}$;

R^6 is -O-, -N(H)- or a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

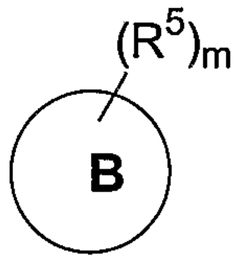
each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of this embodiment, another further embodiment are those compounds wherein:

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$, or $-N(R^8)C(O)OR^{10}$;



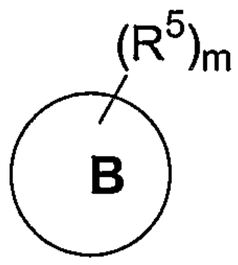
is indolyl, benzimidazolyl, pyrazolyl or benzodioxinyl; and

each R^5 is independently selected from the group consisting of hydrogen, alkyl, and optionally substituted aralkyl.

Another embodiment of the compounds of formula (IV) are those compounds wherein:

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$, or $-N(R^8)C(O)OR^{10}$;

or R^1 is pyridinylalkyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ and $-N(R^8)C(O)OR^{10}$;



is indolyl, benzimidazolyl or pyrazolyl;

each R^5 is independently selected from the group consisting of hydrogen, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, and $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

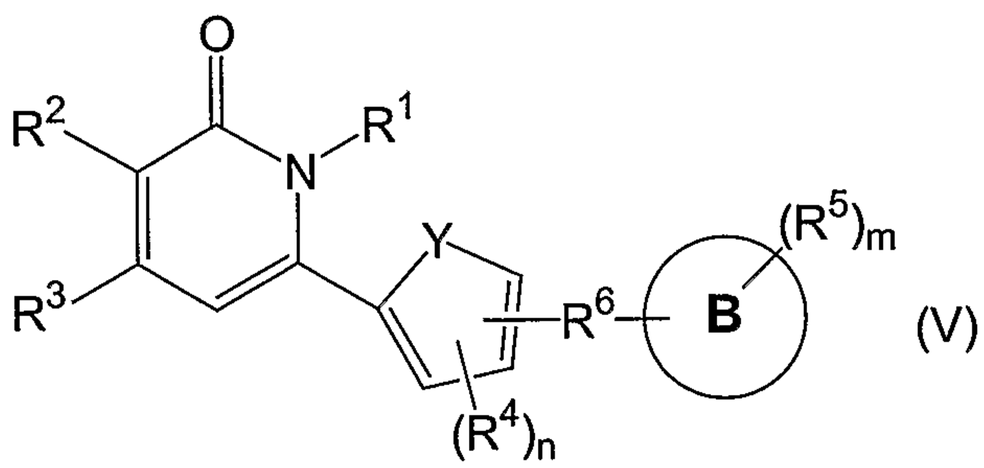
each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

Of the compounds of formula (I) as set forth above in the Summary of the Invention, another embodiment are those compounds having the following formula (V):



(V)

wherein:

n is 1 or 2;

m is 1 to 4;

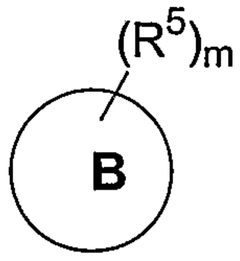
Y is oxygen or sulfur;

R^1 is optionally substituted aralkyl;

R^2 is cyano or $-R^7-N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;



is naphthyl, heterocyclyl or heteroaryl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, heterocyclyl, $-R^7-OR^8$, $-R^7-CN$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

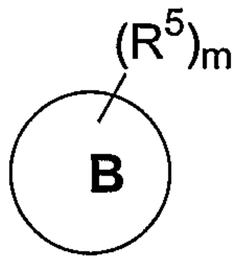
or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

Of these compounds of formula (V), one embodiment are those compounds wherein:

Y is -O-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is a *N*-heteroraryl selected from the group consisting of pyrimidinyl and pyridinyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, morpholinyl, piperazinyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

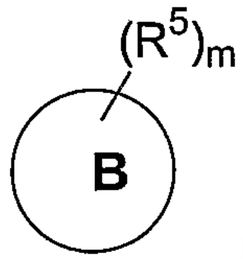
R^{10} is alkyl or cycloalkylalkyl.

Another embodiment of the compounds of formula (V) are those compounds wherein:

Y is -O-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

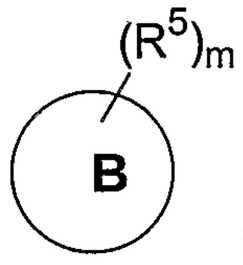
R^{10} is alkyl or cycloalkylalkyl.

Another embodiment of the compounds of formula (V) are those compounds wherein:

Y is -S-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is a *N*-heteroaryl selected from the group consisting of pyridinyl, indolyl and pyrimidinyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, morpholinyl, piperazinyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

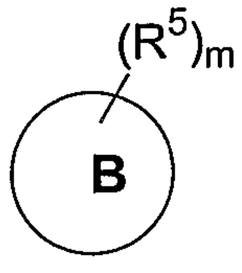
R^{10} is alkyl or cycloalkylalkyl.

Another embodiment of the compounds of formula (V) are those compounds wherein:

Y is -S-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

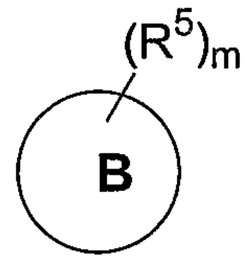
R^{10} is alkyl or cycloalkylalkyl.

Another embodiment of the compounds of formula (V) are those compounds wherein:

Y is -S-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

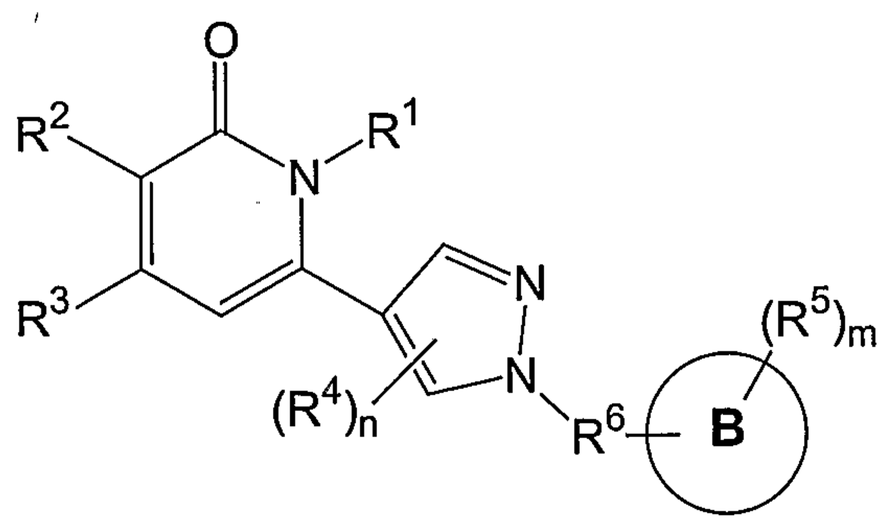
R^3 is alkyl, hydroxyalkyl or haloalkyl;



is naphthyl; and

each R^5 is independently selected from hydrogen, alkyl, halo or haloalkyl.

Of the compounds of formula (I) as set forth above in the Summary of the Invention, another embodiment are those compounds having the following formula (VI):



(VI)

wherein:

n is 1 or 2;

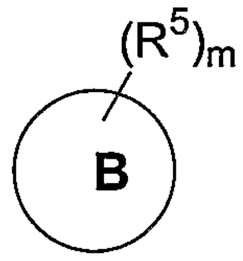
m is 1 to 4;

R^1 is optinally substituted aralkyl;

R^2 is cyano or $-R^7-N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;



is aryl or heteroaryl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or a straight or branched alkylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and

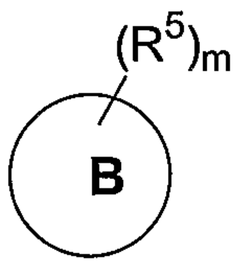
R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

Of these compounds of formula (VI), one embodiment are those compounds wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl; and



is phenyl or pyridinyl;

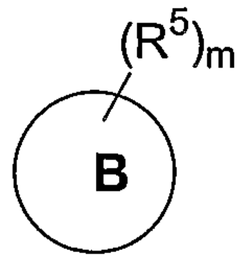
each R^5 is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is a direct bond or a straight or branched alkylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl.

Of this embodiment, a further embodiment are those compounds wherein:

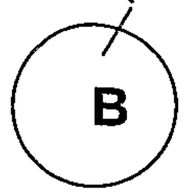


is phenyl; and

each R^5 is independently selected from the group consisting of alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2).

Another embodiment of the compounds of formula (VI) are those compounds wherein:

m is 1 or 2;



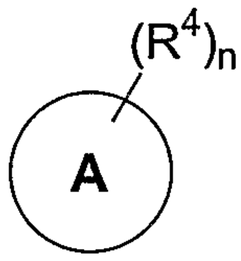
is pyridinyl; and

each R^5 is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2).

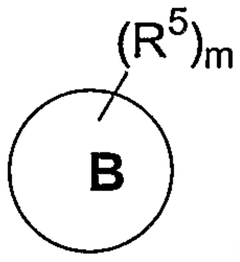
Of the compounds of formula (I) as set forth above in the Summary of the Invention, another embodiment are those compounds wherein:

n is 1 or 2;

m is 1 or 2;



is thienyl or pyridinyl;



is indolyl or benzimidazolyl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$,

$-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

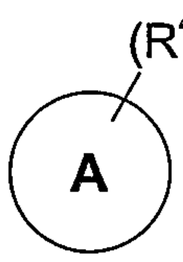
each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

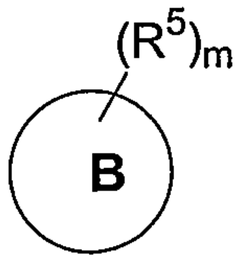
Of this embodiment, a further embodiment are those compounds wherein:

n is 1 or 2;

m is 1 or 2;



is thienyl or pyridinyl;



is indolyl or benzimidazolyl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl; and

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl.

In another embodiment, compounds for use in the composition and methods provided are set forth in Table I.

Of the methods of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, as set forth above in the Summary of the Invention, one embodiment is wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Of the methods of treating, preventing, or amerliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acide levels, as set forth above in the Summary of the Invention, one embodiment is

wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Of the methods of modulating nuclear receptor activity, comprising contacting one or more nuclear receptors with a compound of the invention, as set forth above in the Summary of the Invention, one embodiment is wherein at least one of the nuclear receptors is an orphan nuclear receptors.

Of this embodiment, a further embodiment is wherein at least one nuclear receptor is liver X receptor (LXRα or LXRβ).

Of this embodiment, another further embodiment is wherein at least one nuclear receptor is farnesoid X receptor (FXR) and another nuclear receptor is liver X receptor (LXRα or LXRβ).

Specific embodiments of the of the invention, as set forth above, are disclosed herein in the Examples set forth herein.

Preparation of the Compounds of the Invention

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

It will also be appreciated by those skilled in the art that in the processes described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for 1,2-dihydroxys include ketal- and acetal-forming groups. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein.

The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, Protective Groups in Organic Synthesis (1991), 2nd Ed., Wiley-Interscience. The protecting group may also be a polymer resin such as a Wang resin or a 2-chlorotrityl chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of the invention, as described above in the Summary of the Invention, may not possess pharmacological activity as such, they may be administered to a mammal having a disease associated with defects in cholesterol transport, glucose metabolism, fatty acid metabolism and cholesterol metabolism, and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of the invention are included within the scope of the invention.

It is understood that one of ordinary skill in the art would be able to make the compounds of the invention not specifically prepared herein in light of the following disclosure, including the Preparations and Examples, and information known to those of ordinary skill in the chemical synthesis field.

Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures or by methods disclosed herein. All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. ^1H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Mass spectra were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid) and electrospray (ES) ionization. Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, CH_2Cl_2 (dichloromethane), C_6H_6 (benzene), TFA (trifluoroacetic acid), EtOAc (Ethyl Acetate), Et_2O (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

The compounds of the invention can be prepared according to the methods disclosed herein or by the methods disclosed U.S. Patent Application, Serial No. 10/327,813, which is incorporated herein by reference in its entirety, or by methods

known to one skilled in the art in view of the teachings of this disclosure and the aforementioned application.

Preparation of Compounds of the Invention

For purposes of illustration only, most of the formulae in the following Reaction Schemes are directed to specific embodiments of the compounds of invention. However, one of ordinary skill in the art, in view of the teachings of this specification and U.S. Patent Application, Serial No. 10/327,813 would reasonably be expected to be able to prepare all the compounds of the invention as set forth above in the Summary of the Invention utilizing the appropriately-substituted starting materials and methods known to one skilled in the art.

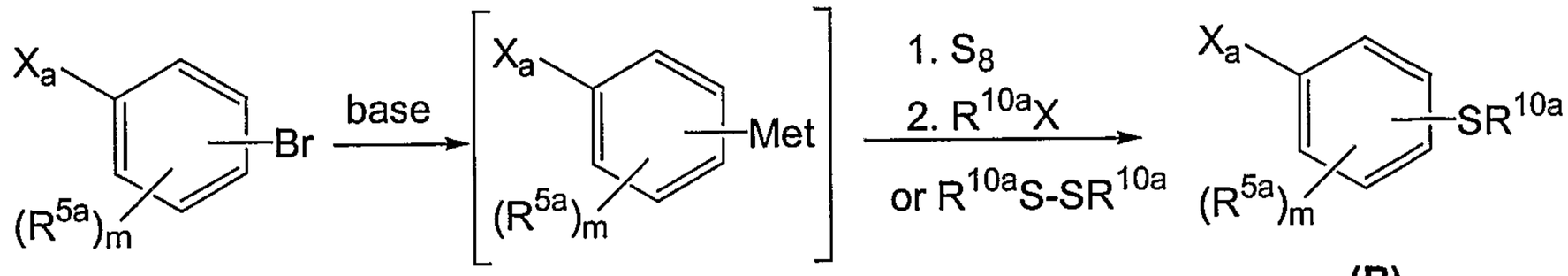
In the general descriptions immediately following each Reaction Scheme, the phrase "standard isolation procedures" is meant to include one or more of the following techniques familiar to one schooled in the art of organic chemistry: organic extraction, washing of organic solutions with dilute aqueous acid or base , use of drying agents, filtration, concentration *in vacuo*, followed by purification using distillation, crystallization, or solid-liquid phase chromatography. The phrase "elevated temperature" refers to a temperature above ambient temperature and the phrase "reduced temperature" refers to a temperature below ambient temperature.

A. Preparation of Compounds of Formula (B)

Compounds of formula (B) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 1, wherein X_a is bromo or iodo; m is 1 to 4; each R^{5a} is independently hydrogen, fluoro, chloro, alkyl, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $-S(O)_tR^8$ (where each R^8 is as defined in the Summary of the Invention), and R^{10a} is alkyl, aryl or aralkyl:

REACTION SCHEME 1

1.



(A) (ZZ) (B)

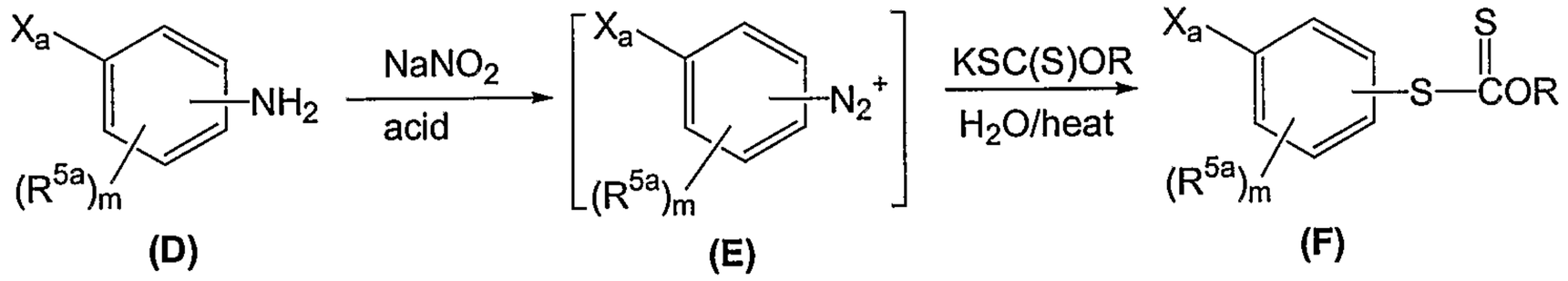
Compounds of formula (A) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

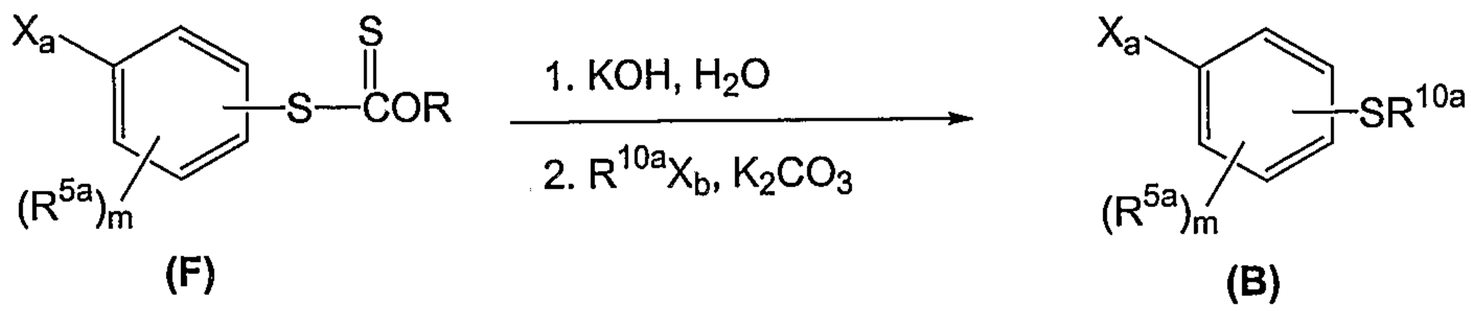
In general, compounds of formula (B) are prepared by first reacting a solution of the arylhalides of formula (A) in an aprotic solvent at reduced temperature with a strong base in a metal-halogen exchange reaction to afford the organometallic reagent of formula (ZZ), which upon reaction with a source of elemental sulfur such as S_8, provides an intermediate arylthiol (not shown). Reaction of this arylthiol with an alkyl halide in the presence of a base provides the compound of formula (B) after isolation using standard procedures. In an alternate manner, the oganometallic reagent of formula (ZZ) is reacted with various alkyl and aryl disulfides to give compounds of formula (B) using standard isolation procedures.

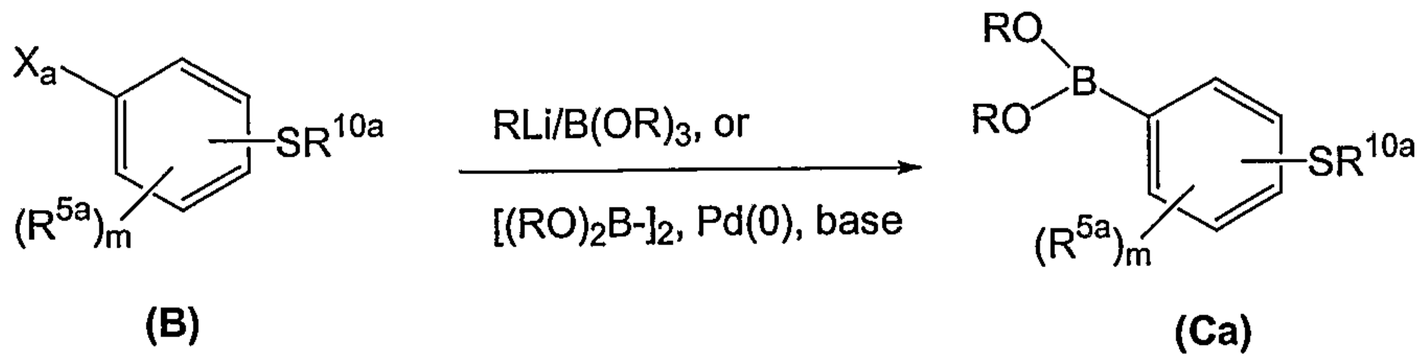
B. Preparation of Compounds of Formula (Ca)

Compounds of formula (Ca) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 2, wherein X_a is bromo or iodo; X_b is bromo, chloro or iodo; m is 1 to 4; each R is hydrogen or alkyl; each R^{5a} is independently hydrogen, fluoro, chloro, alkyl, haloalkyl or $-OR^8$ (where R^8 is as defined in the Summary of the Invention); and R^{10a} is alkyl, aryl or aralkyl:

REACTION SCHEME 2

1. 

2. 

3. 

Compounds of formula (D) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

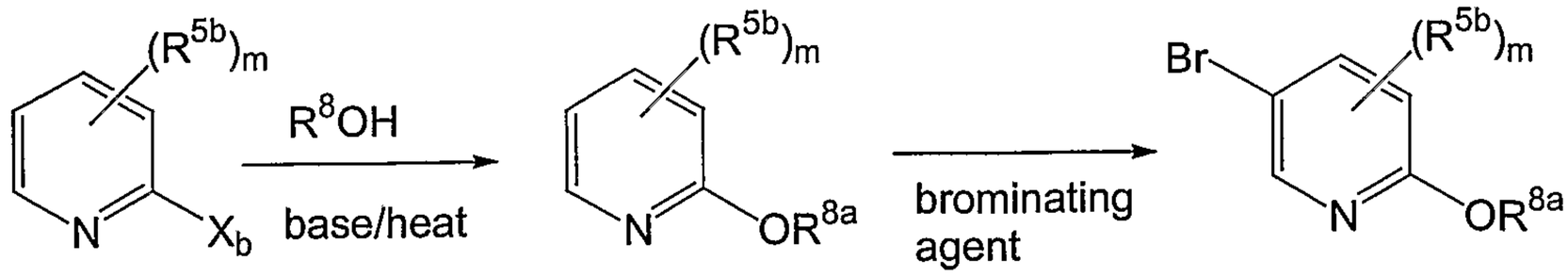
In general, compounds of formula (Ca) are prepared by first exposing an aniline of formula (D) to diazotization conditions to give the aryldiazonium salt of formula (E) which, upon exposure to a source of nucleophilic sulfur such as a xanthate salt at elevated temperature, provides the compound of formula (F) after standard isolation procedures. Hydrolyisis of the compound of formula (F) under basic conditions and exposure to an alkylating agent in the presence of a base then provides a compound of formula (B) using standard isolation procedures. Conversion of the compound of formula (B) to the compound of formula (Ca) is accomplished by treating the compound of formula (B) in an aprotic solvent at reduced temperature with a strong base in a metal-halogen exchange followed by reaction of the intermediate organomettalic reagent (not shown) with a trialkylborate. Alternatively, compounds of formula (B) are reacted with a diboronate or dioxaborolane reagent, such as pinacolborane in a palladium mediated coupling reaction, for example a Suzuki reaction, to give compound of formula (Ca) after standard isolation procedures.

C. Preparation of Compounds of Formula (Ka)

Compounds of formula (Ka) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 3, wherein X_b is bromo, chloro or iodo; m is 1 to 3; each R is hydrogen or alkyl; each R^{5b} is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$, $-SR^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$; and R^{8a} is alkyl, aryl or aralkyl:

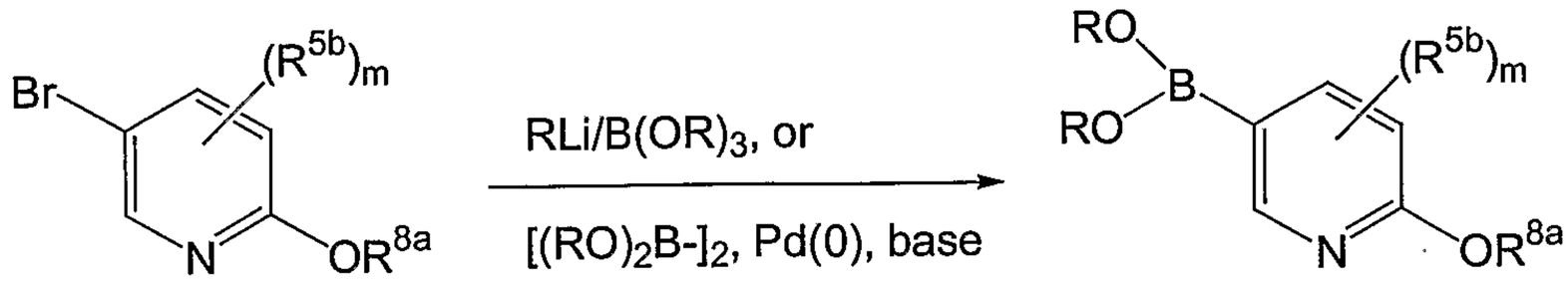
REACTION SCHEME 3

1.



(G) (H) (J)

2.



(J) (Ka)

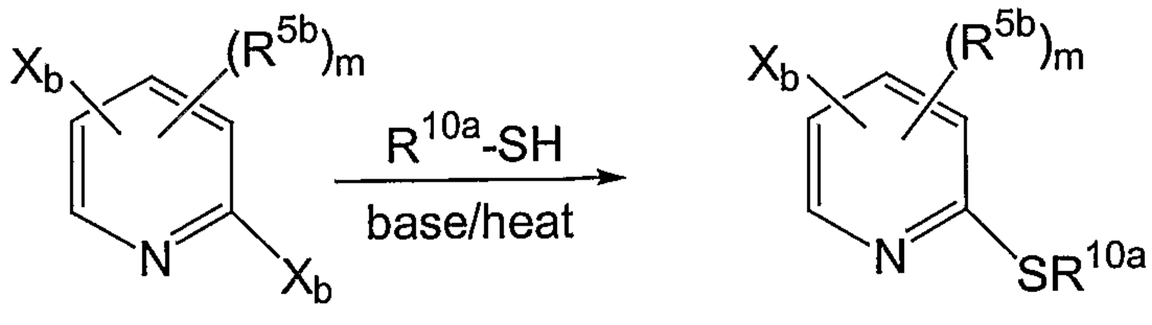
Compounds of formula (G) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

In general, compounds of formula (Ka) are prepared by first reacting halopyridines of formula (G) with alcohols in the presence of base and at elevated temperature to give compounds of formula (H) after standard isolation procedures. In a subsequent step, exposure of compounds of formula (H) to a brominating agent provides halopyridines of formula (J) after standard isolation procedures. Conversion of compounds of formula (J) to compounds of formula (Ka) is then accomplished by treating the compounds of formula (J) in an aprotic solvent at reduced temperature with strong base in a metal-halogen exchange followed by reaction of the intermediate organomettalic reagent (not shown) with a trialkylborate. Alternatively, compounds formula (J) are then reacted with a diboronate or dioxaborolane reagent such as pinacolborane in a palladium mediated coupling reaction, for example a Suzuki reaction, to give compounds of formula (Ka) after standard isolation procedures.

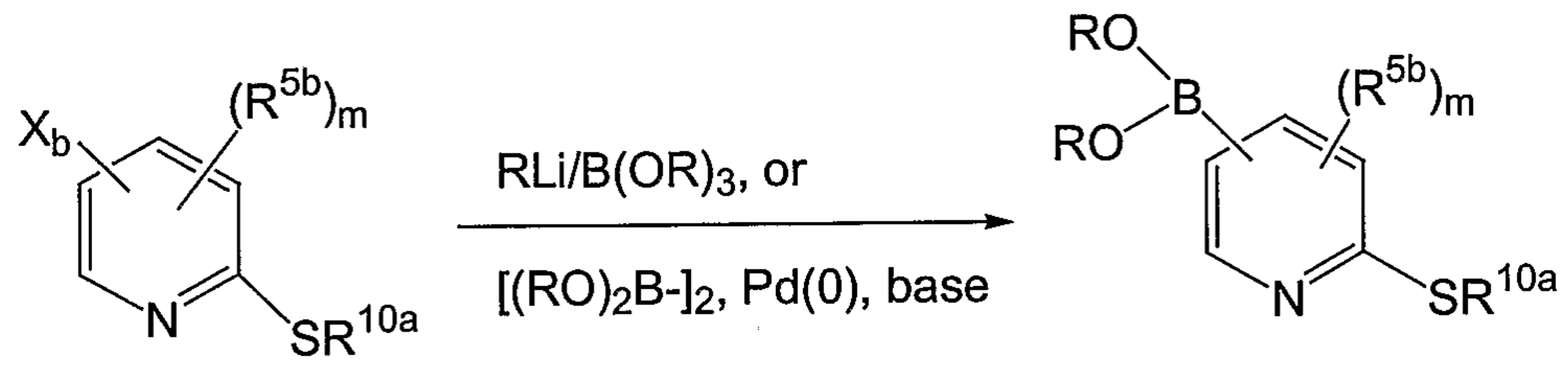
D. Preparation of Compounds of Formula (Kb)

Compounds of formula (Kb) are intermediates in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 4, wherein each X_b is bromo, chloro or iodo; m is 1 to 3; each R is hydrogen or alkyl; each R^{5b} is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$, $-SR^8$, $-C(O)OR^8$, $-C(O)N(R^8)_2$; and R^{10a} is alkyl, aryl or aralkyl:

REACTION SCHEME 4

1. 

(L) (M)

2. 

(M) (Kb)

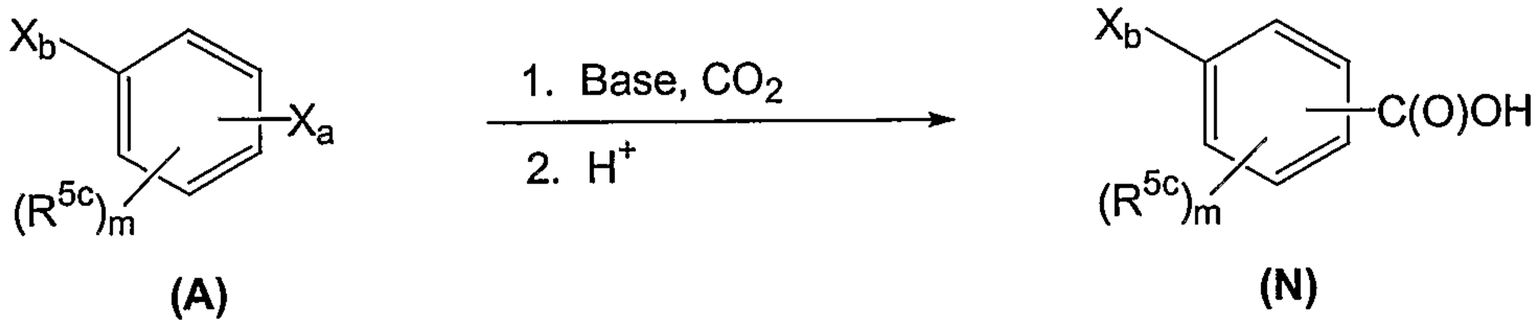
Compounds of formula (L) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

In general, compounds of formula (Kb) are prepared by first reacting dihalopyridines of formula (L) with thiols in the presence of base and at elevated temperature to give sulfides of formula (M) after standard isolation procedures. Conversion of compounds of formula (M) to compounds of formula (Kb) is then accomplished by treating compounds of formula (M) in an aprotic solvent at reduced temperature with strong base in a metal-halogen exchange followed by reaction of the intermediate organomettalic reagent with a trialkylborate. Alternatively, compounds (M) are reacted with a diboronate or dioxaborolane reagent such as pinacolborane in a palladium mediated coupling reaction, for example a Suzuki reaction, to give compounds of formula (Kb) after standard isolation procedures.

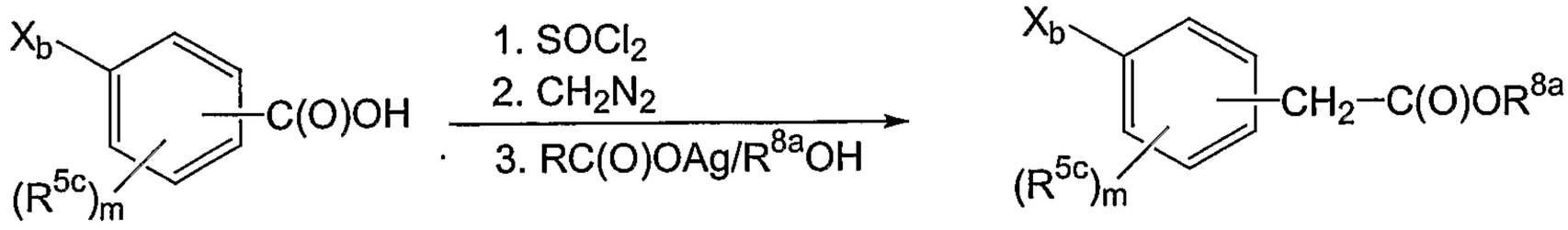
E. Preparation of Compounds of Formula (Cb)

Compounds of formula (Cb) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 5, wherein X_a is bromo or iodo; X_b is bromo, chloro or iodo; each m is 1 to 4; each R is hydrogen or alkyl; each R^{5c} is independently hydrogen, fluoro, chloro, alkyl, haloalkyl, $-OR^8$, $-N(R^8)_2$; and R^{8a} is alkyl, aryl or aralkyl:

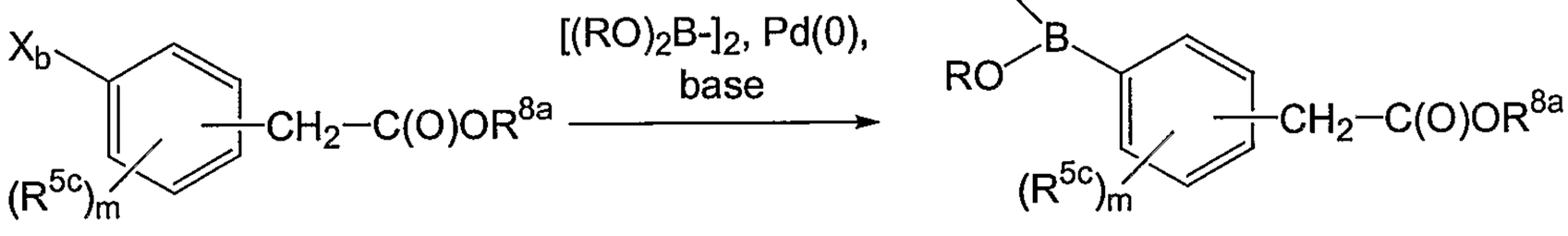
REACTION SCHEME 5

1. 

(A) (N)

2. 

(N) (P)

3. 

(P) (Cb)

Compounds of formula (A) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

In general, compounds of formula (Cb) are prepared by first reacting aryldihalides of formula (A) with strong base in an aprotic solvent at reduced temperature in a metal-halogen exchange reaction followed by carbonylation of the intermediate orgaometallic reagent (not shown) to give the carboxylic acids of formula (N) after standard isolation procedures. Conversion of compounds of formula (N) to compounds of formula (P) is then accomplished using the Arndt-Eistert reaction sequence, namely, preparation of the acylchloride (not shown) using standard methods, generation of the intermediate diazoketone (not shown) by treatment of the acylchloride with diazomethane at reduced temperature, followed by exposure of the diazoketone to a silver-salt of an organic acid in the presence of an alcohol and isolation using standard procedures. Palladium mediated coupling of compounds of formula (P) with a diboronate or dioxaborolane reagent such as pinacolborane provides arylboronates of formula (Cb) after standard isolation procedures.

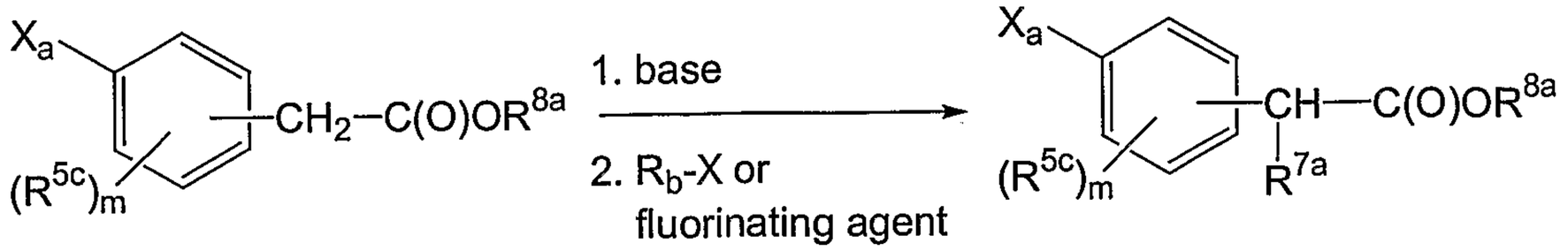
F. Preparation of Compounds of Formula (Pb)

Compounds of formula (Pb) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one

skilled in the art or by the method described below in Reaction Scheme 6, wherein X_a is bromo or iodo; X_b is bromo, chloro or iodo; m is 1 to 4; each R is alkyl or aralkyl; each R^{5c} is independently hydrogen, fluoro, chloro, alkyl, haloalkyl, $-OR^8$ or $-N(R^8)_2$; R^{7a} is alkyl, aralkyl or fluoro, and R^{8a} is alkyl, aryl or aralkyl:

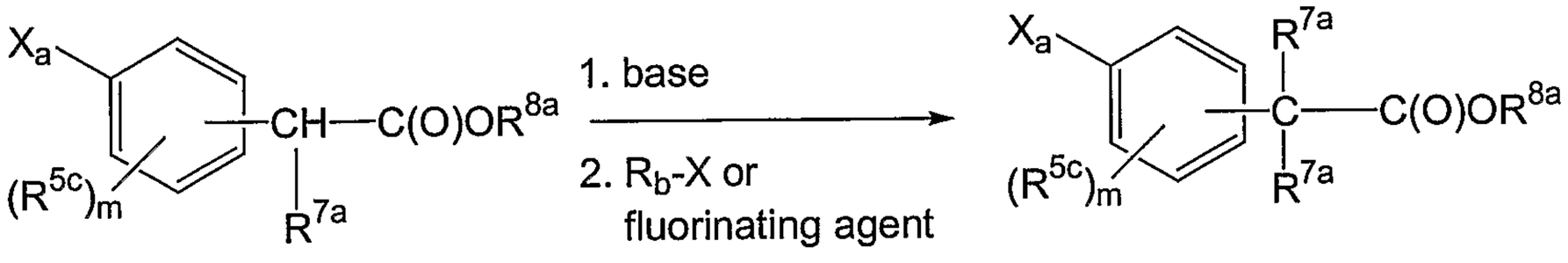
REACTION SCHEME 6

1.



(P) **(Pa)**

2.



(Pa) **(Pb)**

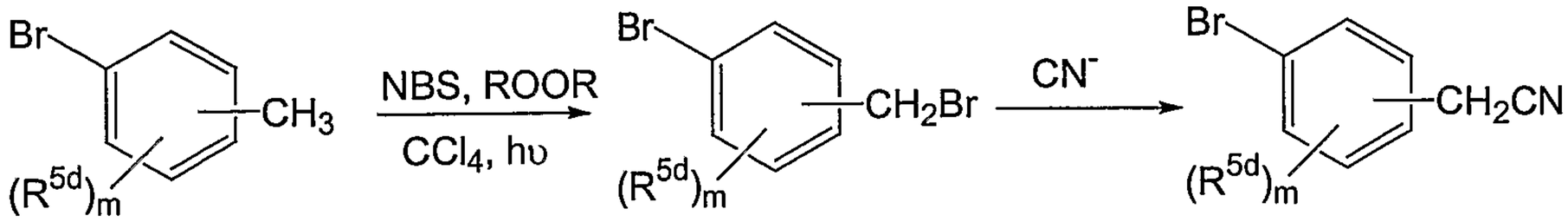
Compounds of formula (P) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

In general, compounds of formula (Pb) are prepared by first treating compounds of formula (P) with a strong base in an aprotic solvent at reduced temperature followed by the addition of an alkylating or fluorinating agent to give compounds of formula (Pa). Reaction of compounds of formula (Pa) with additional base and subsequent treatment with a second portion of alkylating or fluorinating agent provides compounds of formula (Pb) after standard isolation procedures.

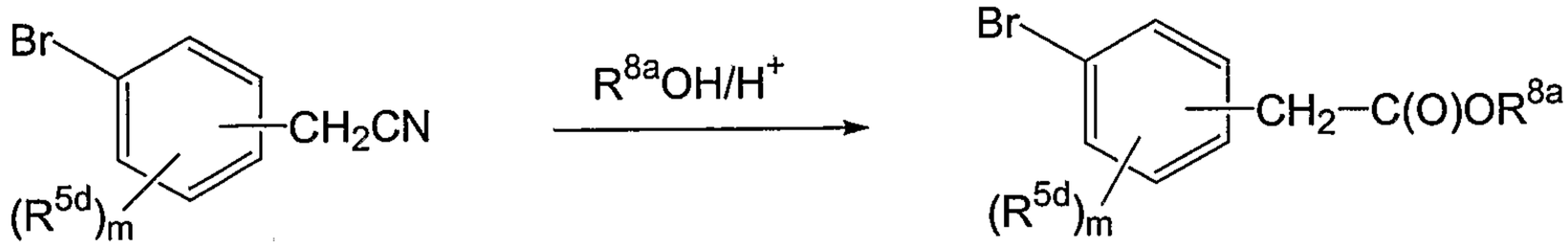
G. Alternate Preparation of Compounds of Formula (Cb)

Compounds of formula (Cb) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 7, wherein each m is 1 to 4; each R is hydrogen or alkyl; each R^{5d} is independently hydrogen, chloro, fluoro, alkyl, haloalkyl; and R^{8a} is alkyl, aryl or aralkyl:

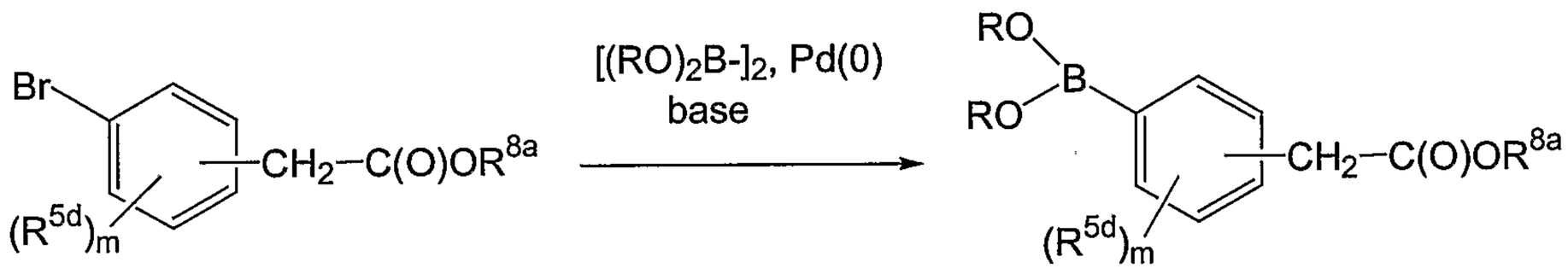
REACTION SCHEME 7

1. 

(Q) (R) (S)

2. 

(S) (P)

3. 

(P) (Cb)

Compounds of formula (Q) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

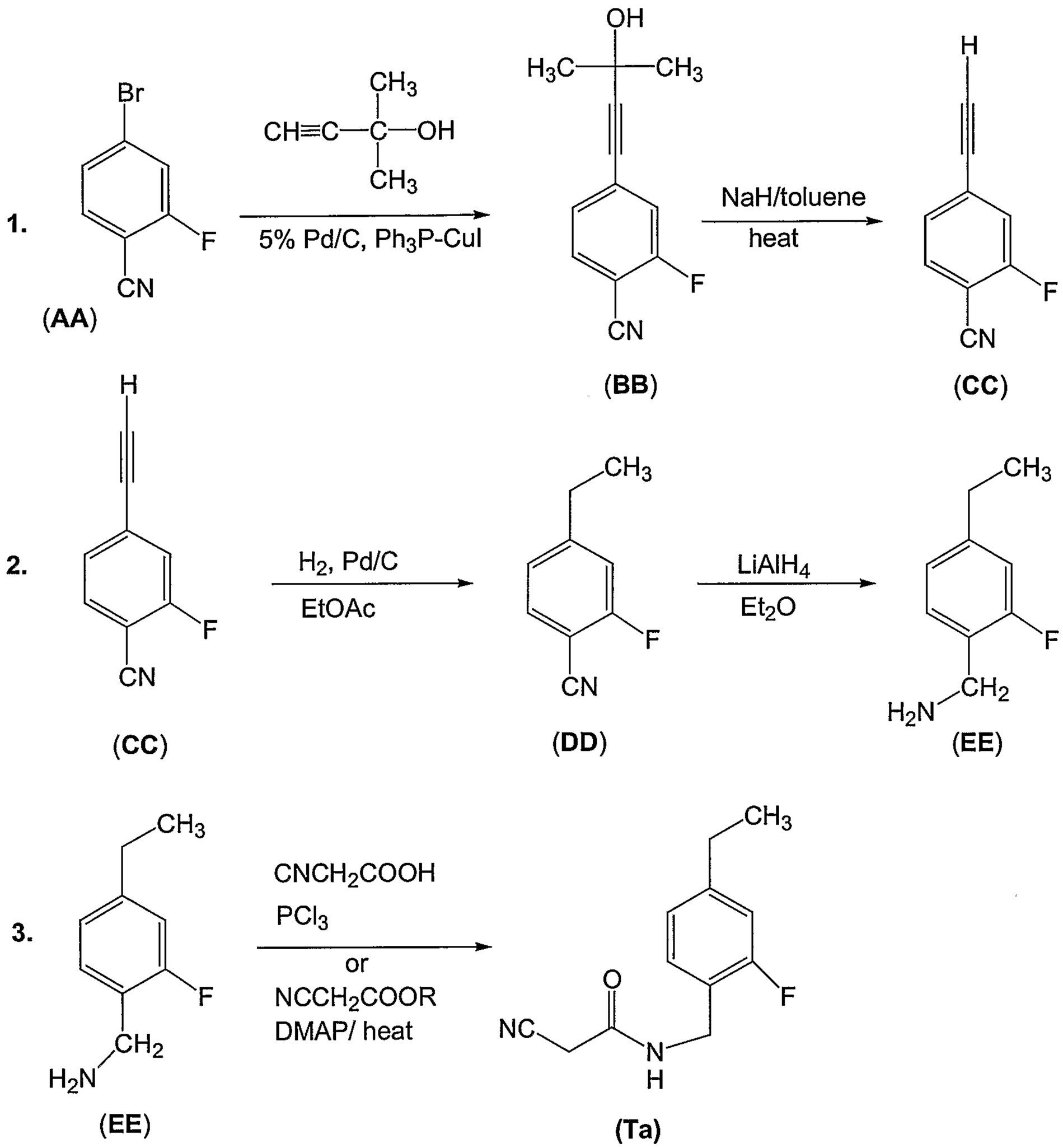
In general, compounds of formula (Cb) are prepared by first reacting substituted methylbenzenes of formula (Q) under free radical conditions in the presence of a halogenating agent to give benzyl halides of formula (R) which, upon exposure to a cyanide source, afford benzyl cyanides of formula (S) after standard isolation procedures. Treatment of an alcoholic solution of benzyl cyanides of formula (S) in the presence of strong acid provides esters of formula (P) after standard isolation procedures. Palladium mediated coupling of compounds of formula (P) with a diboronate or dioxaborolane reagent such as pinacolborane provides arylboronates of formula (Cb) after standard isolation procedures.

Alternatively, compounds of formula (Cb) are prepared by reacting compounds of formula (Pa) or compounds of formula (Pb), as described above in Reaction Scheme 6, under similiar conditions as described above in Step 3 of Reaction Scheme 7 to produce compounds of formula (Cb) wherein the $-CH_2-C(O)OR^{8a}$ substituent is either $-C(R^{7a})H-C(O)OR^{8a}$ or $-C(R^{7a})_2-C(O)OR^{8a}$, respectively.

H. <u>Preparation of Compounds of Formula (Ta)</u>

Compounds of formula (Ta) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 8, wherein R is alkyl:

REACTION SCHEME 8

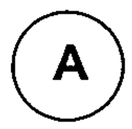


Compounds of formula (AA) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

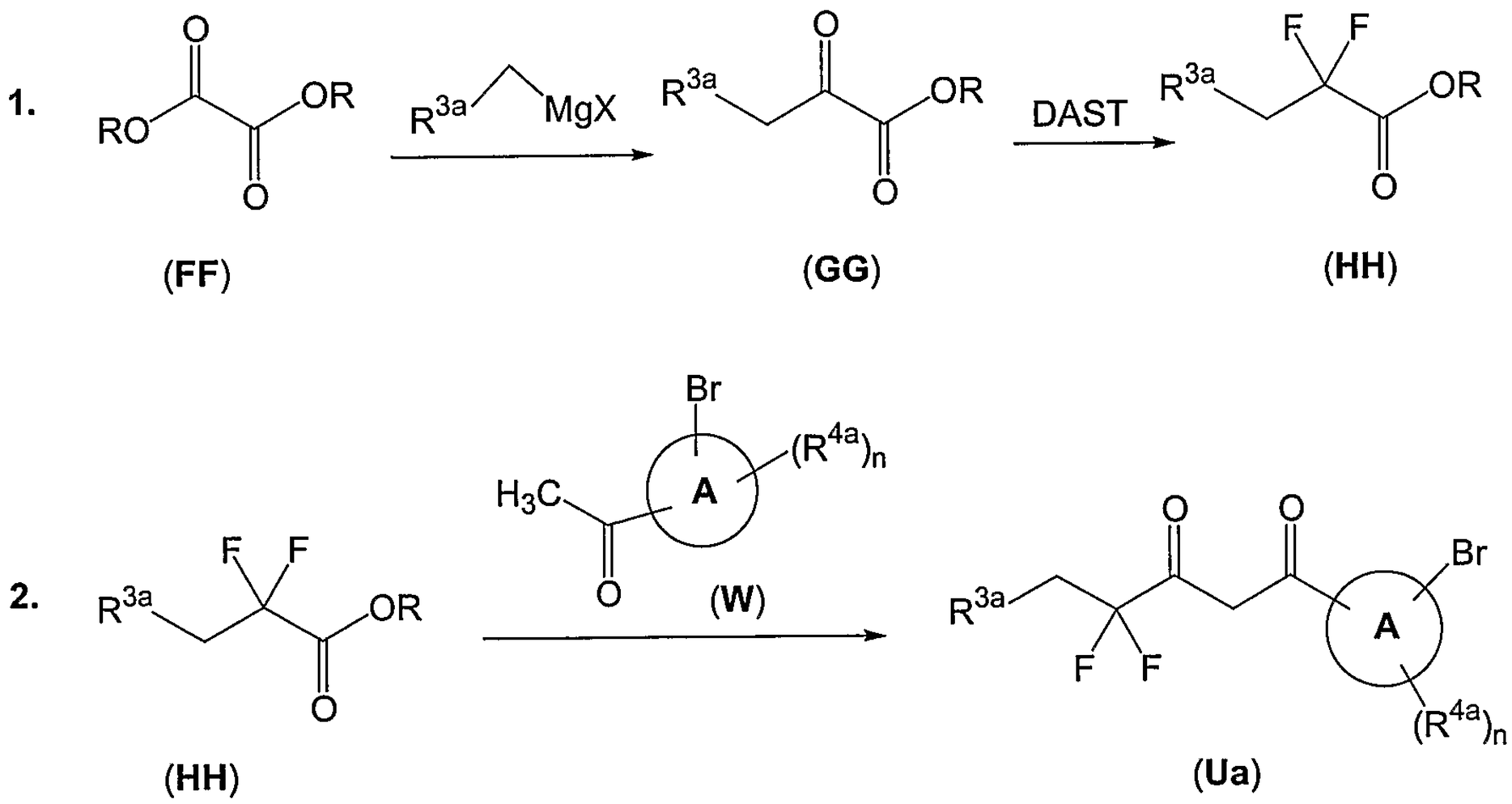
In general, compounds of formula (Ta) are prepared by first reacting the arylhalide of formula (AA) with 2-methyl-3-butyn-2-ol in the presence of palladium and a copper(I) salt to give the alkyne of formula (BB) after standard isolation procedures. Exposure of alkyne of formula (BB) to strong base at elevated temperature affords the alkyne of formula (CC) which is then, under standard conditions of catalytic

hydrogenation, converted to the nitrile of formula (DD) after standard isolation procedures. Reduction of the nitrile of formula (DD) with a metalhydride reagent provides the benzylamine of formula (EE) after standard isolation procedures. Conversion of the benzylamine of formula (EE) to the compound of formula (Ta) is then accomplished by either treating a solution of the benzylamine of formula (EE) with the acylchloride prepared from cyanoacetic acid under standard conditions, in the presence of a base, or by heating a solution of the benzylamine of formula (EE) with a cyanoacetic ester in the presence of a base such as *N,N*-dimethylaminopyridine (DMAP) to give the compounds of formula (Ta) after standard isolation procedures.

I. Preparation of Compounds of Formula (Ua)

Compounds of formula (Ua) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 9, wherein n is 1 to 4; each R is alkyl or aralkyl; R^{3a} is alkyl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl or heterocyclylalkyl; each R^{4a} is hydrogen, fluoro, chloro, alkyl or haloalkyl; and  is aryl or heteroaryl:

REACTION SCHEME 9



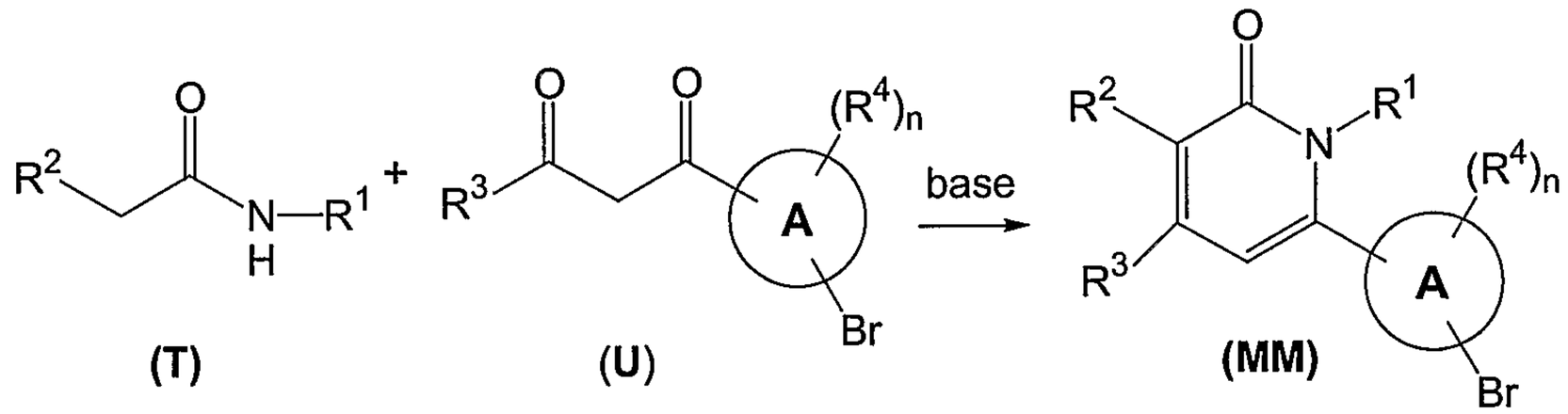
Compounds of formula (FF) and (GG) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

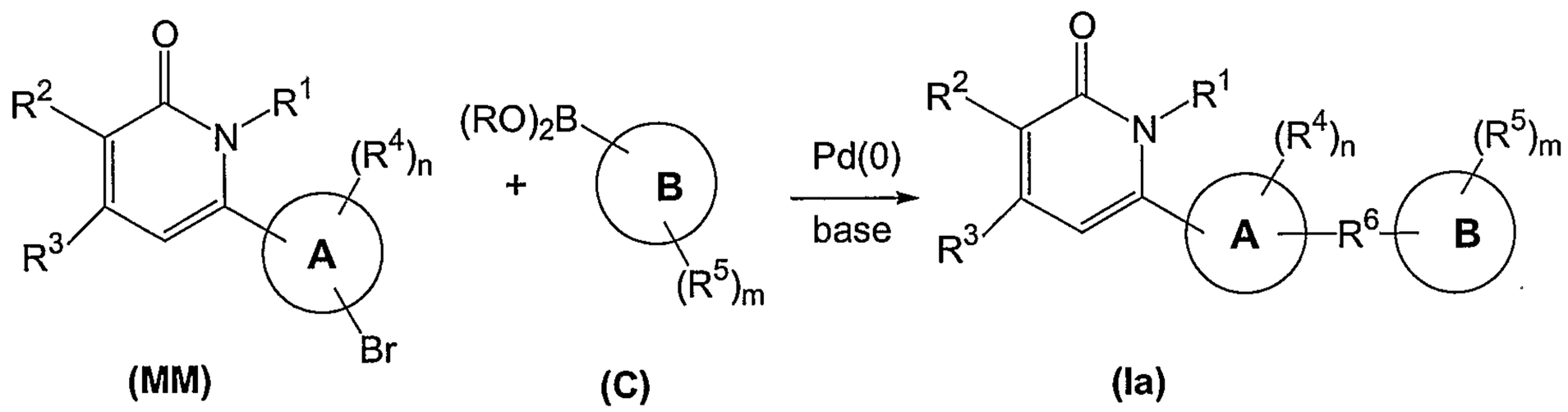
In general, compounds of formula (Ua) are prepared by first treating the oxalate diesters of formula (FF) with an organometallic reagent , such as a Grignard reagent, in an aprotic solvent at reduced temperature to give the α-ketoesters of formula (GG) after standard isolation procedures. Treatment of the ketoesters of formula (GG) with a fluorinating agent, such as (diethylamino)sulfur trifluoride (DAST), affords the 2,2-difluoroesters of formula (HH) after standard isolation procedures. Reaction of 2,2-difluoroesters of formula (HH) with methylketones of formula (W) under Claisen condensation conditions provides the diketones of formula (Ua) after standard isolation procedures.

J. Preparation of Compounds of Formula (I)

Compounds of formula (Ia) are compounds of formula (I) wherein R^6 is a direct bond and are prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 10, wherein n, m, R^1, R^2, R^3, R^4 and R^5 are as defined above in the Summary of the Invention, and (A) is aryl or heteroaryl and (B) is aryl or heteroaryl:

REACTION SCHEME 10

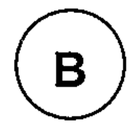
1. 

2. 

Compounds of formula (T) and (U) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

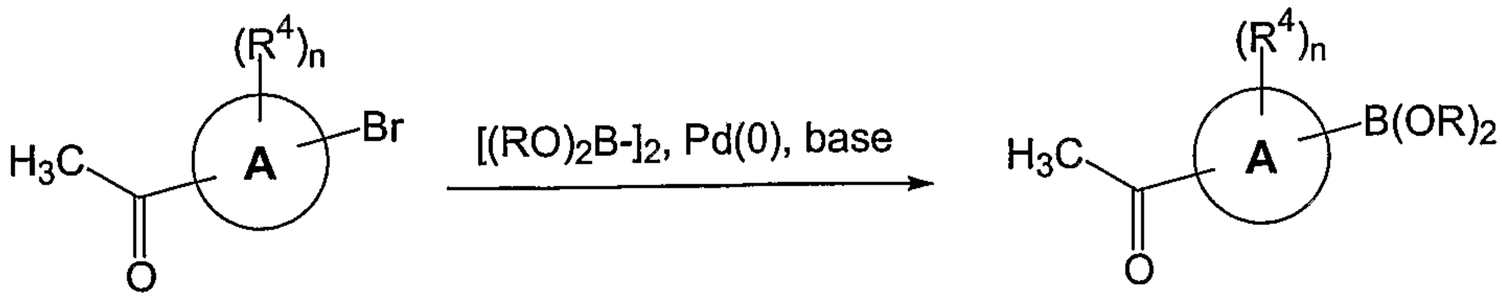
In general, compounds of formula (Ia), which are compounds of formula (I), are prepared by first combining cyanoacetamides of formula (T) with diketones of formula (U) in the presence of base and at elevated temperature to give 2-pyridones of formula (V) after standard isolation procedures. Treatment of the pyridones of formula (V) with boronates of formula (C) under palladium-catalyzed coupling conditions (Suzuki reaction) provides the compounds of formula (Ia) after standard isolation procedures. Compounds of formula (Ia) can be further converted to various derivatives using general methods of organic chemistry known to those skilled in the art and/or by methods disclosed herein.

K. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) are compounds of formula (I) wherein R^6 is a direct bond and are prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 11, wherein R is hydrogen or alkyl, X_b is bromo, chloror or iodo, and n, m, R^1, R^2, R^3, R^4 and R^5 are as defined above in the Summary of the Invention, and is aryl or heteroaryl and  is aryl or heteroaryl:

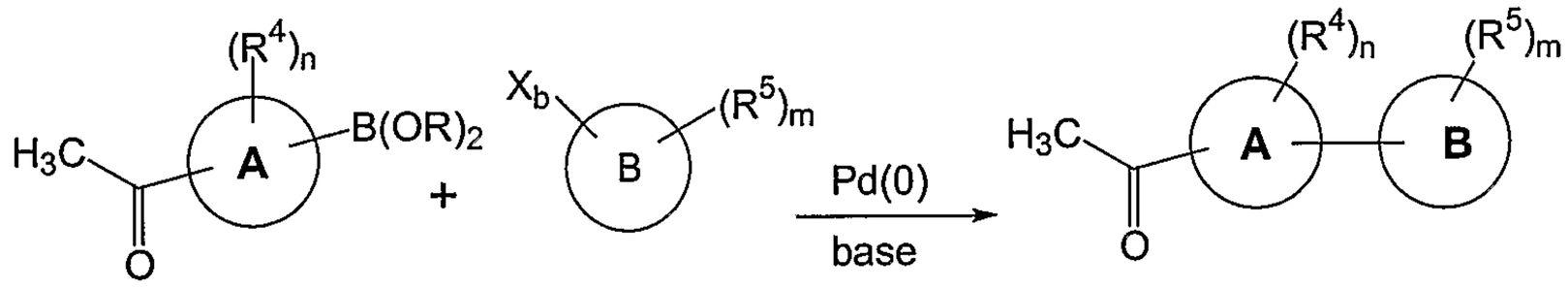
REACTION SCHEME 11

1.



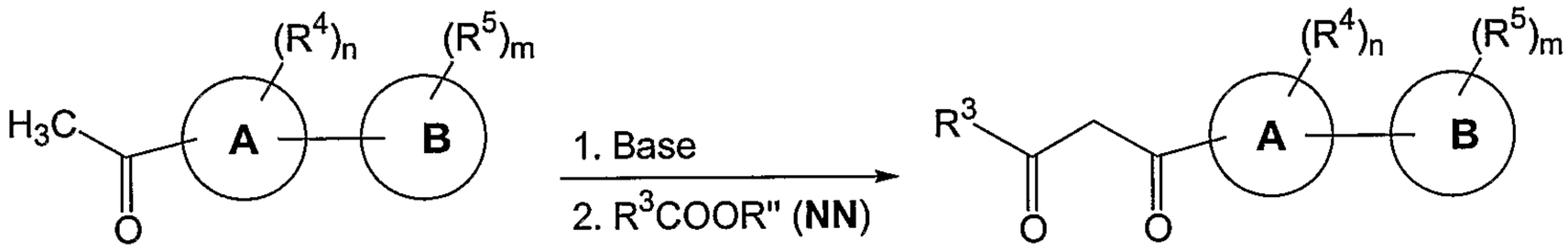
(W) (X)

2.



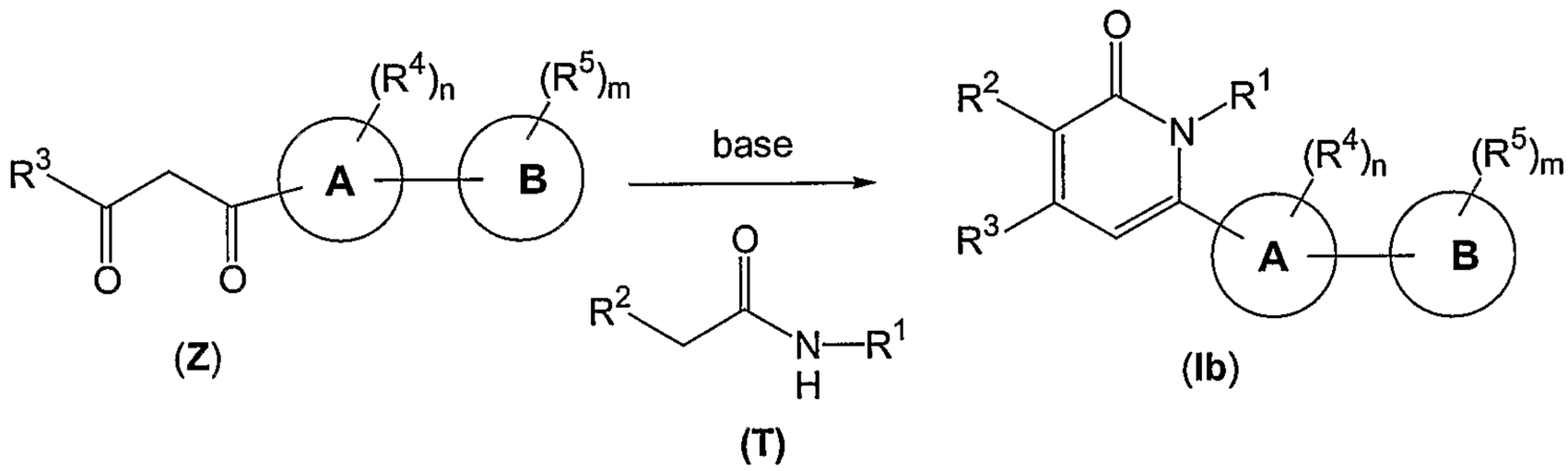
(X) (Ga) (Y)

3.



(Y) (Z)

4.



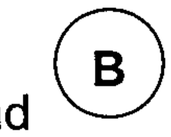
(Z) (T) (Ib)

Compounds of formula (W) and (Ga) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

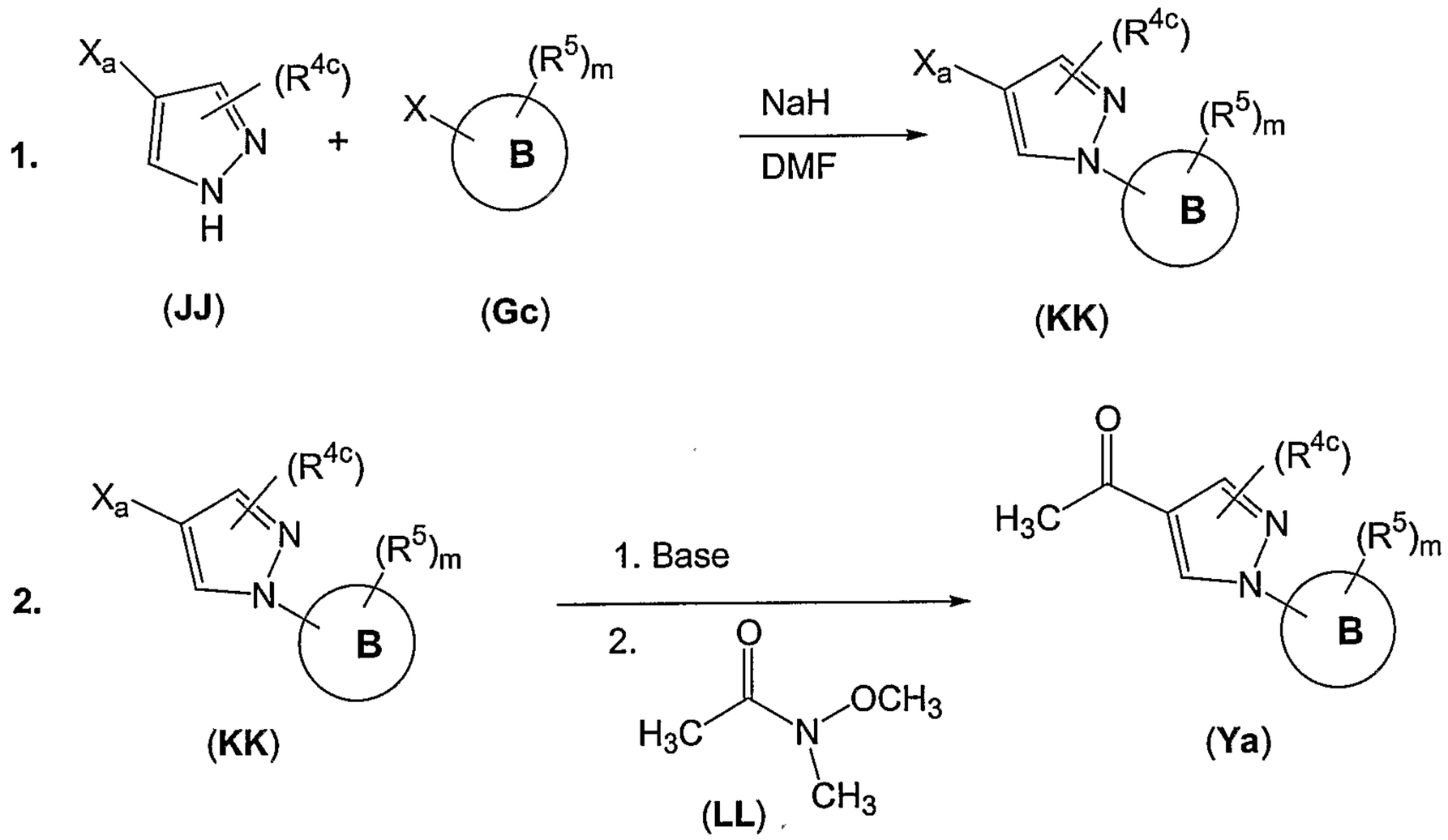
In general, compounds of formula (Ib) are prepared by first , which are compounds of formula (I), are prepared by first treating compounds of formula (W) with a diboronate or dioxaborolane reagent such as pinacolborane under palladium mediated coupling conditions to give the boronates of formula (X) after standard isolation procedures. In a second palladium catalyzed coupling (Suzuki reaction), boronates of formula (X) are combined with halides of formula (Ga) to give methylketones of formula (Y) after standard isolation procedures. The reaction of esters of formula (NN) with

methylketones of formula (Y) in the presence of strong base, for example, under Claisen condensation conditions, provides the diketones of formula (Z) after standard isolation procedures. The diketones of formula (Z) undergo a condensation reaction with amides of formula (T) in the presence of base and at elevated temperature to give the 2-pyridones of formula (Ib) after standard isolation procedures. Compounds of formula (Ib) can be further converted to various derivatives using general methods of organic chemistry known to those skilled in the art and/or by methods disclosed herein.

L. Preparation of Compounds of Formula (Ya)

Compounds of formula (Ya) are starting materials in the preparation of the compounds of the invention and can be prepared according to methods known to one skilled in the art or by the method described below in Reaction Scheme 12, wherein each X is halo; X_a is bromo or iodo; n is 1 or 2; R^{4c} is hydrogen, fluoro, chloro, alkyl or haloalkyl; m, R^1, R^2, R^3, R^4 and R^5 are as defined above in the Summary of the Invention, and  is aryl or heteroaryl:

REACTION SCHEME 12



Compounds of formula (JJ), (Gc) and (LL) are commercially available or may be prepared according to methods disclosed herein or known to one skilled in the art or by methods disclosed in U.S. Patent Application, Serial No. 10/327,813.

In general, compounds of formula (Ya) are prepared by first reacting halopyrazoles of formula (JJ) with halides of formula (Gc) in the presence of base at elevated temperatures to give the pyrazole derivatives of formula (KK) after standard isolation procedures. Treatment of the pyrazole derivatives of formula (KK) with strong base in an aprotic solvent at reduced temperature under conditions of metal-halogen exchange gives the intermediate organometallic reagent (not shown), followed by the addition of an acylating agent effective at reduced temperatures, such as the compound of formula (LL), provides the pyrazolemethylketones of formula (Ya) after standard isolation procedures.

* * * * *

In addition to the foregoing Reaction Schemes, compounds of the invention may be prepared by the methods disclosed in the following Preparations (for intermediates) and Examples (for compounds, pharmaceutical compositions and methods of use of the invention). The following specific Preaparations and Examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

PREPARATION 1

1-bromo-3-ethyl-5-isopropylsulfanyl-benzene

1,3-Dibromo-5-ethyl-benzene (1.54g, 5.8mmoles) was dissolved into anhydrous THF (20mL) under nitrogen, and was chilled to -78°C. To this stirring solution was slowly (over 10min) added *t*-BuLi (3.8mL, 6.5mmoles, 1.7M solution in pentane). After the addition was complete the mixture was allowed to stir at -78°C for an additional 30 min. After this period isopropyl disulfide (1.4mL, 8.8mmoles) was added and the mixture was allowed to warm to ambient temperature. The reaction was then warmed to 75°C, and was stirred at this temperature for 16 hours. After this period the reaction mix was evaporated *in vacuo* and was purified using flash silica chromatography (0-1% EtOAc/Hexane) to yield 1-bromo-3-ethyl-5-isopropylsulfanyl-benzene (1.08g, 72%) (a compound of formula (B)) as a clear liquid. ^{1}H-NMR ($CDCl_3$): δ 7.34-7.32 (m, 1H), 7.19-7.17 (m, 1H), 7.13-7.11 (m, 1H), 3.39 (m, J=6.6Hz, 1H), 2.59 (q, J=7.6Hz, 2H), 1.30 (d, J=6.6hz, 6H), 1.22 (t, J=7.6Hz, 3H).

PREPARATION 2

S-(3-bromo-5-trifluoromethyl-phenyl) ester O-ethyl ester

3-Bromo-5-trifluoromethyl-phenylamine (4.0mL, 28.3mmoles) was dissolved into concentrated HCl (70mL). This solution was chilled to 0°C and to it was slowly added a solution of sodium nitrite (2.5g, 36.2mmoles) in 50mL of water. After completion of the addition enough ethanol (90%) was added (25mL) to affect nearly complete dissolution of the resultant mixture. The mixture was stirred at 0°C for an additional 20 minutes. After this period the heterogeneous mixture was quickly transferred (cold) to an addition funnel. The diazonium mixture was added to a solution of *O*-ethylxanthic acid, potassium salt (5.7g, 35.6mmoles) in 50mL of water at 60°C. The mixture was next heated to 90°C and was stirred at this temperature for 2 hours. After this period the mixture was allowed to cool to ambient temperature, and the crude xanthate (a red liquid) was removed from the bottom of the aqueous mixture via pipette. The crude product taken up in 100mL of diethyl ether and was washed with water (2x25mL) and brine (20mL). The ether layer was evaporated *in vacuo* to yield crude xanthate. The crude product was purified using flash silica chromatography (0-1% EtOAc/Hexane) to yield 4.7g (51% yield) of dithiocarbonic acid S-(3-bromo-5-trifluoromethyl-phenyl) ester O-ethyl ester (a compound of formula (F)) as a red liquid. ^{1}H-NMR ($CDCl_3$): δ 7.83(d, J=5.8Hz, 2H), 7.71 (s, 1H), 4.63 (q, J=7.1Hz, 2H), 1.36 (t, J=7.1Hz, 3H).

PREPARATION 3

1-bromo-3-ethylsulfanyl-5-trifluoromethyl-benzene

Dithiocarbonic acid S-(3-bromo-5-trifluoromethyl-phenyl) ester O-ethyl ester (3.3g, 10.3mmoles) was dissolved into 30mL of EtOH, 10mL of H_2O, and was sealed under nitrogen. To this stirring mixture was added KOH (2.8g, 50mmoles) and this mix was stirred at reflux (under nitrogen) for 12 hours. After this period the reaction mixture was evaporated *in vacuo* and combined with 50mL of water. The pH was adjusted to <2 using 6N HCl and the resulting mixture was extracted with diethyl ether (3x50mL). The combined ethereal layer was washed with brine and dried over anhydrous $MgSO_4$. Following evaporation *in vacuo* the crude thiol was dissolved into 50mL of acetone. Ethyl bromide (1.5mL, 20.1mmoles) and K_2CO_3 (5g, 36.2mmoles) were added, and the mixture was stirring at ambient temperature (under nitrogen) for 6 hours. After this period the mixture was gravity filtered, and evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-1%

EtOAc/Hexane) to yield 1-bromo-3-ethylsulfanyl-5-trifluoromethyl-benzene (1.33g, 45% yield) (a compound of formula (B)) as a yellowish liquid. ^{1}H-NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 3.0 (q, J=7.3Hz, 2H), 1.36 (t, J=7.3Hz, 3H).

PREPARATION 4

2-(3-ethylsulfanyl-5-trifluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

1-Bromo-3-ethylsulfanyl-5-trifluoromethyl-benzene (1.33g, 4.7mmoles) was placeD into a 50mL pear-shaped flask and was sealed under nitrogen. The material was then solubilized with 25mL of anhydrous DMSO, and the resulting solution was degassed by passing a steady stream of nitrogen through the solution for 10 min. In a separate round-bottom flask were combined bis(pinacolato)diboron (1.3g, 5.1mmoles), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (1:1) (0.11g, 0.13mmoles) and potassium acetate (1.4g, 14.3mmoles) with a stirring bar under nitrogen. Following degassification the bromide solution was transferred to the "catalytic" mixture and the resulting mix was stirred at 90°C for 16hours. After this period the reaction mix was combined with 100mL of water and was extracted with benzene (4x30mL). The combined benzene layer was washed with water (4x50mL) and was dried over anhydrous Na_2SO_4. Following evaporation *in vacuo* the crude product was purified using flash silica chromatography (0-1% EtOAc/Hexane) to yield 2-(3-ethylsulfanyl-5-trifluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (651mg, 41% yield) (a compound of formula (Ca)) was a thick, clear liquid. Note: TLC visualization accomplished using ceric ammonium molybdate stain. ^{1}H-NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.83 (s, 1H), 7.60 (s, 1H), 3.01 (q, J=7.3Hz, 2H), 1.35 (s, 12H), 1.33 (t, J=7.3Hz, 3H).

PREPARATION 5

5-bromo-2-ethoxy-3-trifluoromethyl-pyridine

A. 2-Chloro-3-trifluoromethyl-pyridine (4.43g, 24.4mmol) was dissolved in 42 ml 21% (wt.) sodium ethoxide in ethanol. The mixture was stirred at ambient temperature for 1.5 days. After this period of time, the solvent was evaporated and the residue was taken into water and extracted with dichloromethane three times. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give 2-ethoxy-3-trifluoromethyl-pyridine as a light liquid (3.42g, 73% yield). The crude product (compound of formula (H)) was used directly for the next

step. 1H-NMR (400MHz, $CDCl_3$): δ 1.42 (t, 3H, *J*=7.07), 4.49 (q, 2H, *J*=7.07), 6.94 (dd, 1H, *J*=7.45, *J*=5.05), 7.85 (dd, 1H, *J*=1.26, *J*=7.45), 8.30 (dd, 1H, *J*=1.26, *J*=5.06).

B. 2-Ethoxy-3-trifluoromethyl-pyridine (900mg, 4.71mmol) and 1,3-dibromo-5,5-dimethylhydantoin (1.35g, 4.71mmol) were placed in a round-bottom flask. To this mixture was slowly added 10mL trifluoroacetic acid. The mixture was stirred at ambient temperature for overnight. More 1,3-dibromo-5,5-dimethylhydantoin (540mg, 1.9mmol) was added and the reaction mixture was stirred at ambient temperature for another day. After the completion of the reaction, TFA solvent was evaporated in *vacuo* and the resulting residue was neutralized to pH 7 by the addition of saturated $NaHCO_3$. The aqueous layer was extracted with dichloromethane three times and the combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give a mixture of oil and white solid. The residue was redissolved into 20% EtOAc/Hexane, and the unsoluable white solid was filtered out. The filtrate was concentrated and then purified by column chromatography on silica gel (10% EtOAC/Hexane) to give 5-bromo-2-ethoxy-3-trifluoromethyl-pyridine (a compound of formula (J)) as a colorless liquid (1.0g, 79% yield). 1H-NMR (400MHz, $CDCl_3$): δ 1.41 (t, 3H, *J*=7.07), 4.46 (q, 2H, *J*=7.07), 7.94 (dd, 1H, *J*=0.51, *J*=2.53), 8.34 (dd, 1H, *J*=0.51, *J*=2.53).

PREPARATION 6

2-ethoxy-3-trifluoromethylpyridine-5-boronic acid

A. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1), (286mg, 0.35mmol), potassium acetate (1.55g, 15.8mmol), and bis(pinacolato)diboron (1.3g, 5.3mmol) were placed into a vial and degassed with stream of nitrogen for 20min. In a separate vial, 5-bromo-2-ethoxy-3-trifluoromethyl-pyridine (945mg, 3.5mmol) was dissolved in 7ml anhydrous DMSO and degassed with stream of nitrogen for 20min. The DMSO solution of 5-bromo-2-ethoxy-3-trifluoromethyl-pyridine was added to the "catalyst" vial, and then heated at 80°C overnight. After cooling to ambient temperature, water and ethyl acetate were added to the reaction mixture and the aqueous layer was extracted with ethyl acetate. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo*. The crude product was purified by column chromatography on silica gel (10→30% EtOAC/Hexane) to give 2-ethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trifluoromethyl-pyridine as solid (1.08g, 97% yield). 1H-NMR (400MHz, $CDCl_3$): δ 1.35 (s, 12H), 1.42 (t, 3H, *J*=7.07), 4.52 (q, 2H, *J*=7.07), 8.20 (d, 1H, *J*=1.01), 8.64 (d, 1H, *J*=1.26).

B. Alternatively, n-butyl lithium (1.6 M solution in hexane, 0.9mL, 1.43mmol) was slowly added to a solution of 5-bromo-2-ethoxy-3-trifluoromethyl-pyridine (352mg, 1.3mmol) in 2.6mL anhydrous Et_2O at -78°C under nitrogen. The mixture was kept at -78°C for 1 hr, and then to this mixture was added triisoporpyl borate (489mg, 2.6mmol). The mixture was allowed to warm to ambient temperature overnight. The reaction was quenched by water and the pH was adjusted to 5 by carefully addition of 1N aqueous HCl. Two layers were separated and the aqueous layer was extracted with ethyl acatate three times. The extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give 2-ethoxy-3-trifluoromethylpyridine-5-boronic acid (a compound of formula (Ka)) as a brown oil (240mg, 67% yield). The product was used for the next step without purification.

PREPARATION 7

4-bromo-2-ethylsulfanyl-6-ethylpyridine

A. 2,5-Dibromo-pyridine (3.0g, 12.7mmol) and sodium thiomethoxide (0.84g, 12mmol) were dissolved in 18ml anhydrous N, N-dimethylformamide. The mixture was heated at 160°C under nitrogen for 6 hrs. After cooling to ambient temperature, water and ethyl acetate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate several times. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo*. The crude product was purified by column chromatography on silica gel (0→6% EtOAC/Hexane) to give 5-bromo-2-methylsulfanyl-pyridine as a white solid (2.18g, 84% yield). 1H-NMR (400MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.09 (dd, 1H, *J*=0.7, *J*=8.6), 7.59 (dd, 1H, J=2.4, *J*=8.6), 8.50 (m, 1H).

B. Alternatively, 2-bromo-5-nitro-pyridine (1.22g, 6.0mmoles), TMS-acetylene (0.9mL, 6.4mmoles), CuI (11mg, 0.06mmoles) and dichlorobis(triphenylphosphine)palladium (II) (210mg, 0.3mmoles) were combined and flushed with dry nitrogen for 10 min. After this period the mix was solubilized with 24mL of anhydrous triethylamine (degassed), and the mix was stirred at ambient temperature for 4 hours. After this period the reaction mix was evaporated *in vacuo* and purified directly using flash silica chromatography (0-10% EtOAc/Hexane) to yield 5-nitro-2-trimethylsilanylethynyl-pyridine as a brown solid. This material was dissolved into THF (10mL) and to this solution was added 100mg of TFAB (on silica gel, 1.0-1.5 mmole F/g resin). The solution was stirred at ambient temperature for 15 min. After this period the reaction mix was evaporated *in vacuo* purified directly using flash silica chromatography (0-20% EtOAc/Hexane) to yield 2-ethynyl-5-nitro-pyridine as a clear liquid. This product

was combined with 10% Pd/C (90mg) and ethanol (20ml) and was flushed with dry nitrogen. After oxygen exclusion the stirring mix was flushed with H_2 and stirred under H_2 pressure (balloon) for 16 hours. After this period the reaction mixture was flushed with nitrogen and then filtered through Celite. The filtrate was evaporated *in vacuo* and purified using flash silica chromatography (0-10% MeOH/DCM w/0.1% diethylamine) to yield 6-ethyl-pyridin-3-ylamine (442mg, 60% - 3 steps) as a brownish residue. ^{1}H-NMR ($CDCl_3$): δ 8.05-8.02 (m, 1H), 6.96-6.93 (m, 2H), 3.55 (br s, 2H), 2.71 (q, J=7.3Hz, 2H), 1.25 (t, J=7.3Hz, 3H).

C. 6-Ethyl-pyridin-3-ylamine (442mg, 3.62mmoles) was dissolved into 30mL of MeOH and 3mL of HOAc and the resulting solution was chilled to 0°C. To this stirring mixture was slowly added a solution of bromine (0.41mL, 8.0mmoles) in 5mL of HOAc. The mix was then allowed to warm to ambient temperature and was stirred at this temperature for 16 hours. Afte this period the reaction mix was evaporated *in vacuo*, combined with saturated $NaHCO_3$ (15mL), and extracted with DCM (3x20mL). The DCM layer was dried over anhydrous Na_2SO_4 and was evaporated *in vacuo* to yield the crude product was a brownish solid. The crude product was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield 2,4-dibromo-6-ethyl-pyridin-3-ylamine (868mg, 86%) as a brown solid. ^{1}H-NMR ($CDCl_3$): δ 252-827.18 (s, 1H), 4.41 (br s, 2H), 2.68 (q, J=7.6Hz, 2H), 1.24 (t, J=7.6Hz, 3H).

D. 2,4-Dibromo-6-ethyl-pyridin-3-ylamine (105mg, 0.38mmoles) was combined with 80% sodium thioethoxide (50mg, 0.48mmoles) in anhydrous DMF (2mL) and was stirred at 50°C under nitrogen for 2 hours. After this period the reaction mix was combined with water (20mL) and was extracted with EtOAc (3x20mL). The combined EtOAc layer was washed with water (3x15mL) and brine. After drying over anhydrous Na_2SO_4 the organic layer was evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-15% EtOAc/Hexane) to yield 4-bromo-6-ethyl-2-ethylsulfanyl-pyridin-3-ylamine (83mg, 84%) as a clear residue. ^{1}H-NMR ($CDCl_3$): δ 6.94 (s, 1H), 4.34 (br s, 2H), 2.95 (q, J=7.3Hz, 2H), 2.68 (q, J=7.6Hz, 2H), 1.33 (t, J=7.3Hz, 3H), 1.24 (t, J=7.6Hz, 3H).

E. 4-Bromo-6-ethyl-2-ethylsulfanyl-pyridin-3-ylamine (476mg, 1.82mmoles) was dissolved into EtOH (5mL) and chilled to -10°C under nitrogen. At -10°C 48% wt. aq. HBF_4 (1.0mL) was added and the temperature was further lowered to -25°C. At -25°C isoamyl nitrite (0.256mL, 1.9mmoles) was slowly added (over 1 min), and the temperature was allowed to warm to -5°C. The reaction was stirred at -5°C for 30 min. After this period the reaction mix was chilled to -25°C and an excess of 50%

aqueous H_3PO_2 (5.0mL) was added. The mix was then allowed to warm to ambient temperature and was stirred at this temperature for 1 hour (vigorous bubbling is observed). After this period the reaction was combined with 40mL of diethyl ether followed (carefully) by saturated $NaHCO_3$ (10mL). The mix was then extracted with diethyl ether (2x20mL) and the resultant ether layer was washed with brine. After drying over anhydrous $MgSO_4$ the ethereal layer was evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield 4-bromo-2-ethylsulfanyl-6-ethylpyridine (340mg, 76%) (a compound of formula (M)) as a golden-yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 7.09 (br d, J=1.3Hz, 1H), 6.90 (br d, J=1.5Hz, 1H), 3.0 (q, J=7.3Hz, 2H), 2.73 (q, J=7.6Hz, 2H), 1.39 (t, J=7.3Hz, 3H), 1.27 (t, J=7.6Hz, 3H).

PREPARATION 8

2-methylsulfanyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine

Palladium catalyst ([1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1), 167mg, 0.21mmol), potassium acetate (1.81g, 18.5mmol, Aldrich), and bis(pinacolato)diboron (1.56g, 6.1mmol) were placed into a vial and degassed with stream of nitrogen for 20min. In a separate vial, 5-bromo-2-methylsulfanylpyridine (836mg, 4.1mmol) was dissolved in 8ml anhydrous DMSO and degassed with stream of nitrogen for 20min. The DMSO solution of 5-bromo-2-methylsulfanylpyridine was added to the "catalyst" vial, and then heated at 80°C overnight. After cooling to ambient temperature, water and ethyl acetate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in *vacuo*. The crude product was purified by column chromatography on silica gel (10→30% EtOAC/Hexane, 0.25% Et_3N in hexane) to give 2-methylsulfanyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (a compound of formula (Kb)) as a colorless oil (1.00g, 97% yield). 1H-NMR (400MHz, $CDCl_3$): δ 1.35 (s, 12H), 2.58 (s, 3H), 7.16 (dd, 1H, *J*=1.0, *J*=8.0), 7.83 (dd, 1H, *J*=1.8, *J*=8.0), 8.50 (dd, 1H, *J*=1.7, *J*=1.0)

PREPARATION 9

3-bromo-5-isopropyl-benzoyl chloride

1,3-Dibromo-5-isopropyl-benzene (1.57g, 5.65mmoles) was dissolved into anhydrous THF (50mL) under nitrogen, and was chilled to -78°C. To this stirring solution was slowly (over 10min) added *t*-BuLi (3.6mL, 6.1mmoles, 1.7M solution in pentane). After the addition was complete the mixture was allowed to stir at -78°C for an additional

30 min. After this period CO_2 was bubbled through the stirring solution and the temperature was allowed to warm to ambient temperature. CO_2 bubbling was continued for 3 hours and afterwards the reaction was allowed to stir for an additional 6 hours. After this period 1H HCl (10mL) was added and the mix was evaporated *in vacuo* (-THF). The resulting aqueous mixture was extracted with DCM (3x20mL) and the organic layer was dried over anhydrous Na_2SO_4. Evaporation *in vacuo* yielded the crude carboxylic acid as a white solid. The crude acid (1.22g, ~5.0mmoles) was dissolved into C_6H_6 (20mL) and to this was added freshly distilled thionyl chloride (0.5mL, 6.9mmoles). This mixture was heated to reflux and stirred at this temperature for 16 hours. After this period the reaction mix was evaporated *in vacuo* to yield crude 3-bromo-5-isopropyl-benzoyl chloride (1.0g, 68% - 2 steps) (a compound of formula (N)) as a yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 8.08 (t, J=1.8Hz, 1H), 7.89-7.87 (m, 1H), 7.68-7.66 (m, 1H), 2.98 (m, J=6.8Hz, 1H), 1.28 (d, J=6.8Hz, 6H).

PREPARATION 10

(3-bromo-5-isopropyl-phenyl)-acetic acid methyl ester

A. Potassium Hydroxide (1g) was added to an erlenmeyer flask containing water (40mL) and diethyl ether (50mL) at 0°C. The mixture was stirred to fully solubilize the hydroxide. 1-Methyl-3-nitro-1-nitrosoguanidine (2.24g, 15.2mmoles) was added to this flask in aliquots to generate a solution of diazomethane in ether. A separate erlenmeyer flask was chilled to -78°C. Ether from the diazomethane "generator" was transferred via pipette to this "cold" flask. When nearly all of the ether (diazomethane) had been transferred to the "cold" flask, a solution of 3-Bromo-5-isopropyl-benzoyl chloride (796mg, 3.0mmoles) in 10mL of diethyl ether was added to the "cold" flask. The "cold" flask was then allowed to warm to 0°C and was stirred at this temperature for 2 hrs. After this period the reaction mixture was thoroughly purged using nitrogen gas (bubbling). The resulting ether solution was evaporated *in vacuo* and the crude product was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield the intermediate diazoketone (696mg, 86%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.66 (br t, J=1.8Hz, 1H), 7.57-7.55 (m, 1H), 7.54-7.52 (m, 1H), 5.86 (s, 1H), 2.94 (m, J=6.8Hz, 1H), 1.26 (d, J=6.8Hz, 6H).

B. The diazoketone (696mg, 2.61mmoles) was dissolved into MeOH (20mL) and to this solution at ambient temperature was added a solution of AgOBz (340mg, 1.49mmoles) in NEt_3 (4.2mL). This mixture was stirred at ambient temperature for 30 min. After this period the reaction mix was filtered through Celite and evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica

chromatography (0-10% EtOAc/Hexane) to yield (3-bromo-5-isopropyl-phenyl)-acetic acid methyl ester (0.514g, 62% - 2 steps) (a compound of formula (P)) as a yellow residue. ^{1}H-NMR ($CDCl_3$): δ 7.28-7.25 (m, 2H), 7.06-7.04 (m, 1H), 3.71 (s, 3H), 3.57 (s, 2H), 2.86 (m, J=6.8Hz, 1H), 1.23 (d, J=6.8Hz, 6H).

PREPARATION 11

2-methyl-2-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionic acid methyl ester

A. (3-Bromo-5-isopropyl-phenyl)-acetic acid methyl ester (0.514g, 1.9mmoles) was place into a 25mL pear-shaped flask and was sealed under nitrogen. The material was then solubilized with 13mL of anhydrous DMSO, and the resulting solution was degassed by passing a steady stream of nitrogen through the solution for 10 min. In a separate round-bottom flask were combined bis(pinacolato)diboron (0.58g, 2.3mmoles), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (1:1) (50mg, 0.061mmoles) and potassium acetate (0.56g, 5.7mmoles) with a stirring bar under nitrogen. Following degassification the bromide solution was transferred to the "catalytic" mixture and the resulting mix was stirred at 90°C for 16hours. After this period the reaction mix was combined with 60mL of water and was extracted with benzene (4x15mL). The combined benzene layer was washed with water (4x25mL) and was dried over anhydrous Na_2SO_4. Following evaporation *in vacuo* the crude product was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield [3-isopropyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester (502mg, 83% yield) was a thick, greenish liquid. TLC visualization accomplished using ceric ammonium molybdate stain. ^{1}H-NMR ($CDCl_3$): δ 269-167.58 (br s, 1H), 7.53 (br s, 1H), 7.26-7.23 (m, 1H), 3.68 (s, 3H), 3.62 (s, 2H), 2.91 (m, J=6.8Hz, 1H), 1.34 (s, 12H), 1.25 (d, J=6.8Hz, 6H).

B. Alternatively, a suspension of 2-(3-bromo-phenyl)-2-methyl-propionic acid methyl ester (755 mg, 2.9 mmol), and potassium acetate (880 mg, 8.9 mmol) was prepared in DMSO (15 mL). Nitrogen was bubbled through the suspension to deoxygenate the mixture. Bis(pinacolato)diboron (980 mg, 3.8 mmol) was added to the suspension, followed by dichloro[1,1'-bis(diphenylphosphino)ferrocene)palladium (II) dichloromethane adduct (88 mg, 0.11 mmol). The mixture rapidly turned brown. The suspension was then immersed in an oil bath held at 80°C. After 20 minutes the nitrogen bubbling was discontinued. After stirring for 16 hours at 80°C, heating was discontinued, and the black reaction mixture was allowed to cool to ambient temperature. The reaction mixture was then diluted with H_2O (100 mL) and ether (100 mL). The

aqueous layer was extracted with ether (4 x 20 mL), and the combined organic layers were washed with water (2 x 20 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown oil. The oil was azeotroped with toluene to remove any residual H_2O. The crude material was purified by flash chromatography eluting with a gradient from 0% to 14% ethyl acetate / hexane to afford 2-methyl-2-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionic acid methyl ester (790 mg, 88 % yield) (a compound of formula (Cb)) as a clear bluish oil. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.77 (1H, br s), 7.72-7.67 (1H, m), 7.43-7.39 (1H, m), 7.35-7.30 (1H, m), 3.65 (3H, s), 1.60 (6h, s), 1.34 (12H, s).

PREPARATION 12

2-(3-bromo-phenyl)-2-methyl-propionic acid methyl ester

A. A solution of (3-bromo-phenyl)-acetic acid (10.4 g, 48.5 mmol), in methanol (80 mL), was treated with trimethyl orthoformate (6.5 mL, 59.4 mmol). HCl gas was bubbled through the stirred solution for 10 minutes. The HCl addition was exothermic. After stirring for 15 minutes HPLC analysis of the solution showed complete conversion to product. After stirring for 16 hrs at ambient temperature the solution was diluted with toluene (100 mL) and concentrated under reduced pressure to afford a biphasic mixture. This liquid was diluted with toluene and concentrated under reduced pressure to afford (3-bromo-phenyl)-acetic acid methyl ester (11.2 g, quantitative yield) as a pale yellow liquid. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.46-7.38 (2H, m), 7.23-7.18 (2H, m), 3.71 (3H, m), 3.60 (2H, m).

B. Sodium hydride (2.5 g of a 60% suspension in mineral oil, 62 mmol) was placed in a flask under nitrogen. The suspension was washed with hexane (2 x) then suspended in THF (30 mL), and DMF (30 mL), and cooled in an ice bath. To the cold suspension was added (3-bromo-phenyl)-acetic acid methyl ester (4.8 g, 21 mmol) dropwise as a solution in THF (10 mL). The ester containing flask was then rinsed with an additional portion of THF (10 mL) which was then added to the reaction to insure complete transfer. Iodomethane (4.0 mL, 64 mmol) was then added dropwise over several minutes. The iodomethane addition led to the formation of thick slurry at first, which slowly thinned as the reaction mixture was stirred. The ice bath was removed and the reaction was allowed to warm to ambient temperature. After stirring for 16 hrs at ambient temperature, HPLC analysis of a quenched aliquot (HOAc) showed several peaks present. There were several product peaks visible. The reaction was quenched by the addition of methanol (10 mL). The methanol addition did not lead to gas evolution. The reaction mixture was diluted with 1N HCl (70 mL), water (50 mL), and ether (200

mL). The aqueous layer was extracted with ether (4 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown liquid. The crude material was purified by flash chromatography eluting with a gradient from 0% to 10% ethyl acetate / hexane to afford 2-(3-bromo-phenyl)-2-methyl-propionic acid methyl ester (2.93 g, 54 % yield) (a compound of formula (Pb)) as a clear colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.49-7.47 (1H, m), 7.39-7.36 (1H, m), 7.27-7.24 (1H, m), 7.22-7.17 (1H, m), 3.66 (3H, s), 1.56 (6H, s).

PREPARATION 13

4-bromo-1-bromomethyl-2-chloro-benzene

4-Bromo-2-chloro-1-methyl-benzene (2.5mL, 18.7mmoles) and N-bromosuccinimide (4.0g, 22.5mmoles) were dissolved into 50mL of CCl_4. To this stirring mix was added benzoyl peroxide (0.5g, 2.1mmoles) and the solution was irradiated using white light. Enough light intensity was utilized to affect gentle reflux for 2 hours. After this period the mixture was cooled to ambient temperature and benzoyl peroxide (0.5g, 2.1mmoles) was added. Again, the mix was irridiated to reflux for a period of 2 hours. After this period the reaction mix was chilled to ambient temperature and was gravity filtered. The filtrate was evaporated *in vacuo* and the resulting crude residue was purified using flash silica chromatography (0-1% EtOAc/Hexane) to yield 4-bromo-1-bromomethyl-2-chloro-benzene (3.04g, 60%) (a compound of formula (R)) as a clear liquid. ^{1}H-NMR ($CDCl_3$): δ 7.57 (d, J=2.0Hz, 1H), 7.39 (dd, J'=8.3Hz, J"=1.8Hz, 1H), 7.31 (d, J=8.1Hz, 1H), 4.53 (s, 2H).

PREPARATION 14

(4-bromo-2-chloro-phenyl)-acetonitrile

4-Bromo-1-bromomethyl-2-chloro-benzene (3.04g, 10.7mmoles) was dissolved into anhydrous CH_3CN. To this mixture (under N_2 at ambient temp) was added TMSCN (2.1mL, 15.7mmoles) followed by 1.0M TBAF (15.7mL, 15.7mmoles, soln in THF). The resulting mixture was stirred at ambient temperature for 15 min after which time it was evaporated *in vacuo* to yield crude residue. The crude residue was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield (4-bromo-2-chloro-phenyl)-acetonitrile (1.98g, 80%) (a compound of formula (S)) as an off-white solid. ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, J=2.0Hz, 1H), 7.47 (dd, J'=8.1Hz, J"=1.8Hz, 1H), 7.39 (d, J=8.1Hz, 1H), 3.79 (s, 2H).

PREPARATION 15

(4-bromo-2-chloro-phenyl)-acetic acid methyl ester

(4-Bromo-2-chloro-phenyl)-acetonitrile (1.98g, 8.6mmoles) was dissolved into MeOH (50mL) and water (5mL), and the resulting homogeneous mixture was chilled to 0°C. To this stirring (cold) mixture was slowly (carefully) added concentrated HCl (25mL). After the addition was complete the mixture was refluxed for 16 hours. After this period the reaction mixture was combined with ice and the resulting heterogeneous mixture was extracted with diethyl ether (3x50mL). The combined ethereal layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to yield clean (4-bromo-2-chloro-phenyl)-acetic acid methyl ester (2.3g, 80%) (a compound of formula (P)). ^{1}H-NMR ($CDCl_3$): δ 7.56 (d, J=2.0Hz, 1H), 7.37 (dd, J'=8.3Hz, J"=2.0Hz, 1H), 7.16 (d, J=8.3Hz, 1H), 3.73 (s, 2H), 3.72 (s, 3H).

PREPARATION 16

[2-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetic acid methyl ester

(4-Bromo-2-chloro-phenyl)-acetic acid methyl ester (705mg, 2.68mmoles) was place into a 25mL pear-shaped flask and was sealed under nitrogen. The material was then solubilized with 20mL of anhydrous DMSO, and the resulting solution was degassed by passing a steady stream of nitrogen through the solution for 10 min. In a separate round-bottom flask were combined bis(pinacolato)diboron (0.82g, 3.2mmoles), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (1:1) (66mg, 0.081mmoles) and potassium acetate (0.79g, 8.05mmoles) with a stirring bar under nitrogen. Following degassification the bromide solution was transferred to the "catalytic" mixture and the resulting mix was stirred at 90°C for 16 hours. After this period the reaction mix was combined with 60mL of water and was extracted with benzene (4x15mL). The combined benzene layer was washed with water (4x25mL) and was dried over anhydrous Na_2SO_4. Following evaporation *in vacuo* the crude product was purified using flash silica chromatography (0-10% EtOAc/Hexane) to yield [2-chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetic acid methyl ester (502mg, 83% yield) (a compound of formula (Cb)) as a thick, clear residue. Note: TLC visualization accomplished using ceric ammonium molybdate stain. ^{1}H-NMR ($CDCl_3$): δ 7.83-7.81 (br s, 1H), 7.65 (br d, J=7.6Hz, 1H), 7.29 (d, J=7.3Hz, 1H), 3.80 (s, 2H), 3.70 (s, 3H), 1.34 (s, 12H).

PREPARATION 17

2-fluoro-4-(3-hydroxy-3-methyl-but-1-ynyl)-benzonitrile

A mixture of 4-bromo-2-fluoro-benzonitrile (2.6 g, 13 mmol), 10% palladium on carbon (300 mg), triphenylphosphine (300 mg, 1.2 mmol), CuI (108 mg, 0.57 mmol), and K_2CO_3 (4.55 g, 33 mmol), was prepared in 1,2-dimethoxyethane (20 mL), and H_2O (20 mL). The resulting suspension was stirred under nitrogen for 30 minutes, and was then treated with 2-methyl-but-3-yn-2-ol (2.6 mL, 27 mmol). The reaction was then heated in an 80°C oil bath. After stirring for 15 hours at 80°C, TLC analysis of the reaction mixture showed some of the starting 4-bromo-2-fluoro-benzonitrile remaining. A small amount of $PdCl_2$ was then added in an attempt to drive the reaction to completion. After an additional 2 hr stirring at 80°C the TLC had changed very little. The reaction mixture was allowed to cool to ambient temperature, and was filtered through a pad of Celite. The Celite pad was washed thoroughly with EtOAc, and the filtrate was diluted with EtOAc and H_2O. The layers were separated and the aqueous was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a dark oil. The crude material was purified by flash chromatography eluting with a gradient from 10% to 40% ethyl acetate / hexane to afford 2-fluoro-4-(3-hydroxy-3-methyl-but-1-ynyl)-benzonitrile (2.60 g, 98% yield) (a compound of formula (BB)) as a yellow oil. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.58-7.53 (1H, m), 7.30-7.22 (2H, m), 2.10 (1H, s), 1.62 (6H, s).

PREPARATION 18

4-ethynyl-2-fluoro-benzonitrile

To a solution of 2-fluoro-4-(3-hydroxy-3-methyl-but-1-ynyl)-benzonitrile (2.6 g, 13 mmol) in toluene (55 mL) was added NaH (53 mg of a 60% suspension in mineral oil, 1.3 mmol). The reaction mixture was heated to reflux. After refluxing for several hours, heating was discontinued, and the cooled reaction mixture was quenched by the addition of 2M Na_2CO_3 solution. The layers were separated and the toluene layer was washed with H_2O (2 x 20 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. The crude material was purified by flash chromatography eluting with a gradient from 0% to 10% ethyl acetate / hexane to afford 4-ethynyl-2-fluoro-benzonitrile (1.25 g, 66% yield) (a compound of formula (CC)). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.61-7.57 (1H, m), 7.38-7.30 (2H, m), 3.36 (1H, s).

PREPARATION 19

4-ethyl-2-fluoro-benzonitrile

A solution of 4-ethynyl-2-fluoro-benzonitrile (1.29 g, 8.9 mmol) in EtOAc (30 mL) was placed in a Parr pressure bottle and palladium on carbon (130 mg of 10% on carbon) was added. The bottle was placed on the Parr hydrogenation apparatus and shaken under 10 psi of hydrogen pressure. After shaking for two hours the black suspension was filtered through a pad of Celite. The pad was washed thoroughly with EtOAc, and the combined filtrates were concentrated under reduced pressure. The residue was taken up in toluene and concentrated under reduced pressure to afford 4-ethyl-2-fluoro-benzonitrile (1.19 g, 89% yield) (a compound of formula (DD)). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.55-7.50 (1H, m), 7.11-7.03 (2H, m), 2.72 (2H, q, J = 7.6 Hz), 1.26 (3H, t, J = 7.6 Hz).

PREPARATION 20

4-ethyl-2-fluoro-benzylamine

A solution of 4-ethyl-2-fluoro-benzonitrile (1.19 g, 8.0 mmol) in ether (70 mL) was cooled in an ice bath. To the cold, stirred solution was added $LiAlH_4$ (600 mg, 16 mmol). The suspension was then heated to reflux. After several hours at reflux, the suspension was allowed to cool to ambient temperature and was quenched by the careful addition of H_2O (600 µL), followed by 15% aqueous NaOH (600 µL), and finally H_2O (1.8 mL). The resulting suspension was filtered, and the solids were washed thoroughly with ether. The filtrate was concentrated under reduced pressure to afford 4-ethyl-2-fluoro-benzylamine (1.16 g, 95% yield) (a compound of formula (EE)) as a liquid. This material was used for the subsequent amide formation without further purification. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.21 (1H, app t, J = 7.6 Hz), 6.96-6.86 (2H, m), 3.85 (2H, s), 2.63 (2H, q, J = 7.6 Hz), 1.22 (3H, t, J = 7.6 Hz).

PREPARATION 21

2-cyano-N-(4-ethyl-2-fluoro-benzyl)-acetamide

Methyl cyanoacetate (1.16 mL, 13 mmol) and 4-ethyl-2-fluoro-benzylamine (1.15 g, 7.5 mmol) were combined in ethanol (20 mL). 4-(N,N-dimethylamino)pyridine (catalytic) was added and the reaction was heated in a 60°C oil bath. After 16 hours heating, the reaction was concentrated under reduced pressure to afford crude product which was purified by flash chromatography eluting with a gradient from hexane to 60% ethyl acetate / hexane to afford 2-cyano-N-(4-ethyl-2-fluoro-benzyl)-

acetamide (652 mg, 40% yield) (a compound of formula (Ta)). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.26-7.20 (1H, m), 6.98-6.90 (2H, m), 6.39 (1h, br s), 4.49 (2H, d, J = 5.8 Hz), 3.38 (2H, s), 2.64 (2H, q, J = 7.6 Hz), 1.23 (3H, t, J = 7.6 Hz).

PREPARATION 22

2-oxo-butyric acid benzyl ester

A. Magnesium turnings (720 mg, 30 mmol) were suspended in THF (30 mL) in a 250 mL round bottom flask fitted with a thermometer. A solution of 1-bromohexane (3.2 mL, 23 mmol) in THF (10 mL) was prepared after first drying the 1-bromohexane by passing it through a pad of activated basic alumina. About 10% of the halide solution was added to the Mg suspension, followed by a small pellet of iodine. The addition of the iodine led to an increase in the reaction temperature indicating the initiation of the Grignard reagent formation. The remaining halide solution was added dropwise over ~15 minutes. After the completion of the addition of the halide, the suspension was held at ~ 55°C to complete the formation of the Grignard reagent. While the Grignard reagent was forming, a suspension of dibenzyl oxalate (5.1g, 19 mmol) was prepared in a mixture of ether (50 mL), and THF (15 mL). This suspension was cooled to < -70°C (internal monitoring) and then treated with the Grignard solution prepared previously at a rate sufficient to keep the internal temperature below –70° C. After stirring for 3 hours at < -70°C, the reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by addition of 1 N HCl (25 mL). The cold solution was then allowed to come to ambient temperature. After ~ 64 hours the reaction mixture was diluted with ether and the layers were separated. The acidic aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale brown oil. The crude material was purified by flash chromatography eluting with a gradient from 0% to 30% ethyl acetate / hexane to afford 2-oxo-octanoic acid benzyl ester (3.43 g, 73% yield) as a pale yellow oil. The material was not completely pure by NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.33 (5H, m), 5.27 (2H, m), 2.82 (2H, t, J = 7.3 Hz), 1.66-1.56 (2H, m), 1.35-1.23 (6H, m), 0.89-0.85 (3H, m).

B. A mixture of 2-oxobutyric acid (11.5 g, 113 mmol), and benzyl alcohol (14.0 mL, 135 mmol) in benzene (100 mL) was heated to reflux under a Dean-Stark water separator. After refluxing for 16 hrs ~ 2mL of water had collected in the trap (~100 % of theoretical). The reaction mixture was allowed to cool to ambient temperature, and then concentrated under reduced pressure to afford a pale yellow oil.

The crude material was purified by flash chromatography eluting with a gradient from 0% to 15% ethyl acetate / hexane to afford 2-oxo-butyric acid benzyl ester (13.0 g, 60% yield) (a compound of formula (GG)) as a clear colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.35 (5H, m), 5.28 (5H, s), 2.87 (2H, q, J = 7.2 Hz), 1.12 (3H, t, J = 7.2 Hz).

PREPARATION 23

2,2-difluoro-butyric acid benzyl ester

In a reaction vial under nitrogen, 2-oxo-butyric acid benzyl ester (12.4 g, 64.7 mmol) was treated dropwise with (diethylamino)sulfur trifluoride (10.5 mL, 79.5 mmol). The addition is exothermic and leads to a darkening of the reaction mixture. After standing at ambient temperature for ~64 hours the reaction mixture was poured onto ice (~100g), and diluted with ether (250 mL). The layers were separated and the aqueous was extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a pale orange oil. The crude material was purified by flash chromatography eluting with a gradient from 0% to 20% ethyl acetate / hexane to afford 2,2-difluoro-butyric acid benzyl ester (13.0 g, 94% yield) (a compound of formula (HH)) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (5H, m), 5.29 (2H, s), 2.09 (2H, t of q, J_{H-H} = 7.6 Hz, J_{H-F} = 16.7 Hz), 1.00 (3H, t, J = 7.6 Hz).

PREPARATION 24

1-(4-bromo-furan-2-yl)-4,4-difluoro-hexane-1,3-dione

A solution of lithium hexamethyldisilazide (2.4 mL of a 1.0M solution in THF, 2.4 mmol) was diluted with THF (2 mL) and cooled in a –78°C bath. To this cold solution was added 1-(4-bromo-furan-2-yl)-ethanone (317 mg, 1.68 mmol) dropwise as a solution in THF (4 mL), followed by a THF (1 mL) rinse of the vial and syringe to insure complete transfer. After ~ 2 minutes the resulting red enolate solution was treated with a solution of 2,2-difluoro-butyric acid benzyl ester (357 mg, 1.67 mmol) in THF (4 mL), followed by a THF (1 mL) rinse of the vial and syringe to insure complete transfer. After the completion of the addition, the cooling bath was removed and the reaction was allowed to warm to ambient temperature. After stirring for 16 hrs at ambient temperature, the reaction was quenched by the addition of H_2O (10 mL), and diluted with ether (50 mL). Phosphoric acid (2M, aqueous) was added to the mixture to bring the pH below 3. The layers were separated and the aqueous was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered,

and concentrated under reduced pressure to afford a dark brown oil. The crude material was purified by flash chromatography eluting with a gradient from 0% to 30% ethyl acetate / hexane to afford 1-(4-bromo-furan-2-yl)-4,4-difluoro-hexane-1,3-dione (224 mg, 46% yield) (a compound of formula (Ua)) as a red oil. The compound exists primarily in its' enolic form. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 14.77 (1H, br s), 7.62 (1H, s), 7.27 (2H, s), 6.45 (1H, s), 2.12 (2H, t of q, J_{H-H} = 7.6 Hz, J_{H-F} = 16.7 Hz), 1.05 (3H, t, J = 7.6 Hz).

PREPARATION 25

6-(4-bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile

To a solution of 1-(4-bromo-furan-2-yl)-4,4-difluoro-hexane-1,3-dione (220 mg, 0.75 mmol), and 2-cyano-N-(2,4-difluoro-benzyl)-acetamide (300 mg, 1.4 mmol) in benzene (4 mL) was added 1,8-diaza-bicycle-[5.4.0]-undec-7-ene (60 µL, 0.4 mmol). The red reaction mixture was then heated to reflux. After 3 hours, heating was discontinued and the reaction was allowed to cool to ambient temperature. After stirring at ambient temperature for 16 hours the reaction mixture was diluted with CH_2Cl_2 and purified by adsorbing the material onto silica gel, loading the resulting solid onto the column and eluting with a gradient from 0% to 30% ethyl acetate / hexane to afford 6-(4-bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (188 mg, 54% yield) (a compound of formula (V) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, s), 7.1-7.03 (1H, m), 6.86-6.78 (2H, m), 6.76 (1H, s), 6.64 (1H, s), 5.46 (2H, s), 2.31 (2H, t of q, J_{H-H} = 7.6 Hz, J_{H-F} = 16.9 Hz), 1.11 (3H, t, J = 7.6 Hz).

PREPARATION 26

1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-furan-2-yl]-ethanone

Palladium catalyst ([1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1), 1.3g, 1.59mmol), potassium acetate (4.7g, 47.7mmol), and bis(pinacolato)diboron (6.05g, 23.8mmol) were placed into a flask and degassed with stream of N_2 for 20min. In a separate flask, 1-(4-bromo-furan-2-yl)-ethanone (3.0g, 15.9mmol) was dissolved in 30ml anhydrous DMSO and degassed with stream of N_2 for 20min. The DMSO solution of 1-(4-bromo-furan-2-yl)-ethanone was added to the "catalyst" flask, and then heated at 80°C overnight. After cooling to ambient temperature, water and ethyl acetate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in *vacuo*.

The crude product was purified by column chromatography on silica gel (10→30% EtOAC/Hexane, 0.25% Et_3N in hexane) to give 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-furan-2-yl]-ethanone as a colorless oil (3.27g, 87% yield) (a compound of formula (X)). 1H-NMR (400MHz, $CDCl_3$): δ 1.33 (s, 12H), 2.47 (s, 3H), 7.37 (d, 1H, *J*=0.60), 7.89 (d, 1H, *J*=0.68).

PREPARATION 27

4-chloro-6-ethoxy-2-methylsulfanylpyrimidine

To a solution of 4,6-dichloro-2-methylsulfanylpyrimidine (500 mg, 2.56 mmol) in anhydrous DMF (6 mL) was added sodium ethoxide (174 mg, 2.56 mmol). The reaction mixture was stirred at 70°C for overnight. The resulting mixture was poured into 30 mL of water and was extracted with diethyl ether (20 mL X 3) three times. The ether layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product 4-chloro-6-ethoxy-2-methylsulfanylpyrimidine (525 mg) (a compound of formula (Ga)). ^{1}H-NMR ($CDCl_3$): δ 6.39 (s, 1 H), 4.43 (q, J = 7.1 Hz, 2 H), 2.54 (s, 3 H), 1.38 (t, J = 7.1H, 3 H).

PREPARATION 28

1-[5-(6-ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-ethanone

The crude product of Preparation 27, 4-chloro-6-ethoxy-2-methylsulfanylpyrimidine, (525 mg, 2.56 mmol) was dissolved in DMF (4 mL). To this solution was added 5-acetyl-2-thiopheneboronic acid (523 mg, 3.08 mmol), $PdCl_2$dppf (209 mg, 0.26 mmol), potassim carbonate (1.06 g, 7.69 mmol) and water (0.4 mL). The reaction mixture was heated at 80°C under nitrogen atmosphere for overnight. The reaction mixture was cooled and poured into 30 mL of water and was then extracted with diethyl ether (20mL X 3) three times. The ether layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by flash silica column chromatography (20% ethyl acetate in hexane) to give product 1-[5-(6-ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-ethanone (210 mg, 28% yield over two steps) (a compound of formula (Y)). ^{1}H-NMR ($CDCl_3$): δ 7.67 (m, 2 H), 6.68 (s, 1 H), 4.46 (q, J = 7.1 Hz, 2 H), 2.60 (s, 3 H), 2.59 (s, 3 H), 1.40 (t, J =7.1 Hz, 3 H).

PREPARATION 29

4,4,4-trifluoro-1-[1-(3-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-butane-1,3-dione

A. 1-[5-(6-Ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-ethanone (210 mg, 0.71 mmol) was dissolved in anhydrous THF (7 mL) and cooled to

-78°C under nitrogen atmosphere. A solution of lithium bis(trimethylsilyl)amide (0.71 mL, 1.0 M) in THF was added. The reaction mixture was stirred at –20°C under nitrogen atmosphere for 1 h. The reaction mixture was then cooled to –78°C. To this reaction mixture was added ethyl trifluoroacetate (170 μL, 1.43 mmol). The vigorously stirred solution was allowed to warm to ambient temperature overnight. The reaction mixture was poured into 20 mL of ice and water and was brought to pH = 3~4 by adding 10% HCl aqueous solution. The mixture was then extracted with diethyl ether (20mL X 3) three times. The ether layer was separated and dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product 1-[5-(6-ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-4,4,4-trifluoro-butane-1,3-dione (272 mg, 98% yield). ^{1}H-NMR ($CDCl_3$): δ 7.81 (m, 1 H), 7.68 (m, 1 H), 6.70 (s, 1 H), 6.47 (s, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 2.61 (s, 3 H), 1.41 (t, J =7.1 Hz, 3 H).

B. Alternatively, lithium bis(trimethylsilyl)amide (1.0M solution in THF, 1.1mL, 1.1mmol) was slowly added to a solution of 1-[1-(3-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-ethanone (240mg, 0.94mmol) in 2mL anhydrous THF at -78°C under nitrogen. The mixture was then allowed to warm to -20°C and kept at -20°C to -5°C for 3 hrs. After this period of time the mixture was cooled to -78°C and to it was added ethyl trifluoroacetate (200mg, 0.41mmol). The mixture was next allowed to warm to ambient temperature overnight. 1N aqueous HCl was carefully added to adjust the pH 2. Two layers were separated and the aqueous layer was extracted with chloroform three times. The extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give 4,4,4-trifluoro-1-[1-(3-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-butane-1,3-dione as a yellow solid (290mg, 88% yield) (a compound of formula (Z)). The product was used for the next step without purification. 1H-NMR (400MHz, $CDCl_3$): δ 6.35 (s, 1H), 7.59 (dd, 1H, *J*=4.80, *J*=7.83), 8.21 (s, 1H), 8.28 (dd, 1H, *J*=1.77, *J*=3.80), 8.75 (dd, 1H, *J*=4.80, *J*=1.77), 8.76 (d, 1H, J=0.51)

PREPARATION 30

2-(4-iodo-pyrazol-1-yl)-3-trifluoromethyl-pyridine

Sodium hydride (60% dispersion in mineral oil, 243mg, 6.07mmol) was suspended in 4mL anhydrous N, N-dimethylformamide. To this solution was added 4-iodo-1*H*-pyrazole (982mg, 5.06mmol) in 4mL anhydrous N,N-dimethylformamide at 0°C under nitrogen. The mixture was stirred at 0°C for 15min, and then allowed to warm to ambient temperature and stirred at the same temperature for 2hrs. After this period of time, a solution of 2-chloro-3-trifluoromethyl-pyridine (1.01g, 5.56mmol) in 4mL N, N-dimethylformamide was added and the mixture was heated at 90°C for 5hrs. After

cooling off, the mixture was poured into water and extracted with ethyl acetate three times. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo* to give 2-(4-iodo-pyrazol-1-yl)-3-trifluoromethyl-pyridine as a white solid (1.406g, 74% yield) (a compound of formula (KK)). The product was used for the next step without purification. 1H-NMR (400MHz, $CDCl_3$): δ 7.48 (dd, 1H, *J*=4.80, *J*=8.08), 7.79 (s, 1H), 8.21 (dd, 1H, *J*=1.52, *J*=8.08), 8.27 (s, 1H), 8.67 (dd, 1H, J=1.52, *J*=4.80).

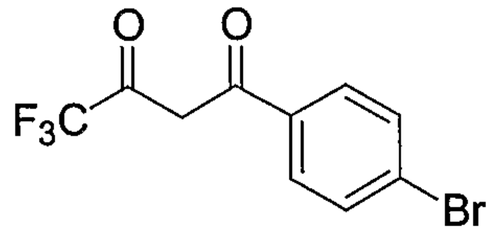
PREPARATION 31

1-[1-(3-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-ethanone

Isopropylmagnesium bromide (2.0M in Et_2O, 1.11ml, 2.22mmol) was added slowly to a solution of 2-(4-iodo-pyrazol-1-yl)-3-trifluoromethyl-pyridine (627mg, 1.85mmol) in 3mL anhydrous THF at 0°C under nitrogen. The reaction mixture was stirred at the same temperature for 2hrs, and then followed by the addition of N-methoxy-N-methyl-acetamide (286mg, 2.78mmol). The mixture was allowed to warm to ambient temperature overnight. Saturated ammonium chloride was added to quench the reaction. Two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in *vacuo.* The crude product was purified by column chromatography on silica gel (25% EtOAC/Hexane) to give 1-[1-(3-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-ethanone as a white solid (277mg, 59% yield) (a compound of formula (Ya)). 1H-NMR (400MHz, $CDCl_3$): δ 2.53 (s, 3H), 7.57 (dd, 1H, *J*=5.05, *J*=8.08), 8.18 (s, 1H), 8.27 (dd, 1H, *J*=1.52, *J*=8.08), 8.65 (s, 1H), 8.73 (d, 1H, J=4.03).

PREPARATION 32

1-(4-Bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione

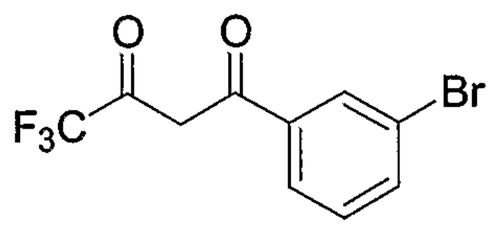


To a solution of 1-(4-bromo-phenyl)-ethanone (30.0 g, 0.151 mol) in anhydrous THF (300 mL) cooled with an ice bath at 0°C was added potassium tert-butoxide (20.3 g, 0.181 mol) slowly. The ice bath was removed after addition was complete. After stirring for 10 minutes at room temperature, trifluoro-acetic acid ethyl ester (25.7 g, 0.181 mol) was added and the reaction mixture was continued to stir at room temperature for 16 hours. After the reaction was complete, the reaction mixture

was concentrated in vacuo to remove THF. Water was subsequently added to the residue, and the resulting solid was collected by filtration. The solid was taken up into 1N HCl, extracted with ethyl acetate (x 2), washed with brine, then dried with Na_2SO_4, filtered and concentrated in vacuo to afford 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione as a light brown crystalline solid (42.4 g, 95.3%). ^1H NMR (400 MHz, d_6-$CDCl_3$) δ 15.02 (br s, 1H), 7.81 (m, 2H), 7.67 (m, 2H), 6.55 (s, 1H). MS (ESI-) for $C_{10}H_6BrF_3O_2$: 293.0/295.0 (M-H).

PREPARATION 33

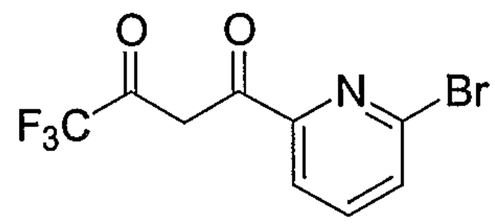
1-(3-Bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione



1-(3-Bromo-phenyl)-ethanone (3.1mls, 23.4mmol) was dissolved in dry THF (30mls) and cooled in an icebath. Potassium t-butoxide (3.3g, 28.0mmol) was added in portions. After addition was complete, the mixture was removed from the icebath and allowed to stir at room temperature for 30-60 min. The mixture was recooled in an icebath and trifluoro-acetic acid ethyl ester (3.4mls, 28.6mmol) was added. The mixture was removed from the icebath and stirred at room temperature overnight. The reaction mixture was con'd in vacuo, the resulting residue suspended in H_2O and the mixture acidified to neutral pH with 10% H_2SO_4. The aqueous mixture was extracted with Et_2O (3x). The combined Et_2O extractions were washed with saturated NaCl, dried (Na_2SO_4), and concentrated to give 1-(3-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione as an orange oil (6.1g, 88%) which was used without further purification. MS (ESI-) for $C_{10}H_6BrF_3O_2$: 293.0/295.0 (M-H).

PREPARATION 34

1-(6-Bromo-pyridin-2-yl)-4,4,4-trifluoro-butane-1,3-dione

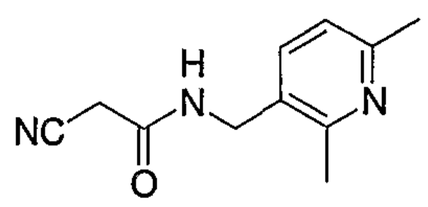


To a stirred solution of ethyl trifluoroacetate (572 μL, 4.79 mmol) and NaH (134 mg, 5.58 mmol) in anhydrous THF (12 mL) was added a solution containing EtOH (2 drops), THF (anhyd., 3.5 mL) and 1-(6-bromo-pyridin-2-yl)-ethanone (563 mg, 2.81

mmol), which was prepared according to M. A. Peterson's method (J. Org. Chem. 1997, 62, 8237). The resulting mixture was stirred at room temperature for 7 hours before addition of 2N HCl to adjust to pH= 2. Water was added to dissolve the precipitated solids. The aqueous phase was extracted with EtOAc. The combined organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash chromatography (silica gel, 3:2 EtOAc:Hexanes) to give 1-(6-bromo-pyridin-2-yl)-4,4,4-trifluoro-butane-1,3-dione as a brown oil (680 mg, 81.9% yield) (Note: it contained ~12 mol% of the starting ketone by ^1H NMR). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 1H), 7.76 (m, 1H), 7.70 (m, 1H), 7.25 (m, 1H). MS (ESI-) for $C_9H_5BrF_3NO_2$: 294 (M-H).

PREPARATION 35

2-Cyano-N-(2,6-dimethyl-pyridin-3-ylmethyl)-acetamide



A. A mixture of 3-bromo-2,6-dimethyl-pyridine (1.0 g, 5.38 mmol) and copper(I) cyanide 0.554 g, 6.18 mmol) in DMF (1.25 mL) was heated at 165°C in a seal tube for 16 hours. After the reaction was complete, the reaction mixture was partitioned between ethyl acetate and 10% sodium cyanide solution. The organic layer was washed with 10% sodium cyanide and brine, dried with Na_2SO_4, filtered and concentrated in vacuo to give 2,6-dimethyl-nicotinonitrile (0.45 g, 63.4%).

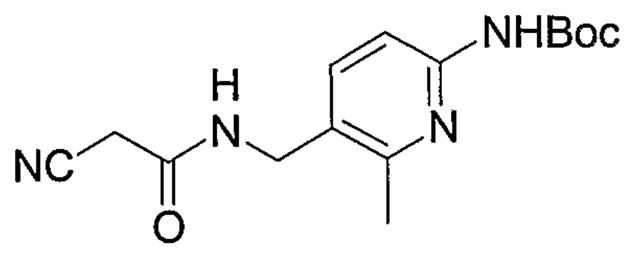
B. To a solution of 2,6-dimethyl-nicotinonitrile (0.45 g, 3.40 mmol) in ethanol (10 mL) was added ammonium hydroxide (28-30% in water, 0.5 mL, 3.40 mmol) and Raney® 2800 Nickel (slurry in water, 0.5 mL). The reaction mixture was subjected to the presence of H_2 at 45 psi on a Parr apparatus for 60 hours. The reaction was filtered through Celite, washed with ethanol, and concentrated in vacuo to give C-(2,6-dimethyl-pyridin-3-yl)-methylamine (0.445 g, 76.3%). ^1H NMR (400 MHz, d_6-DMSO) δ 7.57 (d, 1H), 7.03 (d, 1H), 3.70 (s, 2H), 2.40 (s, 6H).

C. C-(2,6-Dimethyl-pyridin-3-yl)-methylamine (0.445 g, 3.27 mmol) and cyanoacetic acid (0.253 g, 2.97 mmol) in DMF (10 mL) was added 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.425 g, 7.43 mmol). After stirring at 80°C for 16 hours, the mixture was diluted with ethyl acetate and partitioned between ethyl acetate and 1N HCl, and the organic layer was washed again with 1N HCl. The combined aqueous layer was basified with saturated $NaHCO_3$ solution to pH 8-9, and then re-extracted with EtOAc (x2), washed with brine and dried with Na_2SO_4, filtered and

concentrated in vacuo to yield 2-cyano-N-(2,6-dimethyl-pyridin-3-ylmethyl)-acetamide (0.250 g, 41.7%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.64 (s, 1H), 7.45 (d, 1H), 7.04 (d, 1H), 4.24 (d, 2H), 3.70 (s, 2H), 2.40 (d, 6H).

PREPARATION 36

{5-[(2-Cyano-acetylamino)-methyl]-6-methyl-pyridin-2-yl}-carbamic acid tert-butyl ester

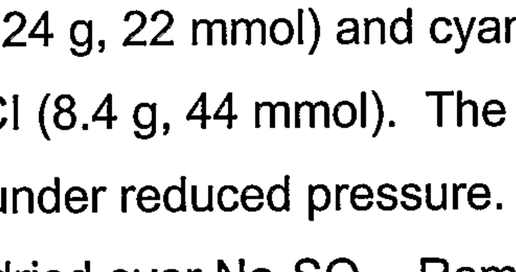


A. (5-Aminomethyl-6-methyl-pyridin-2-yl)-carbamic acid tert-butyl ester was prepared according to the literature procedure (J. Med. Chem. 1998, 41, 4466.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1 H), 7.57 (d, 1 H), 7.25 (br s, 1 H), 3.81 (s, 2 H), 2.43 (s, 3 H), 1.50 (s, 9 H).

B. To a 80 °C solution of (5-aminomethyl-6-methyl-pyridin-2-yl)-carbamic acid tert-butyl ester (5.24 g, 22 mmol) and cyanoacetic acid (1.87 g, 22 mmol) in DMF (80 mL) was added EDCI (8.4 g, 44 mmol). The stirring was continued for 4 h. Most of the DMF was removed under reduced pressure. The residue was dissolved in EtOAc, washed with brine, and dried over Na_2SO_4. Removal of organic solvents gave {5-[(2-cyano-acetylamino)-methyl]-6-methyl-pyridin-2-yl}-carbamic acid tert-butyl ester (3.7 g, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1 H), 7.51 (d, 1 H), 7.19 (br s, 1 H), 4.40 (m, 2 H), 3.43 (s, 2 H), 2.43 (s, 3 H). 1.51 (s, 9 H); MS (ESI+) for $C_{15}H_{20}N_4O_3$: 305 (M+H).

PREPARATION 37

2-Cyano-N-(2,4-dimethyl-benzyl)-acetamide

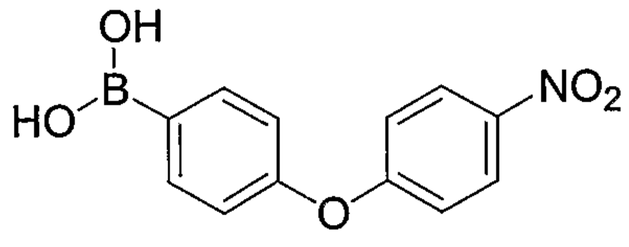


To a solution containing 2,4-dimethylbenzylamine (12.1 g, 89.5 mmol) and cyanoacetic acid (7.05 g, 82.9 mmol) in anhydrous DMF (200 mL) was added EDCI-HCl (39.7 g, 207 mmol). The resulting solution was heated to 80°C for 16 hours. After

allowing it to cool to room temperature, the mixture was diluted with EtOAc (400 mL) and washed with water. The aqueous phase was back extracted with EtOAc and the combined organic phases were washed with 5% LiCl, 0.5M HCl, $NaHCO_3$ (satd.) and brine, dried over Na_2SO_4 and concentrated to dryness, affording 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide as a white solid (13.7 g, 82% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H), 7.03 (s, 1H), 7.01 (d, 1H), 6.17 (br s, 1H), 4.44 (d, 2H), 3.38 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H).

PREPARATION 38

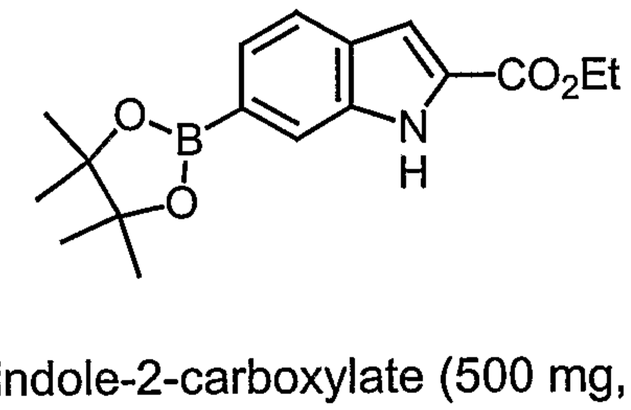
4-(4-Nitrophenoxy)phenylboronic acid



4-(4-Nitrophenoxy)phenylboronic acid. A mixture of 4-hydroxyphenylboronic acid (4.14 g, 30 mmol), DMF (60 ml) and potassium carbonate (16.5 g, 120 mmol) was stirred at RT for 5 minutes. 1-Fluoro-4-nitrobenzene (4.23 g, 30 mmol) added and the mixture heated to 60° C for 2 hr then stirred at room temperature for another 16 hr. The mixture was then diluted with water and acidified to pH 1 with conc. HCl. The precipitate was filtered to give 4-(4-nitrophenoxy)phenylboronic acid as solid (6.5 g). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29-8.27 (2H, d), 8.24-8.22 (2H, d), 7.20-7.18 (2H, d), 7.11-7.08 (2H, d). MS (ESI-) for $C_{12}H_{10}BNO_5$: 258 (M-H).

PREPARATION 39

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester

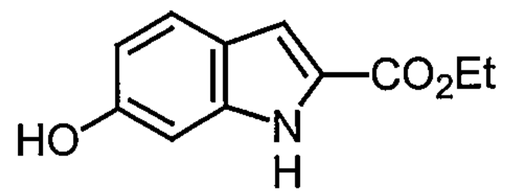


Ethyl 6-bromoindole-2-carboxylate (500 mg, 1.86 mmol), bis(pinacolato)diborane (472 mg, 1.86 mmol) and KOAc (545 mg, 1.86 mmol) were dissolved in 1,2-dimethoxyethane (5 mL). The atmosphere was inerted with N_2 and $Pd(dppf)Cl_2$ (41.9 mg, 0.0572 mmol) was then added. The mixture was placed in a microwave reactor at 150°C for 30 min. The crude reaction mixture was impregnated on

silica gel and purified by flash chromatography (silica gel, 1:9 EtOAc:Hexanes) to yield 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester as a white solid (216 mg, 36.8 % yield). MS (ESI+) for $C_{17}H_{22}BNO_4$: 316 (M+H).

PREPARATION 40

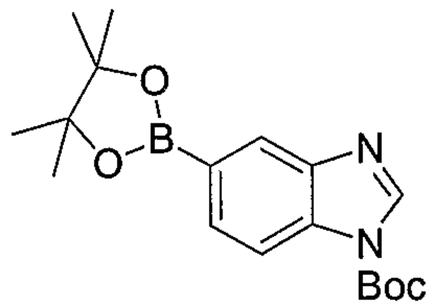
6-Hydroxy-1H-indole-2-carboxylic acid ethyl ester



To a solution containing 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester (618 mg, 1.96 mmol) in 1,2-dimethoxyethane (130 mL) was added 5M NaOH (aq., 160 μL, 0.80 mmol) and H_2O_2 (50% in water, 135 μL, 2.38 mmol). After stirring at room temperature for 3.5 hours, 1M HCl was added to adjust to pH = 3. The reaction mixture was concentrated *in vacuo* and the crude solids were impregnated on silica gel. Purification by flash chromatography afforded 6-hydroxy-1H-indole-2-carboxylic acid ethyl ester as a off white solid (357 mg, 89.0% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.4 (s, 1H), 9.38 (s, 1H), 7.42 (d, 1H), 7.01 (d, 1H), 6.78 (d, 1H), 6.61 (m, 1H), 4.29 (q, 2H), 1.31 (t, 3H). MS (ESI-) for $C_{11}H_{11}NO_3$: 204 (M-H).

PREPARATION 41

5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoimidazole-1-carboxylic acid tert-butyl ester



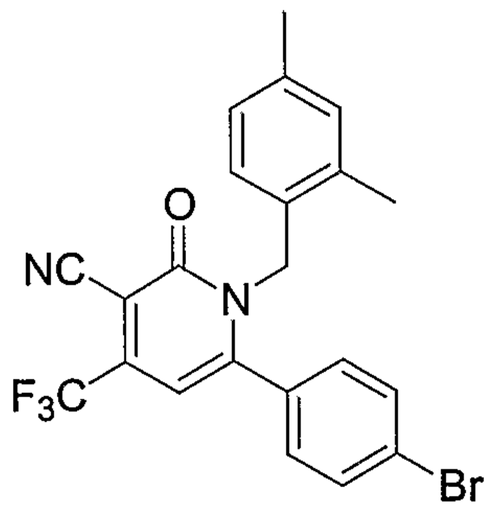
A. A solution of 4-bromo-Benzene-1,2-diamine(5g, 26.7 mmol) in 50 mL of triethyortholformate was refluxed for 1h at 146^0 C. After cooling to RT, the reaction mixture was concentrated in vacuo to give a product of 5-bromo-1H-benzoimidazole. To the crude product dissolved in DCM (100 mL) was added BOC-anhydride (6.54 g, 30 mmoles) and sodiumcarbonate (3.20 g, 30 mmoles). The mixture was stirred at RT for 3 h. On monitoring the reaction completion by LC/MS and TLC, the reaction mixture was poured into water, extracted with EtOAC (X3), washed the organic layer with 1 N HCl

(X2), saturated $NAHCO_3$ (X2), Brine (X2) and dried over Na_2SO_4. The organic layer was filtered and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAC in hexanes) to yield a mixture of two regiomers of 5- and 6-bromo-benzoimidazole-1-carboxylic acid tert-butyl ester (4g, 60% yield). ^1H NMR (400 MHz, d_6-DMSO) δ 8.40 (s, 1H), 8.20 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 1.70 (s, 9H). MS (ESI-) for $C_{12}H_{13}BrN_2O_2$: 243 (M - t-butyl).

B. A solution containing isomeric mixture of 5- and 6-bromo-benzoimidazole-1-carboxylic acid tert-butyl ester (1.48 g, 5mmol), bis(pinacolato)diborane (1.26 g, 5 mmol) and KOAc (1.47 g, 15 mmol) in 1,2-dimethoxyethane (15 mL) in a sealed tube was inerted with N_2 and $Pd(dppf)Cl_2$ (122 mg, 0.15 mmol) was then added. The resulting mixture was heated to 90°C for 16 hours. The crude product was impregnated on silica gel and purified by flash chromatography (silica gel, 15:85 EtOAc:hexanes) to give 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoimidazole-1-carboxylic acid tert-butyl ester as a coorless solid (1.4 g, 82% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.4 (s, 1H), 7.80 (m, 2H), 1.65 (s, 9H), 1.40 (s, 12H).

PREPARATION 42

6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

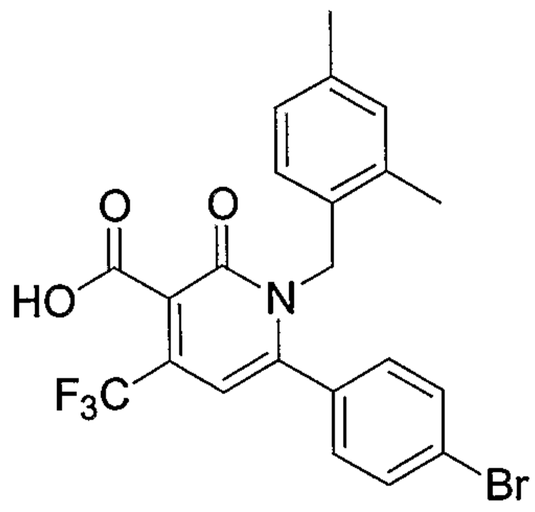


A solution containing 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (10.3 g, 34.9 mmol) and 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide (7.07 g, 35.0 mmol) in benzene (150 mL) was inerted with N_2 before adding DBU (5.3 mL, 35.2 mmol). The resulting mixture was heated to reflux for 22 hours before concentrating *in vacuo*. The crude residue was impregnated on silica gel and purified by flash chromatography (silica gel, 15:85 EtOAc:hexanes), affording the product as a yellow solid. Further purification to remove the trace amount of the diketone was achieved by triturating in hexanes (100 mL), sonicating and filtering then drying *in vacuo* to give 6-(4-bromo-phenyl)-1-(2,4-

dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a white solid (8.33 g, 51.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H), 7.02 (d, 2H), 6.95 (d, 1H), 6.95 (s, 1H), 6.58 (d, 1H), 6.41 (s, 1H), 5.08 (s, 2H), 2.29 (s, 3H), 1.94 (s, 3H).

PREPARATION 43

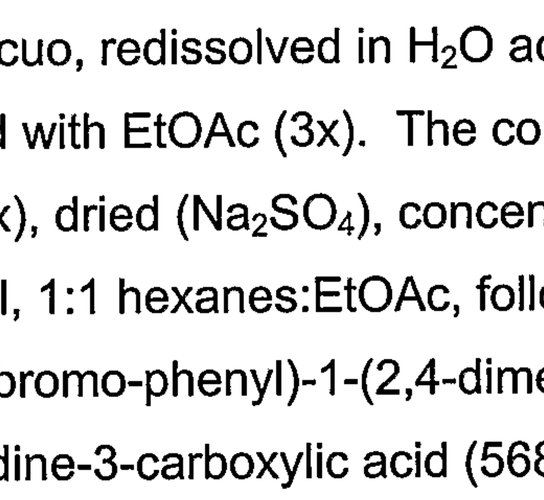
6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carboxylic acid



6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (803 mg, 1.74 mmol), and KOH (865 mg, 15.4 mmol) were combined in 80% aqueous EtOH (25ml) and heated to reflux for 4 days. The reaction mixture was concentrated in vacuo, redissolved in H_2O acidified to pH 2-3 with concentrated HCl and extracted with EtOAc (3x). The combined EtOAc extractions were washed with saturated NaCl (1x), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (silica gel, 1:1 hexanes:EtOAc, followed by 1:1 hexanes:EtOAc plus 2% AcOH), affording 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carboxylic acid (568 mg). MS (ESI+) for $C_{22}H_{17}BrF_3NO_3$: 480.1/482.1 (M+H).

PREPARATION 44

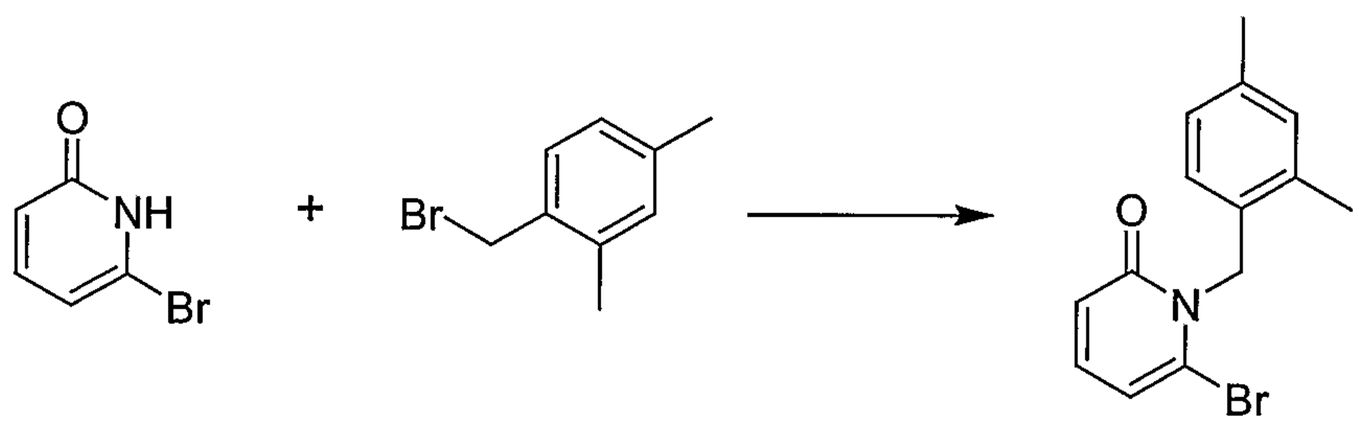
6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-trifluoromethyl-1H-pyridin-2-one



6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carboxylic acid (568 mg, 1.18 mmol) and copper powder (44 mg) are combined in quinoline (5.0 ml) and heated to 200°C overnight. The reaction mixture is allowed to cool to room temperature, diluted with EtOAc and washed with 1N HCl (3x), saturated NaCl (1x), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue is purified by flash chromatography (silica gel, 10%EtOAc, 2% triethylamine in hexanes) to give 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-trifluoromethyl-1H-pyridin-2-one (179 mg, 35%). MS (ESI+) for $C_{21}H_{17}BrF_3NO$: 436.1/438.1 (M+1).

PREPARATION 45

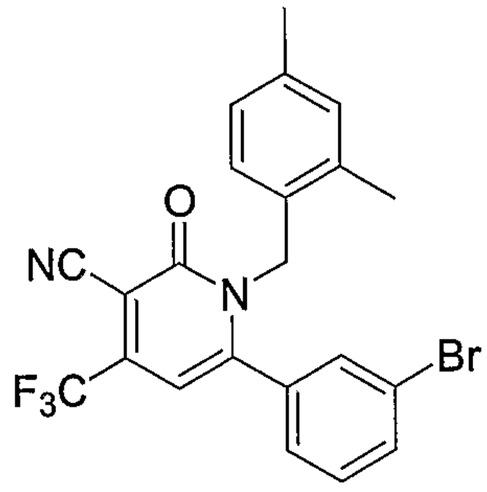
6-Bromo-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one



To a solution of 6-bromo-1H-pyridin-2-one (1.89 g, 10.86 mmol) prepared according *Communications,* **1974**, 70, anhydrous DMF (15 ml) was added sodium hydride (60% in mineral oil, 0.65 g, 16.3 mmol). The mixture was stirred for 5 minutes at room temperature, then cooled in ice/water bath and 2,4-dimethylbenzyl bromide (10.86 mmol, 2.16 g) was added. The resulting mixture was stirred at room temperature over night, quenched with water and extracted with ethyl acetate. The organic phase, after concentrated in vacuo, was purified on column chromatography with 5% EtOAc/hexanes to gave 6-bromo-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one (2.26 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (1H, t), 7.32-7.30 (1H, d), 7.08-7.01 (3H, m), 6.71-6.69 (1H, d), 5.31 (2H, s), 2.37 (3H, s), 2.32 (3H, s); MS (ESI+) for C14H14BrNO: 292 (M+H).

PREPARATION 46

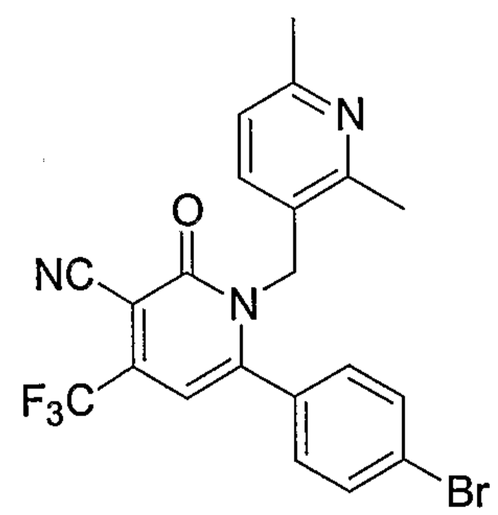
6-(3-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile



1-(3-Bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (1.55g, 5.25mmol), 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide (1.06g, 5.24mmol), benzene (15mls), and DBU (235μl, 1.56mmol) were combined and heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo, and immediately purified by flash chromatography (silica gel, 5% EtOAc in hexanes, followed by 12.5% EtOAc in hexanes) to give 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as an off-white solid (1.60g, 66%). MS (ESI-) for $C_{22}H_{16}BrF_3N_2O$: 459.1/461.1 (M-H).

PREPARATION 47

6-(4-Bromo-phenyl)-1-(2,6-dimethyl-pyridin-3-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile

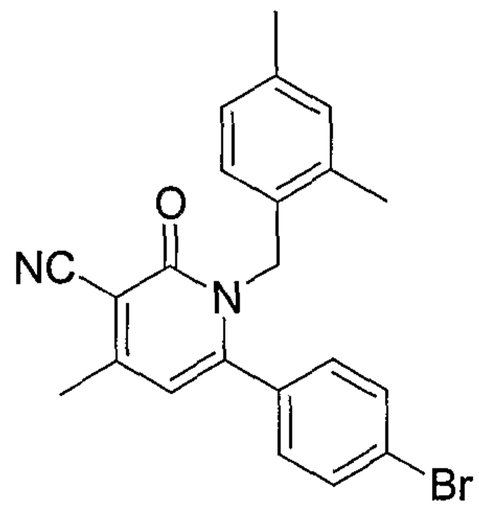


To a mixture of 2-cyano-N-(2,6-dimethyl-pyridin-3-ylmethyl)-acetamide (0.250 g, 1.23 mmol), 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (0.363 g, 1.23 mmol) and anhydrous benzene (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.187 g, 1.23 mmol). The reaction mixture was heated in a sealed pressure tube at 105°C for 16 hours. After the reaction was complete, solvent was evaporated in vacuo. The crude product was purified by flash column chromatography with 40:60 EtOAc/Hex

to give 6-(4-Bromo-phenyl)-1-(2,6-dimethyl-pyridin-3-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.225 g, 39.6%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.68 (d, 2H), 7.33 (d, 2H), 7.30 (s, 1H), 7.17 (d, 1H), 6.99 (d, 1H), 6.82 (s, 1H), 5.03 (s, 2H), 2.38 (s, 3H), 2.14 (s, 3H).

PREPARATION 48

6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile

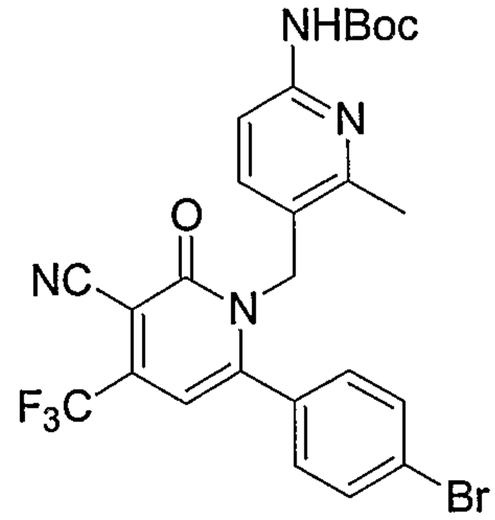


A. 1-(4-Bromo-phenyl)-ethanone (2.54 g, 12.8 mmol) was dissolved in dry THF (20 ml) and cooled in an ice bath. Potassium t-butoxide (1.7 g, 15.1 mmol) was added in portions. After addition was complete, the mixture was removed from the ice bath and allowed to stir at room temperature for 30-60 min. The mixture was recooled in an ice bath and ethyl acetate (4.0 ml, 51 mmol) was added. The mixture was removed from the ice bath and stirred at room temperature overnight. The reaction mixture was concentrated in vacuo, the resulting residue suspended in H_2O and the mixture acidified to neutral pH with 10% H_2SO_4. The aqueous mixture was extracted with Et_2O (3x). The combined Et_2O extractions were washed with saturated NaCl, dried (Na_2SO_4), and concentrated to give 1-(4-bromo-phenyl)-butane-1,3-dione as an orange oil (2.5 g, 81%) which was used without further purification.

B. 1-(4-Bromo-phenyl)-butane-1,3-dione (1.54 g, 6.4 mmol), 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide (1.30 g, 6.4 mmol), benzene (25 ml), and DBU (500 μl, 3.3 mmol) were combined and heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo, and immediately purified by flash chromatography (silica gel, 1:1 hexanes:EtOAc) to give 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile as an off-white solid (610 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 2H), 6.97 (d, 2H), 6.92 (m, 1H), 6.88 (s, 1H), 6.60 (d, 1H), 6.09 (s, 1H), 5.00(s, 2H), 2.50 (s, 3H), 2.27 (s, 3H), 1.91 (s, 3H). MS (ESI-) for $C_{22}H_{19}BrN_2O$: 405.1/407.1 (M-H).

PREPARATION 49

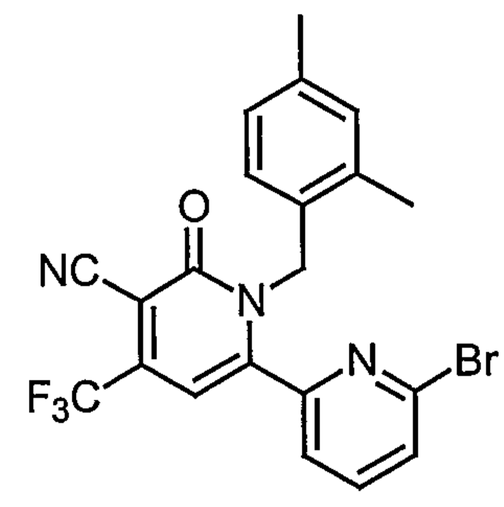
5-[6-(4-Bromo-phenyl)-3-cyano-2-oxo-4-trifluoromethyl-2H-pyridin-1-ylmethyl]-6-methyl-pyridin-2-yl}-carbamic acid tert-butyl ester



A solution of {5-[(2-cyano-acetylamino)-methyl]-6-methyl-pyridin-2-yl}-carbamic acid tert-butyl ester. (5-Aminomethyl-6-methyl-pyridin-2-yl)-carbamic acid tert-butyl ester (2.1 g, 6.8 mmol), 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (2.0 g, 6.8 mmol), and DBU (515 mg, 3.4 mmol) in benzene (80 mL) was heated to reflux. The stirring was continued for 24 h. Benzene was removed. The residue was purified by column chromatography (hexanes:AcOEt = 2:1). {5-[6-(4-Bromo-phenyl)-3-cyano-2-oxo-4-trifluoromethyl-2H-pyridin-1-ylmethyl]-6-methyl-pyridin-2-yl}-carbamic acid tert-butyl ester was obtained as a pale yellow solid (0.84 g, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 3 H), 7.05 (m, 4 H), 6.42 (s, 1 H), 5.09 (s, 2 H), 2.04 (s, 3 H), 1.45 (s, 9 H); MS (ESI+) for $C_{25}H_{22}BrF_3N_4O_3$: 563,565 (M+H).

PREPARATION 50

6'-Bromo-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-[2,2']bipyridinyl-5-carbonitrile

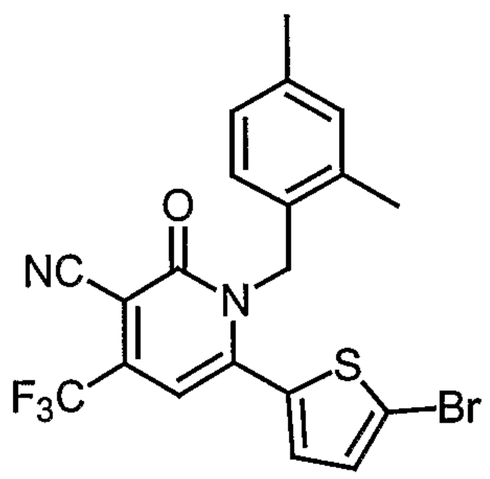


A solution containing 1-(6-bromo-pyridin-2-yl)-4,4,4-trifluoro-butane-1,3-dione (667 mg, 2.25 mmol) and 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide (478 mg, 2.36 mmol) in benzene (11.5 mL) was inerted with N_2 before adding DBU (174 μL, 1.15

mmol). The resulting mixture was heated to reflux for 16 hours before concentrating *in vacuo*. The resulting residue was dissolved in EtOAc and washed with 0.4M HCl, water and brine, dried over Na_2SO4 and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, 1:4 EtOAc:Hexanes) to yield 6'-bromo-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-[2,2']bipyridinyl-5-carbonitrile as a yellow solid (530 mg, 51% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.48 (m, 1H), 7.03 (m, 1H), 6.80 (m, 2H), 6.46 (m, 2H), 5.50 (s, 2H), 2.21 (s, 3H), 2.02 (s, 3H). MS (ESI-) for $C_{21}H_{15}BrF_3N_3O$: 460 (M-H).

PREPARATION 51

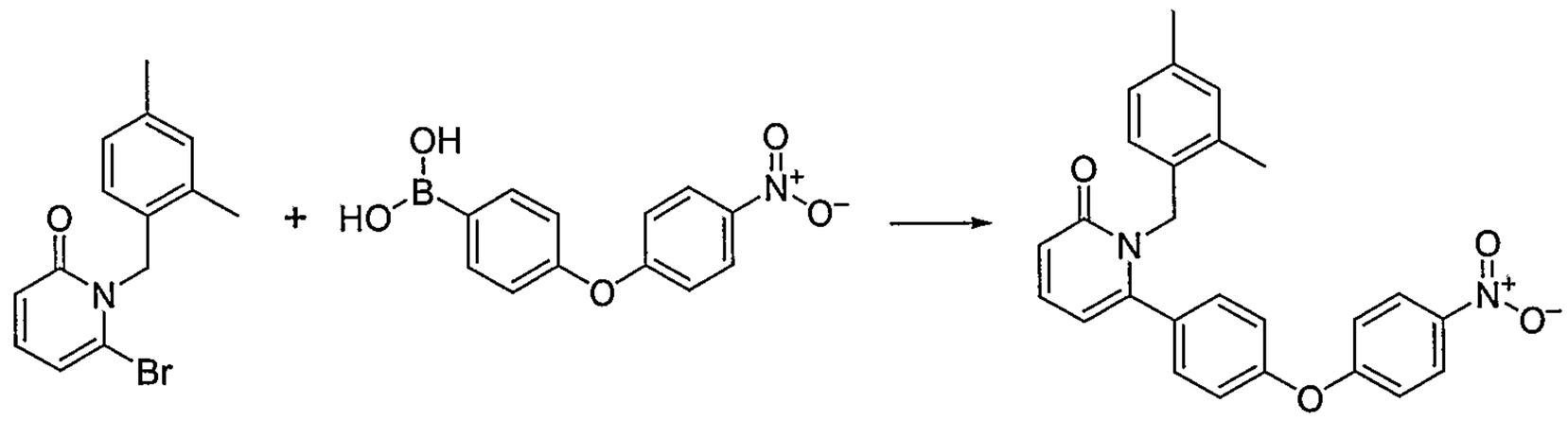
6-(5-Bromo-thiophen-2-yl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile



A mixture containing 1-(5-bromo-thiophen-2-yl)-4,4,4-trifluoro-butane-1,3-dione (0.745 g, 2.5 mmol), 2-cyano-N-(2,4-dimethyl-benzyl)-acetamide (0.50 g, 2.5 mmol) and DBU (0.138g, 1.25 mmol) in benzene (10 mL) was heated in a sealed tube at 90°C for 24 hours. After the reaction was complete the benzene was removed. The crude solids were impregnated on silica gel and purified by flash chromatography (1:4 EtOAc:Hexanes) to give 6-(5-bromo-thiophen-2-yl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow solid (0.158g, 14% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 3H), 6.78 (d, 1H), 6.60 (s, 1H), 6.54 (d, 1H), 5.25 (s, 2H), 2.32 (s, 3H), 2.17 (s, 3H). MS (ESI-) for $C_{20}H_{14}BrF_3N_2OS$: 467 (M-H).

PREPARATION 52

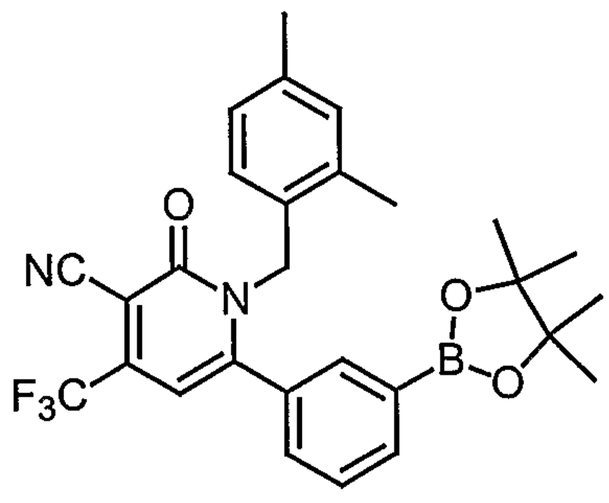
1-(2,4-Dimethyl-benzyl)-6-[4-(4-nitro-phenoxy)-phenyl]-1H-pyridin-2-one



A mixture of 6-Bromo-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one (2.26 g, 7.74 mmol), 4-(4-nitrophenoxy)phenylboronic acid (2 g, 7.74 mmol), toluene (50 ml), water (50 ml), potassium carbonate (4.14 g, 30 mmol), and dichloro [1,1'-bis (diphenylphosphino) ferocene]palladium (II) dichloromethane adduct (0.816 g, 1 mmol) was heated at reflux over night. The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. Organic layer was separated, washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified on column chromatography using 5% EtOAc/hexanes to gave 1-(2,4-dimethyl-benzyl)-6-[4-(4-nitro-phenoxy)-phenyl]-1H-pyridin-2-one (2.1 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (2H, d), 8.14-8.11 (2H, d), 7.68-7.63 (1H, t), 7.36-7.33 (2H, d), 7.20-7.17 (2H, d), 7.10-7.07 (2H, d), 7.06-7.02 (2H, m), 6.75-6.73 (1H, d), 5.46 (2H, s), 2.40 (3H, s), 2.33 (3H, s); MS (ESI+) for $C_{26}H_{22}N_2O_4$: 427 (M+H).

PREPARATION 53

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile



6-(3-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (2.28 g, 4.94 mmol), bis(pinacolato)diborane (1.37 g, 5.38 mmol) and KOAc (1.50 mg, 15.2 mmol) were dissolved in 1,2-dimethoxyethane (30 mL)

in a sealed tube. The atmosphere was inerted with N_2 and Pd(dppf)Cl_2 (108 mg, 0.147 mmol) was then added. The resulting mixture was heated to 90°C for 13 hours. More diborane (165 mg, 0.650 mmol) and catalyst (29.5 mg, 0.040 mmol) were added and the reaction mixture was heated back to 90°C for 2.5 hours. After allowing to cool to room temperature, the reaction mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solids were impregnated on silica gel and purified by flash chromatography (silica gel, 3:7 EtOAc:hexanes) to give 1-(2,4-dimethyl-benzyl)-2-oxo-6-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a light yellow solid (1.18 g, 47.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.59 (s, 1H), 7.34 (t, 1H), 7.15 (m, 1H), 6.95 (d, 1H), 6.87 (s, 1H), 6.62 (d, 1H), 6.45 (s, 1H), 5.09 (s, 2H), 2.27 (s, 3H), 1.87 (s, 3H), 1.33 (s, 12H).

EXAMPLE 1

Compounds of Formula (Ia)

A. To a solution of 6-(4-bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (75 mg, 160 µmol) and 2-(3-ethylsulfanyl-5-isopropyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (73 mg, 240 µmol) in 1,2-dimethoxyethane (2.0 mL) was added K_2CO_3 (68 mg, 490 µmol) and H_2O (200 µL). Dichloro[1,1'-bis(diphenylphosphino)ferrocene)palladium (II) dichloromethane adduct (11 mg, 15 µmol, ~ 9 mol %) was added and the resulting dark mixture was sparged with nitrogen for ~ 5 minutes. The reaction vial was sealed with a septum that had been pierced with a needle to allow for pressure release, and immersed in an oil bath heated to 80°C. After 5 ½ hours stirring at 80°C, heating was discontinued and the reaction was allowed to stir at ambient temperature for 16 hrs. The reaction mixture was then diluted with ether and H_2O, the layers were separated, and the aqueous was extracted with ether (3 x 20 mL). The combined ether layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a dark oil. The crude product was purified by silica gel column chromatography by adsorbing the material onto silica gel from a CH_2Cl_2 solution, loading the resulting solid onto the column and eluting with a gradient from 0% to 20% ethyl acetate / hexane to afford 1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(3-ethylsulfanyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (40 mg, 44% yield) as a brown foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 0.8 Hz), 7.18-7.15 (2H, m), 7.12-7.03 (2H, m), 7.00 (1H, d, J = 0.8 Hz), 6.87-6.79 (2H, m), 6.76 (1H, s), 5.56 (2H, s),

2.98 (2H, q, J = 7.3 Hz), 2.90 (1H, heptet, J = 7.1 Hz), 2.34 (2H, t of q, J_{H-H} = 7.6 Hz, J_{H-F} = 16.9 Hz), 1.34 (3H, t, J = 7.3 Hz), 1.27 (6H, d, J = 7.1 Hz), 1.13 (3H, t, J = 7.3 Hz).

B. Alternatively, to 6-(5-bromo-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (134 mg, 0.28 mmol) was added 2-methyl-2-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionic acid methyl ester (1.2 mL of a 0.47 M solution in 1,2-dimethoxyethane, 0.56 mmol). The mixture was diluted with 1,2-dimethoxyethane (1.6 mL) and nitrogen was bubbled through the solution as an aqueous solution of K_2CO_3 (0.3 mL of a 35% w/v solution in H_2O, 0.8 mmol) was added. The addition of the K_2CO_3 solution caused the reaction mixture to turn dark. The mixture was then treated with dichloro[1,1'-bis(diphenylphosphino)ferrocene)palladium (II) dichloromethane adduct (21 mg, 26 µmol). After several minutes the nitrogen sparge was discontinued, and the vial was immersed in an oil bath held at 80°C. After stirring for 16 hours the dark reaction was allowed to cool to ambient temperature, and diluted with ether (30 mL), and H_2O (10 mL). The aqueous layer was extracted with ether (1 x 10 ml), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford a dark oil. The crude material was purified by flash chromatography eluting with a gradient from 0% to 20% ethyl acetate / hexane to afford 2-(3-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-2-methyl-propionic acid methyl ester (72 mg, 45% yield) as an orange-yellow oil. This material was not completely pure and was further purified by preparative reverse phase LC/MS chromatography on a C-18 column. The desired fraction was collected by mass and concentrated under reduced pressure to afford 2-(3-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-2-methyl-propionic acid methyl ester (26 mg, 17% yield) as a yellow powder. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.52-7.50 (1H, m), 7.46-7.35 (3H, m), 7.29-7.26 (1H, m), 7.12-7.05 (2H, m), 6.91-6.79 (2H, m), 6.67 (1H, s), 5.46 (2H, s), 3.68 (3H, s), 1.62 (6H, s).

C. Alternatively, to 6-(4-bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (185 mg, 0.40 mmol) was added 2-methyl-2-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]propionic acid methyl ester (1.7 mL of a 0.47 M solution in 1,2-dimethoxyethane, 0.8 mmol). The mixture was diluted with 1,2-dimethoxyethane (2.3 mL) and nitrogen was bubbled through the solution as an aqueous solution of K_2CO_3 (0.4 mL of a 35% w/v solution in H_2O, 1.0 mmol) was added. The addition of the K_2CO_3 solution caused the reaction mixture to turn dark. The mixture was then treated with dichloro[1,1'-bis(diphenylphosphino-)ferrocene)palladium (II) dichloromethane adduct (33 mg, 40 µmol). After several

minutes the nitrogen sparge was discontinued, and the vial was immersed in an oil bath held at 80°C. After stirring for 16 hours the dark reaction was allowed to cool to ambient temperature, and diluted with ether (30 mL), and H_2O (10 mL). The aqueous layer was extracted with ether (1 x 10 ml), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford a dark oil. The crude material was purified by flash chromatography eluting with a gradient from 0% to 20% ethyl acetate / hexane to afford bright yellow product containing fractions from the column. Some of these fractions deposited yellow crystals upon standing. The crystals were collected and found to be pure 2-(3-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-2-methyl-propionic acid methyl ester (74 mg, 33% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.89 (1H, br s), 7.41-7.28 (4H, m), 7.11-7.05 (2H, m), 6.91-6.82 (3H, m), 5.60 (2H, s), 3.67 (3H, s), 1.61 (6H, s).

D. 6-(5-Bromo-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (270mg, 0.57mmol), 2-methylsulfanyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl) pyridine (214mg, 0.85mmol), potassium carbonate (236mg, 1.71mmol), and tetrakis(triphenylphosphine)palladium (0) (66mg, 0.057mmol) were mixed with 6ml 9:1DME/H_2O (v/v), then heated at 80°C overnight. All solvent was removed in *vacuo*. The crude product was purified by column chromatography on silica gel (10→40% EtOAC/Hexane, 0.25% Et_3N in hexane) to give 1-(2,4-difluoro-benzyl)-6-[5-(6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1, 2-dihydro-pyridine-3-carbonitrile as an orange solid (276mg, 93% yield). 1H-NMR (400MHz, $CDCl_3$): δ 2.61 (s, 3H), 5.45 (s, 2H), 6.66 (s, 1H), 6.82 (m, 1H), 6.88 (m, 1H), 7.09 (m, 1H), 7.12 (d, 1H, *J*=3.9), 7.27 (m, 2H, mixed with $CDCl_3$), 7.64 (dd, 1H, *J*=2.4, *J*=8.4), 8.67 (dd, 1H, *J*=2.4, *J*=0.8).

E. 6-(4-Bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (98mg, 0.22mmol), 2-ethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trifluoromethyl-pyridine (125mg, 0.54mmol) (or corresponding 2-ethoxy-3-trifluoromethylpyridine-5-boronic acid), potassium carbonate (149mg, 1.08mmol), and tetrakis(triphenylphosphine)palladium (0) (25mg, 0.1mmol) were mixed with 2.5ml 9:1DME/H_2O (v/v), then heated at 80°C overnight. All solvent was removed in *vacuo*. The crude product was purified by column chromatography on silica gel (10→30% EtOAC/Hexane, 0.25% Et_3N in hexane) to give 1-(2,4-difluoro-benzyl)-6-[4-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow solid (29mg, 37% yield). 1H-NMR (400MHz, $CDCl_3$): δ 1.45 (t, 3H, *J*=7.07), 4.53 (q, 2H, *J*=7.07), 5.58 (s, 2H), 6.83 (s, 1H),

6.84 (m, 1H), 6.87 (m, 1H), 7.04 (d, 1H, *J*=0.76), 7.13 (m, 1H), 7.87 (d, 1H, *J*=2.27), 7.90 (d, 1H, *J*=0.76), 8.38 (d, 1H, *J*=2.27).

F. 6-(4-Bromo-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile 620mg, 1.3mmoles), [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester (520mg, 1.95mmoles), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (1:1) (32mg, 0.39mmoles), and K_2CO_3 (540mg, 3.91mmoles) were combined in 6ml of DME/H_2O (9:1, degassed), and were stirred at 85°C for 5 hours. After this period the reaction mix was evaporated and purified using flash silica chromatography (0-30% EtOAc/Hexane) to yield (3-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester (365mg, 52%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.64 (br d, J=1.3Hz, 1H), 7.39-7.35 (m, 2H), 7.33 (br d, J=1.3Hz, 1H), 7.14-7.07 (m, 1H), 6.92-6.85 (m, 1H), 6.84-6.77 (m, 1H), 6.65 (s, 1H), 5.44 (s, 2H), 3.72 (s, 3H), 3.67 (s, 2H). MS(ES+): 545.3 (M+H).

EXAMPLE 2

Compounds of Formula (Ia) and Oxidation

A. 6-(5-Bromo-furan-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (310mg, 0.7mmoles), 2-(3-Ethylsulfanyl-5-trifluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (287mg, 0.86mmoles), tetrakis(triphenylphosphine)palladium (0) (81mg, 0.07mmoles), K_2CO_3 (450mg, 3.3mmoles) were combined in 12ml of DME/H_2O (9:1, degassed), and were stirred at 85°C for 16 hours. After this period the reaction mix was evaporated and purified using flash silica chromatography (0-20% EtOAc/Hexane) to yield 1-(2,4-difluoro-benzyl)-6-[5-(3-ethylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.23g, 55%) as a yellow residue.

B. 1-(2,4-Difluoro-benzyl)-6-[5-(3-ethylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.23g, 0.39mmoles) was dissolved into 50mL of DCM. To this solution at 0°C was added 60% active m-chloroperbenzoic acid (250mg, ~2.25equiv.). The mix was allowed to warm to ambient temperature and was stirred at this temperature for 30 min. After this period an additional 50mL of DCM was added and this mix was washed with 1N Na_2CO_3 (4x20mL) and brine. The resulting DCM layer was dried over anhydrous Na_2SO_4 and was evaporated *in vacuo* to yield the crude product. The crude product was purified using flash silica chromatography (0-40% EtOAc/Hexane) to yield 1-(2,4-difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-

dihydro-pyridine-3-carbonitrile (205mg, 86% yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.26 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.14-7.07 (m, 1H), 7.06 (d, J=3.8Hz, 1H), 6.98 (d, J=3.8Hz, 1H), 6.92-6.85 (m, 1H), 6.84-6.77 (m, 1H), 6.81 (s, 1H), 5.53 (s, 2H), 3.19 (q, J=7.3Hz, 2H), 1.35 (t, J=7.3Hz, 3H). MS(ES+): 617.1.

EXAMPLE 3

Hydrolysis of Compounds of Formula (I)

A. (3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester (0.988g, 1.81mmoles) was dissolved into THF (20mL) and water (6mL). To this homogeneous mixture was then added LiOH hydrate (152mg, 3.62mmoles). This mix was then stirred at 30°C for 2 hours. After this period the reaction mixture was acidified to pH~3 using 1H HCl and was evaporated *in vacuo*. The resulting residue was extracted with DCM (3x15mL) and the resulting organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (0-5% MeOH/DCM) to yield (3-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid (625mg, 65%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.64 (br d, J=1.5Hz, 1H), 7.41-7.38 (m, 2H), 7.32-7.30 (m, 1H), 7.13-7.06 (m, 1H), 6.90-6.84 (m, 1H), 6.82-6.75 (m, 1H), 6.64 (s, 1H), 5.43 (s, 2H), 3.70 (s, 2H). MS(ES+): 531.1 (M+H).

EXAMPLE 4

Compounds of Formula (Ib)

A. 1-[5-(6-Ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-4,4,4-trifluoro-butane-1,3-dione (128 mg, 0.32 mmol) and 2,4-difluorobenzyl cyanoacetamide (82 mg, 0.39 mmol) were suspended in 2 mL of benzene. To the above reaction mixture was added DBU (24 μL, 0.16 mmol). The mixture was sealed in a vial and stirred at 90°C for overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash silica column chromatography (30% ethyl acetate in hexane) to yield product 1-(2,4-difluoro-benzyl)-6-[5-(6-ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (70 mg, 38% yield). ^{1}H-NMR ($CDCl_3$): δ7.57 (m, 1 H), 7.10 (m, 1 H), 7.09 (m, 1 H), 6.87 (m, 1 H), 6.79 (m, 1 H), 6.65 (s, 1 H),6.64 (s, 1 H), 5.41 (s, 2 H), 4.47 (q, J = 7.1 Hz, 2 H), 2.55 (s, 3 H), 1.41 (t, J =7.1 Hz, 3 H).

B. 4,4,4-Trifluoro-1-[1-(3-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-butane-1,3-dione (143mg, 0.41mmol) and 2-cyano-N-(2,4-difluoro-benzyl)-acetamide

(86mg, 0.41mmol) were suspended in 1.5mL anhydrous benzene. To the above reaction mixture was added 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU (31mg, 0.21mmol). The mixture was heated at 90°C under nitrogen atmosphere for overnight. After this period of time, the mixture was evaporated in *vacuo* and the resulting residue was purified by column chromatography on silica gel (35% EtOAC/Hexane) to give 1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(3-trifluoromethyl-pyridin-2-yl)-1*H*-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile as a yellow solid (78mg, 36% yield). 1H-NMR (400MHz, $CDCl_3$): δ 5.42 (s, 2H), 6.61 (s, 1H), 6.82 (m, 1H), 6.89 (m, 1H), 7.12 (m, 1H), 7.58 (dd, 1H, *J*=4.80, *J*=8.08), 7.73 (s, 1H), 8.28 (dd, 1H, *J*=1.77, *J*=8.08), 8.32 (s, 1H), 8.72 (dd, 1H, *J*=1.77, *J*=4.80).

EXAMPLE 5

Oxidation of Compounds of Formula (I)

A. A solution of 1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(3-ethylsulfanyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (39 mg, 69 µmol) in CH_2Cl_2 was cooled in an ice bath and treated with 3-chloroperoxybenzoic acid (45 mg of 77% pure material, ~200 µmol). After several minutes stirring at 0°C, the ice bath was removed and after an additional 15 minutes, TLC analysis of the reaction mixture showed the starting sulfide to be gone, and the appearance of a single product spot. The reaction mixture was quenched by the addition of 10% sodium thiosulfate solution and diluted with CH_2Cl_2 (50 mL). Saturated $NaHCO_3$ was added to bring the pH > 8. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a yellow film. The crude product was purified by silica gel column chromatography by adsorbing the material onto silica gel from a CH_2Cl_2 solution, loading the resulting solid onto the column and eluting with a gradient from 30% to 50% ethyl acetate / hexane to afford 1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (39 mg, 94% yield) as a yellow foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, s), 7.78 – 7.77 (1H, m), 7.72 – 7.71 (1H, m), 7.53 – 7.51 (1H, m), 7.17 – 7.10 (1H, m), 7.07 (1H, s), 6.87 – 6.80 (2H, m), 6.74 (1H, s), 5.55 (2H, s), 3.15 (2H, q, J = 7.6Hz), 3.10 – 2.99 (1H, m), 2.42 – 2.27 (2H, m), 1.35 – 1.30 (9H, m), 1.14 (3H, t, J = 7.6Hz).

B. 1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (254mg, 0.49mmol) was dissolved in 5ml mixed solvent of 5:1 DCM/MeOH (v/v), and magnesium monoperoxyphthalate hydrate (MMPP, 85% tech., 627mg, 1.08mmol) was

slowly added portionwise. The reaction was complete at ambient temperature after 3hrs. DCM was added to the reaction mixture, and the white precipitate was filtered and thoroughly washed with DCM. The combined organic layers were washed with saturated $NaHCO_3$, brine, and dried over sodium sulfate. After concentration in *vacuo*, the crude product was purified by column chromatography on silica gel (15→50% EtOAC/Hexane, 0.25%Et_3N in hexane) to give 1-(2,4-difluoro-benzyl)-6-[5-(6-methylsulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile as a yellow solid (154mg, 60% yield). 1H-NMR (400MHz, $CDCl_3$): δ 3.28 (s, 3H), 5.43 (s, 2H), 6.66 (s, 1H), 6.81 (m, 1H), 6.90 (m, 1H), 7.14 (m, 1H), 7.19 (d, 1H, *J*=3.9), 7.48 (d, 1H, *J*=3.9), 8.10 (dd, 1H, *J*=2.2, *J*=8.2), 8.17 (dd, 1H, *J*=0.7, *J*=8.2), 8.93 (dd, 1H, *J*=2.2, *J*=0.7).

C. 1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-2-methylsulfanyl-pyrimidin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (49 mg, 0.087 mmol) was dissolved in a mixture of dichloromethane (2 mL) and methanol (0.4 mL). To this solution was added magnesium monoperoxyphthalate hexahydrate, MMPP, (108 mg, 0.218mmol, 80% tech.) and the mixture was stirred at ambient temperature for overnight. After this period the reaction mixture was combined with dichloromethene (20mL) and was washed with 1M $NaHCO_3$ (2x10mL), and brine (10 mL). The resulting organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield crude product. The crude product was purified using flash silica chromatography (25-50% EtOAc/Hexane) to yield 1-(2,4-difluorobenzyl)-6-[5-(6-ethoxy-2-methanesulfonyl-pyrimidin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (42 mg, 80%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 7.72 (m, 1 H), 7.14 (m, 1 H), 7.13 (m, 1 H),7.07 (s, 1 H), 6.88 (m, 1 H), 6.78 (m, 1 H), 6.63 (s, 1 H), 5.40 (s, 2 H), 4.61 (q, J = 7.1 Hz, 2 H), 3.36 (s, 3 H), 1.46 (t, J =7.1 Hz, 3 H). MS(ES+): 597.2 (M+H).

EXAMPLE 6

Following the procedures set forth above in the foregoing preparations and examples and in U.S. Patent Application, Serial No. 10/327,813, the following compounds of the invention were prepared:

1-(2,4-Dimethyl-benzyl)-6-[4-(3-isopropyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.3 (M+H);

6-[4-(4-tert-Butyl-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-fluoro-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):507.1 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,5-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,6-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.4 (M+H);

6-[4-(2-Chloro-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):523.1 (M+H);

6-[4-(3-Chloro-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):523.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(2-trifluoromethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):557.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(3-trifluoromethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):557.4 (M+H);

6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):553.3 (M+H);

6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):555.2 (M+H);

6-[4-(3-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):581.5 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):503.2 (M+H);

6-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):611.4 (M+H);

6-(4-Benzyloxy-phenyl)-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):529.0 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):515.0 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):483.0 (M+H);

1-(2-Chloro-4-fluoro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):499.2 (M+H);

6-(4-Benzyloxy-phenyl)-1-(2-chloro-4-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):513.2 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):564.9 (M+H);

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-phenoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.5 (M+H);

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-o-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.5 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,5-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3,4-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.5 (M+H);

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-m-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(3-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(4-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-p-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.3 (M+H);

6-[4-(4-tert-Butyl-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):573.6 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(4-vinyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-2-methyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-2-methyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-4-methyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-4-methyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.4 (M+H);

6-(4-Benzyloxy-3-chloro-phenyl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.1 (M+H);

6-[3-Chloro-4-(4-fluoro-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-fluoro-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(4-Dimethylamino-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):532.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methoxy-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.3 (M+H);

6-[4-(3-Cyano-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):514.4 (M+H);

6-[4-(4-Benzyloxy-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):595.3 (M+H);

6-[4-(3-Benzyloxy-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):595.5 (M+H);

6-[4-(3-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):500.4 (M+H);

6-[4-(4-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(4-Dimethylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):491.0 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hexyloxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):575.5 (M+H);

1-(2,4-Dimethyl-benzyl)-6-{4-[4-(3-methyl-butoxy)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):561.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hexyloxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):575.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-{4-[3-(3-methyl-butoxy)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):561.3 (M+H);

(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-phenoxy)-acetic acid benzyl ester, MS(ES+):639.1 (M+H);

(4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-phenoxy)-acetic acid benzyl ester, MS(ES+):639.2 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(4-phenylamino-phenoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):566.2 (M+H);

6-[4-(4-Benzylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):580.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxymethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):505.1 (M+H);

6-[4-(3-Benzyloxy-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):623.5 (M+H);

6-[4-(4-Benzyloxy-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):623.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(3-Cyano-4-trifluoromethyl-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):576.0 (M+H);

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-methyl-phenoxy}-benzoic acid methyl ester, MS(ES+):547.3 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-methyl-phenoxy}-benzoic acid methyl ester, MS(ES+):547.4 (M+H);

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid, MS(ES+):519.2 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methyl-benzamide,

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide, MS(ES+):546.5 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-{4-[3-(piperidine-1-carbonyl)-phenoxy]-phenyl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):586.1 (M+H);

1-(2,4-Dimethyl-benzyl)-6-{4-[3-(3-hydroxy-piperidine-1-carbonyl)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):602.4 (M+H);

N-Benzyl-3-{4-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzamide, MS(ES+):608.4 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid N'-phenyl-hydrazide, MS(ES+):609.3 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-cyclopentyl-benzamide, MS(ES+):586.3 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methoxy-N-methyl-benzamide, MS(ES+):562.5 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-((S)-1-phenyl-ethyl)-benzamide, MS(ES+):622.4 (M+H);

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide,

3-Benzyloxy-5-{4-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester,

3-Benzyloxy-5-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide, MS(ES+):660.5 (M+H);

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-5-hydroxy-N,N-dimethyl-benzamide, MS(ES+):570.2 (M+H);

2-Benzyloxy-5-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide, MS(ES+):660.3 (M+H);

5-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-2-hydroxy-N,N-dimethyl-benzamide, MS(ES+):570.7 (M+H);

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methyl-benzamide,

N-tert-Butyl-3-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzamide,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(piperidine-1-carbonyl)-phenoxy]-phenyl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-propionic acid methyl ester, MS(ES+):604.3 (M+H);

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-propionic acid methyl ester, MS(ES+):604.1 (M+H);

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-methyl-butyric acid methyl ester, MS(ES+):632.3 (M+H);

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-methyl-butyric acid methyl ester, MS(ES+):632.5 (M+H);

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-4-methyl-pentanoic acid methyl ester, MS(ES+):646.5 (M+H);

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-4-methyl-pentanoic acid methyl ester, MS(ES+):646.4 (M+H);

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-phenyl-propionic acid methyl ester, MS(ES+):680.3 (M+H);

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-phenyl-propionic acid methyl ester, MS(ES+):680.3 (M+H);

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester, MS(ES+):670.1 (M+H);

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester, MS(ES+):670.2 (M+H);

(*S*)-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-phenyl-acetic acid methyl ester, MS(ES+):666.5 (M+H);

(*R*)-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-phenyl-acetic acid methyl ester, MS(ES+):666.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methylsulfanyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):521.1 (M+H);

1-(2,4-Dimethyl-benzyl)-6-{4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):620.2 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-thiobenzamide, MS(ES+):562.4 (M+H);

6-[3-Chloro-4-(4-methanesulfonyl-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):595.4 (M+H);

1-(2,5-Diethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(4'-ethylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):595.6 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-ethanesulfonyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):627.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-methylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):581.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5'-methylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):581.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-methylsulfanyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):581.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5'-methylsulfanyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):581.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):614.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):614.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-(3'-methanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):613.1 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[5'-trifluoromethyl-3'-(2-trimethylsilanyl-ethanesulfonyl)-biphenyl-3-yl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):699.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):627.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):641.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-(4'-ethoxy-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5'-(propane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):625.3 (M+H);

6-[5'-(Butane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-3-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5'-phenylmethanesulfinyl-3'-trifluoromethyl-biphenyl-3-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):673.4 (M+H);

6-(5'-Cyclopropylmethanesulfinyl-3'-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):637.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5'-(propane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):624.9 (M+H);

6-[5'-(Butane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):639.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5'-phenylmethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):673.0 (M+H);

6-(5'-Cyclopropylmethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):637.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5'-ethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):611.1 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfinyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):625.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):641.4 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):641.1 (M+H);

6-[3'-(Butane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):655.2 (M+H);

6-[3'-(Butane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):655.1 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3'-phenylmethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):689.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3'-phenylmethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):689.3 (M+H);

6-(3'-Cyclopropylmethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):653.3 (M+H);

6-(3'-Cyclopropylmethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(5'-isopropyl-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):587.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5'-ethyl-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):573.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-isopropyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):601.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-(3'-methanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):613.1 (M+H);

6-(3'-Acetyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(4'-Acetyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid amide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid amide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid dimethylamide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid dimethylamide,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(pyrrolidine-1-carbonyl)-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4'-(piperidine-1-carbonyl)-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid ethylamide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid methylamide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid phenylamide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid benzylamide,

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-5-isopropyl-biphenyl-3-carboxylic acid methyl ester, MS(ES+):567.3 (M+H);

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-5-isopropyl-biphenyl-3-carboxylic acid methyl ester;

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-yl}-acetic acid, MS(ES+):525.5 (M+H);

{4'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-yl}-acetic acid, MS(ES+):525.4 (M+H);

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid, MS(ES+):525.3 (M+H);

{4'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid, MS(ES+):591.2 (M+H);

{3-Chloro-3'-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid methyl ester, MS(ES+):573.2 (M+H);

{3-Chloro-3'-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid, MS(ES+):559.1 (M+H);

6-(3',5'-Bis-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(3'-Chloro-4'-ethoxy-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(3',4'-dimethoxy-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(3'-Chloro-4'-ethoxy-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-phenylethynyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):491.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenylethynyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):491.1 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3-((E)-styryl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):493.4 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-((E)-styryl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):493.4 (M+H);

6-(3'-Amino-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(4'-ethoxy-3'-nitro-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(3'-Amino-4'-ethoxy-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-4-ethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):487.2 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.2 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):479.1 (M+H);

6-[5-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.1 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(4-methoxy-3-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):549.2 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-4-trifluoromethyl-6-[5-(2,4,5-trimethyl-phenyl)-thiophen-2-yl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):547.4 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(4-methoxy-2-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(3,5-Bis-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):640.9 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-6-(5-o-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.1 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):565.3 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(3,5-dichloro-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(3,5-Dichloro-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-o-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):487.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):533.2 (M+H);

6-[5-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):551.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.3 (M+H);

6-[5-(2-Bromo-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):488.4 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[5-(3-trifluoromethyl-phenyl)-thiophen-2-yl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):541.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3,5-dimethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxy-3,5-dimethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.0 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxymethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):502.9 (M+H);

6-[4-(3,5-Bis-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):571.0 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-phenylethynyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):497.0 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenylethynyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):497.1 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-((E)-styryl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):499.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-((E)-styryl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):499.4 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-phenethyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):501 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-hydroxymethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(4-methoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):570.9 (M+H);

6-[5-(3-Chloro-4-methyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):521.1 (M+H);

6-[5-(3-Chloro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):575.3 (M+H);

6-[4-(3-Chloro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):574.9 (M+H);

6-[4-(3-Chloro-4-methyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):521.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-methoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):571.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.2 (M+H);

6-{5-[3-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):605.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.9 (M+H);

6-[5-(3-Chloro-4-hydroxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):523.2 (M+H);

6-{5-[3-Chloro-4-(2-hydroxy-ethoxy)-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):567.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):585.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-isopropoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):599.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):599.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):545.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-isopropoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-isopropoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.2 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):583.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):551.1 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):565.1 (M+H);

1-(2,4-Difluoro-benzyl)-3-dimethylaminomethyl-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-pyridin-2-one, MS(ES+):583.5 (M+H);

1-(2,4-Dichloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):583.3 (M+H);

N-{1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl}-methanesulfonamide, MS(ES+):633.3 (M+H);

3-Diethylaminomethyl-1-(2,4-difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-pyridin-2-one, MS(ES+):611.4 (M+H);

N-{1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl}-guanidine, MS(ES+):597.5 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):551.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):565.4 (M+H);

6-[5-(3,5-Bis-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):628.9 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):587.5 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):587.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):586.8 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):587.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methyl-3-methylsulfanyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):533.8 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfinyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(5-methanesulfinyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):620.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):619.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):595.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-{5-[3-(Butane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(3-phenylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(3-Cyclopropylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-{4-[3-(Butane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(3-phenylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(3-Cyclopropylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-{5-[3-(Butane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):661.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(3-phenylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):695.1 (M+H);

6-[5-(3-Cyclopropylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-{4-[3-(Butane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(3-Cyclopropylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593.0 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):619.2 (M+H);

6-[5-(3-Ethanesulfonyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):547.3 (M+H);

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):563.2 (M+H);

1-(2-Fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):533.3 (M+H);

1-(2-Chloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(3-Ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):615.0 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):679.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):679.3 (M+H);

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):631.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid, MS(ES+):515.2 (M+H);

1-(2-Chloro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):591.1 (M+H);

1-(2-Fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):533.2 (M+H);

1-(2-Chloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):549.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.3 (M+H);

6-[5-(3-Ethanesulfonyl-phenyl)-thiophen-2-yl]-1-(4-ethyl-2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):575.2 (M+H);

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):561.2 (M+H);

6-[5-(3-Ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(4-ethyl-2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):603.2 (M+H);

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.3 (M+H);

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.3 (M+H);

4-(1,1-Difluoro-propyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):599.2 (M+H);

6-[5-(3-tert-Butyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.2 (M+H);

6-[4-(3-tert-Butyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-{5-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-{5-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):607.5 (M+H);

1-(4-Chloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):579.0 (M+H);

6-[5-(3-Ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):589.3 (M+H);

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):605.4 (M+H);

1-(4-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):605.6 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropyl-phenyl)-acetic acid, MS(ES+):573.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropyl-phenyl)-acetic acid, MS(ES+):573.3 (M+H);

1-(4-Chloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):549.4 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):617.0 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):631.4 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):617.4 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):589.3 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):603.3 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):589.4 (M+H);

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzenesulfonamide, MS(ES+):552.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-formyl-4-methoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

Carbonic acid tert-butyl ester 4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl ester, MS(ES+):589.4 (M+H);

6-[5-(3-Chloro-4-cyano-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.8 (M+H);

6-[5-(3-Cyano-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):547.4 (M+H);

6-[4-(3-Cyano-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):526.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-nitro-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(3-Amino-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenoxy)-acetic acid ethyl ester, MS(ES+):609.2 (M+H);

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenoxy)-acetic acid, MS(ES+):581.3 (M+H);

6-[5-(4-Amino-3-chloro-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):522.2 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester,

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester,

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid methyl ester, MS(ES+):531.2 (M+H);

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid methyl ester, MS(ES+):530.9 (M+H);

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid,

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid,

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropyl-benzoic acid methyl ester, MS(ES+):573.2 (M+H);

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropyl-benzoic acid methyl ester, MS(ES+):573.2 (M+H);

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-thiobenzamide, MS(ES+):562.4 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid,

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid,

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid,

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester, MS(ES+):545.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):545.3 (M+H);

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):545.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropoxy-phenyl)-acetic acid, MS(ES+):589.2 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methoxy-phenyl)-acetic acid methyl ester, MS(ES+):575.4 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methoxy-phenyl)-acetic acid methyl ester,

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropoxy-phenyl)-acetic acid methyl ester, MS(ES+):603.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-fluoro-phenyl)-acetic acid methyl ester, MS(ES+):563.3 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-methoxy-phenyl)-acetic acid methyl ester, MS(ES+):575.1 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropoxy-phenyl)-acetic acid, MS(ES+):589.2 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methoxy-phenyl)-acetic acid, MS(ES+):561.2 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methoxy-phenyl)-acetic acid, MS(ES+):561.3 (M+H);

2-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-2-methyl-propionic acid methyl ester, MS(ES+):573.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-4-fluoro-phenyl)-acetic acid methyl ester, MS(ES+):563.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-methoxy-phenyl)-acetic acid, MS(ES+):561.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-oxo-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester, MS(ES+):611.5 (M+H);

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):579.3 (M+H);

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester, MS(ES+):579.4 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid tert-butyl ester, MS(ES+):587 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-oxo-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester, MS(ES+):583 (M+H);

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-propionic acid methyl ester, MS(ES+):559.1 (M+H);

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-propionic acid methyl ester, MS(ES+):559.2 (M+H);

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-propionic acid methyl ester, MS(ES+):559.1 (M+H);

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-propionic acid methyl ester, MS(ES+):558.7 (M+H);

6-[5-(3,5-Bis-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593 (M+H);

6-[5-(2-Chloro-5-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxy-3-methoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):503.3 (M+H);

6-[4-(3,5-Bis-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):593.2 (M+H);

6-[4-(3-Chloro-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):555.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-4-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-fluoro-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):542.9 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):555.2 (M+H);

6-[4-(3-Chloro-4-methyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):504.8 (M+H);

6-[4-(3-Chloro-4-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.1 (M+H);

6-[5-(3-Chloro-4-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-fluoro-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.4 (M+H);

6-[5-(3-Chloro-4-methyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):504.9 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):569.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-4-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):569.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):569.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropoxy-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):583.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-ethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):529.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-isopropoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):543.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):503.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):549.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):570.9 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):571.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):571.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):571.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methyl-3-methylsulfanyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):604.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):604.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):603.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):603.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):631.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):616.9 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):630.9 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):631.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):630.9 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):577.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):563.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):563 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):591.2 (M+H);

1-(2-Fluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.4 (M+H);

6-[4-(3-tert-Butyl-5-methanesulfonyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):591.2 (M+H);

1-(2-Fluoro-benzyl)-6-[4-(3-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.2 (M+H);

6-[4-(3-Ethanesulfonyl-phenyl)-furan-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-furan-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):591.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-furan-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):591.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.4 (M+H);

6-[4-(3-Chloro-4-cyano-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):516.5 (M+H);

6-[4-(3-Cyano-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):526.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-nitro-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[4-(4-Amino-3-chloro-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):506.2 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester,

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-2-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester,

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropyl-benzoic acid methyl ester, MS(ES+):557.3 (M+H);

6-[4-(3-Amino-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid,

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid,

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropyl-phenyl)-acetic acid, MS(ES+):557.4 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):529.4 (M+H);

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):529.3 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methoxy-phenyl)-acetic acid methyl ester, MS(ES+):559.3 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropoxy-phenyl)-acetic acid, MS(ES+):573.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-4-methoxy-phenyl)-acetic acid methyl ester, MS(ES+):559.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-4-fluoro-phenyl)-acetic acid methyl ester, MS(ES+):547.4 (M+H);

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methoxy-phenyl)-acetic acid, MS(ES+):545.3 (M+H);

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester, MS(ES+):563.2 (M+H);

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-benzyl)-carbamic acid tert-butyl ester, MS(ES+):602.4 (M+H);

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-propionic acid methyl ester, MS(ES+):543.3 (M+H);

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-propionic acid methyl ester, MS(ES+):543.5 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-thiazol-2-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474.2 (M+H);

5-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid ethyl ester,

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):514.4 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(pyrimidin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):477.1 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):477.2 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(4,6-dimethyl-pyrimidin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):505.3 (M+H);

1-(2,4-Dichloro-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):516.9 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):485.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):505.3 (M+H);

6-[4-(3-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):511.2 (M+H);

6-[4-(6-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):511.2 (M+H);

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile, MS(ES+):501.3 (M+H);

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-6-methyl-nicotinonitrile, MS(ES+):515.4 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):544.3 (M+H);

1-(2,4-Dichloro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):554.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):522.1 (M+H);

1-(2-Chloro-4-fluoro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):538.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):491.3 (M+H);

6-[4-(3-Chloro-pyrazin-2-yloxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):525.4 (M+H);

6-[4-(6-Chloro-pyrazin-2-yloxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):525.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.3 (M+H);

6-[4-(3-Chloro-pyrazin-2-yloxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):553.4 (M+H);

6-[4-(6-Chloro-pyrazin-2-yloxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):553.4 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):547.3 (M+H);

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-isopropyl-phenoxy}-6-methyl-nicotinonitrile, MS(ES+):557.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(pyrimidin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):485.1 (M+H);

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-pyrazine-2-carbonitrile, MS(ES+):510.1 (M+H);

2-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-6-methyl-nicotinonitrile, MS(ES+):523.2 (M+H);

2-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile, MS(ES+):509.2 (M+H);

6-[4-(6-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.3 (M+H);

6-[3-Chloro-4-(pyrimidin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.2 (M+H);

6-[3-Chloro-4-(pyrazin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.2 (M+H);

2-{2-Chloro-4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile, MS(ES+):543.3 (M+H);

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-3,5-dimethyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yl)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):506.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[3-(1H-indol-5-yl)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):506.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-pyridin-3-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-pyridin-4-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):552.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(3-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):552.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(6-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):552.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-6-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-4-trifluoromethyl-nicotinic acid methyl ester, MS(ES+):610.1 (M+H);

1-(2,4-Dichloro-benzyl)-6-[4-(1-methyl-1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

5-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid ethyl ester, MS(ES+):586.2 (M+H);

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidin-4-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474.2 (M+H);

4-{3-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, MS(ES+):575.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474.3 (M+H);

4-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, MS(ES+):575.4 (M+H);

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester, MS(ES+):582.3 (M+H);

6-(3-Benzo[1,3]dioxol-5-yl-phenyl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(4-Benzo[1,3]dioxol-5-yl-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[5-(6-methoxy-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):488.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2,4-dimethoxy-pyrimidin-5-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):519.5 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-4-yl-furan-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):458.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):504.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):536.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-nicotinonitrile, MS(ES+):527.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):502.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-isopropoxy-5-trifluoromethyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):584.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):536 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-nicotinic acid ethyl ester, MS(ES+):574.1 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-2-yl}-2-ethoxy-nicotinic acid ethyl ester, MS(ES+):574 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):550.3 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methanesulfonyl-nicotinic acid methyl ester, MS(ES+):594.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropenyl-6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):544.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):542.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropenyl-6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):576.3 (M+H);

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):560.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):532.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):544.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropyl-6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):578.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):564.2 (M+H);

6-[4-(2-Chloro-pyridin-4-yl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):492.2 (M+H);

1-(2-Fluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):532.4 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(6-piperazin-1-yl-pyridin-3-yl)-furan-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):542.4 (M+H);

6-(5-Benzo[1,3]dioxol-5-yl-furan-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):501.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):515.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-3-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-4-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-3-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-4-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-2-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):474.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-methoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):504.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2,4-dimethoxy-pyrimidin-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyrimidin-5-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):475.2 (M+H);

6-[5-(2,6-Bis-trifluoromethyl-pyridin-4-yl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):610.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):586.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):586.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):520.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):552.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-nicotinonitrile, MS(ES+):543.1 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-ethoxy-nicotinonitrile, MS(ES+):543.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):518.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-isopropoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):600.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(1-oxy-pyridin-4-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):490.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-nicotinic acid ethyl ester, MS(ES+):590.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):534.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):534.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):566.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):566.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methylsulfanyl-nicotinic acid methyl ester, MS(ES+):578.3 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methylsulfanyl-nicotinic acid methyl ester, MS(ES+):578.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methanesulfonyl-nicotinic acid methyl ester, MS(ES+):610.2 (M+H);

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methanesulfonyl-nicotinic acid methyl ester, MS(ES+):610.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropenyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):560.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropenyl-6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):592.2 (M+H);

1-(2-Fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):548.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.3 (M+H);

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):576.2 (M+H);

1-(2-Chloro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):564.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-isopropyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):560.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):548.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):560.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropyl-6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):594.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):580.4 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):580.5 (M+H);

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):548.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2-methanesulfonyl-6-trifluoromethyl-pyridin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):620.3 (M+H);

Acetic acid 1-(5-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methanesulfonyl-pyridin-3-yl)-ethyl ester, MS(ES+):638.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2-ethanesulfonyl-6-ethyl-pyridin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):594.2 (M+H);

1-(4-Chloro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):564 (M+H);

1-(2,4-Difluoro-benzyl)-6-{5-[5-(1-hydroxy-ethyl)-6-methanesulfonyl-pyridin-3-yl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):596.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(6-morpholin-4-yl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-[5-(2-Chloro-pyridin-4-yl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):508.1 (M+H);

1-(4-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):563.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(6-piperazin-1-yl-pyridin-3-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(6-piperazin-1-yl-pyridin-3-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):558.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(6-morpholin-4-yl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):559.3 (M+H);

6-(4-Benzo[1,3]dioxol-5-yl-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

6-(5-Benzo[1,3]dioxol-5-yl-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):516.7 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):531.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzofuran-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):515.3 (M+H);

1-(2,4-Difluoro-benzyl)-6-[4-(2,3-dihydro-benzofuran-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[5-(4-methyl-naphthalen-1-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile,

1-(2,4-Difluoro-benzyl)-6-(5-naphthalen-2-yl-thiophen-2-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):523.2 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5-naphthalen-1-yl-thiophen-2-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):523.3 (M+H);

6-(1-Benzyl-1H-pyrazol-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):471.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(1-phenyl-1H-pyrazol-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):456.8 (M+H);

1-(2,4-Difluoro-benzyl)-6-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):485.2 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-6-(1-phenyl-5-trifluoromethyl-1H-pyrazol-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):525.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):471.2 (M+H);

1-(2,4-Dichloro-benzyl)-6-[1-benzyl-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[1-(4-methoxy-benzyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):501.3 (M+H);

6-[1-(3-Cyano-4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):550.1 (M+H);

6-[1-(3-Chloro-4-cyano-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):516.1 (M+H);

6-[1-(3-Chloro-4-ethoxy-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535.1 (M+H);

1-(2,4-Difluoro-benzyl)-6-[1-(4-methanesulfonyl-phenyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):535 (M+H);

1-(2,4-Difluoro-benzyl)-6-[1-(3,4-dimethoxy-phenyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):517.1 (M+H);

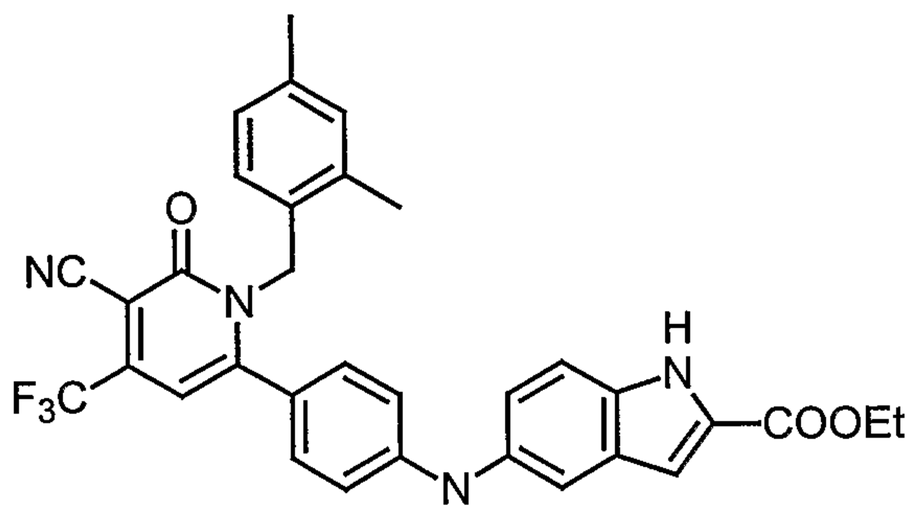
6-[1-(4-Cyano-3-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):550.3 (M+H);

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(6-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):526.3 (M+H); and

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(5-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile, MS(ES+):526.3 (M+H).

EXAMPLE 7

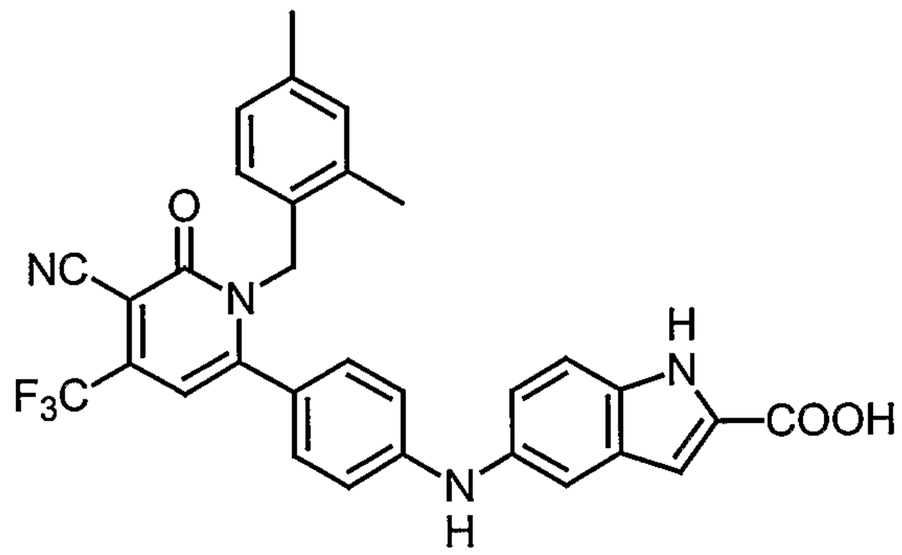
Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylate



1-(2,4-Dimethyl-benzyl)-2-oxo-6-p-tolyl-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (100 mg, 0.22 mmol) was mixed with 5-amino-1H-indole-2-carboxylic acid ethyl ester (44 mg, 0.22 mmol), palladium acetate (5 mg, 0.022 mmol), 2-Di-t-butylphosphino-2'-methyl-biphenyl (10 mg, 0.034 mmol) and K_3PO_4 (92 mg, 0.43 mmol) in PhMe (2 mL). The mixture was stirred at 100 ° C under N_2 for 12 h. PhMe was then removed under reduced pressure. The crude product was loaded on a silica gel column and flashed with EtOAc/hexanes (gradient 10%-95%). Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylate was obtained as a red solid (75 mg, 60%). ^1H NMR (400 MHz, d_6-DMSO) δ 9.05 (s, 1 H), 7.47 (br s, 1 H), 7.41 (d, 1 H), 7.14 (m, 2 H), 7.05 (d, 2 H), 6.95 (m, 2 H), 6.81 (d, 2 H), 6.63 (d, 1 H), 6.48 (s, 1 H), 6.00 (s, 1 H), 5.20 (s, 2 H), 4.40 (q, 2 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 1.42 (t, 3 H); MS (ESI+) for $C_{33}H_{27}F_3N_4O_3$: 585 (M+H).

EXAMPLE 8

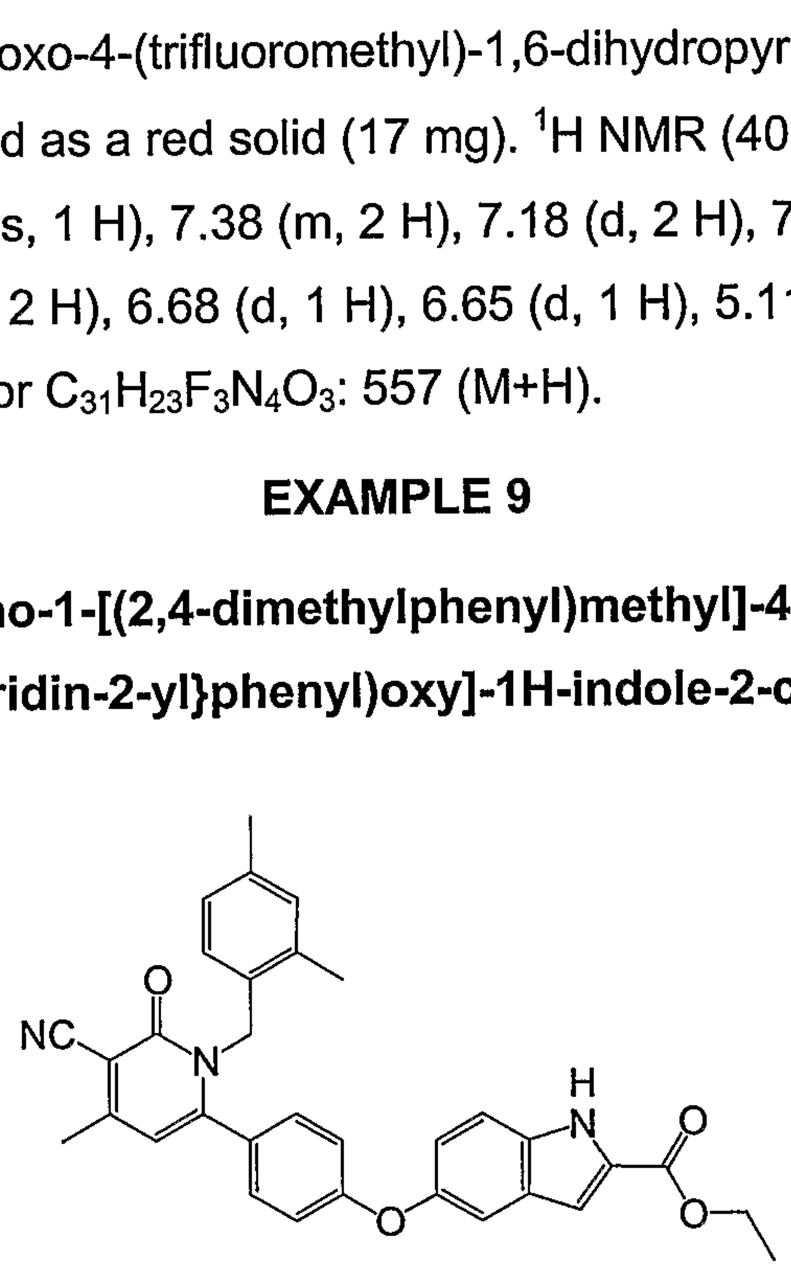
5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylic acid



To a solution of ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylate (60 mg, 0.10 mmol) in THF (2 mL) was added LiOH monohydrate (10 mg, 0.21 mmol) and H_2O (2 mL). The stirring was continued for 12 h at RT. EtOAc was added to the reaction mixture. The organic layer was washed with H_2O and brine. After removal of the organic solvents, the crude product was purified by HPLC, yielding 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylic acid as a red solid (17 mg). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.71 (br s, 1 H), 8.50 (br s, 1 H), 7.38 (m, 2 H), 7.18 (d, 2 H), 7.04 (m, 1 H), 6.98 (m, 2 H), 6.92 (m, 1 H), 6.85 (d, 2 H), 6.68 (d, 1 H), 6.65 (d, 1 H), 5.11 (s, 2 H), 2.21 (s, 3 H), 2.06 (s, 3 H); MS (ESI+) for $C_{31}H_{23}F_3N_4O_3$: 557 (M+H).

EXAMPLE 9

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-4-methyl-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

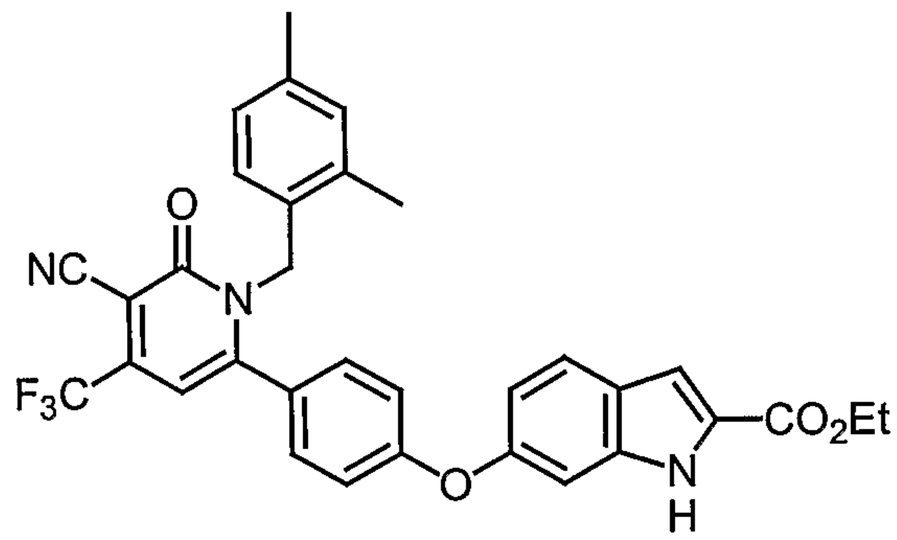


6-(4-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (183 mg, 0.45 mmol), 5-hydroxy-1H-indole-2-carboxylic acid ethyl

ester (212 mg, 1.03 mmol), toluene (4.0mls), K_3PO_4 (204mgs, 0.96mmols), racemic-2-(di-t-butylphospino)-1,1'-binaphthyl (35mgs), and palladium acetate (19mgs) were combined and heated at 115°C overnight. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc and washed with H_2O (2x), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (silica gel, 9:1 hexanes:EtOAc, followed by 8:2 hexanes:EtOAc, followed by 7:3 hexanes:EtOAc, followed by 1:1 hexanes:EtOAc) to give ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-4-methyl-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (27mgs, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.44 (d, 1H), 7.33 (d, 1H), 7.18 (m, 1H), 7.04 (m, 3H), 6.88 (m, 4H), 6.62 (d, 1H), 6.12 (s, 1H), 5.16 (s, 2H), 4.42 (q, 2H), 2.49 (s, 3H), 2.26 (s, 3H), 1.98 (s, 3H), 1.42 (t, 3H). MS (ESI+) for $C_{33}H_{29}N_3O_4$: 532.3 (M+H).

EXAMPLE 10

Ethyl 6-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

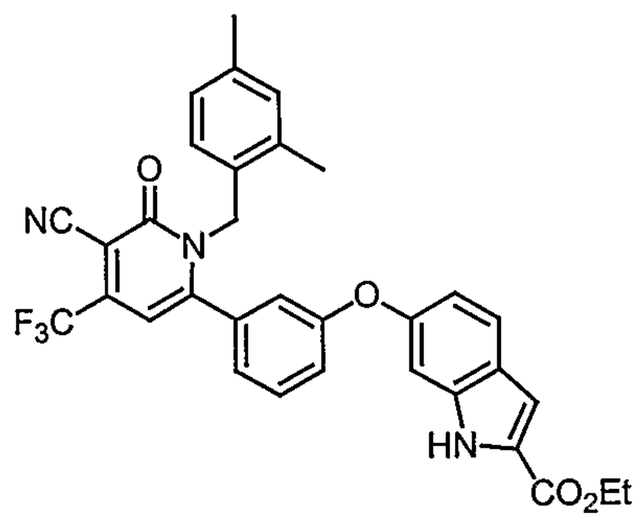


A mixture containing 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (95.4 mg, 0.207 mmol), 6-hydroxy-1H-indole-2-carboxylic acid ethyl ester (42.0 mg, 0.205 mmol) and potassium phosphate (88 mg, 0.41 mmol) in toluene (2.5 mL) was sparged with N_2 in a sealed tube. $Pd(OAc)_2$ (8.0 mg, 0.035 mmol) and 2-(Di-tertbutylphosphino) biphenyl (8.2 mg, 0.021 mmol) were added and the mixture was heated to 110°C for 36 hours. After allowing to cool to room temperature, the reaction mixture was diluted with EtOAc and washed with water, 1N HCl, 10% $NaCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solids were impregnated on silica gel and purified by flash chromatography (1:4 EtOAc:Hexanes), followed by further purification by prep HPLC, affording ethyl 6-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (6.9 mg, 5.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.88 (s, 1H), 7.68 (d, 1H), 7.23 (m, 1H), 7.11 (m, 3H), 6.95 (m, 4H), 6.87 (m, 1H), 6.60 (d, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 4.41 (q, 2H), 2.27 (s, 3H), 2.03 (s, 3H), 1.42 (t, 3H). MS (ESI-) for $C_{33}H_{26}F_3N_3O_4$: 584 (M-H).

EXAMPLE 11

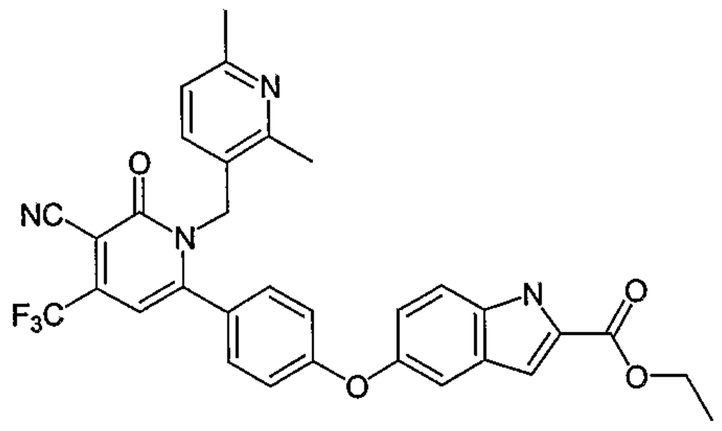
Ethyl 6-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate



A mixture containing 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (111 mg, 0.241 mmol), 6-hydroxy-1H-indole-2-carboxylic acid ethyl ester (52.9 mg, 0.258 mmol) and potassium phosphate (102 mg, 0.480 mmol) in toluene (2.5 mL) was sparged with N_2 in a sealed tube. $Pd(OAc)_2$ (8.5 mg, 0.038 mmol) and 2-(di-tertbutylphosphino) biphenyl (13.9 mg, 0.0349 mmol) were added and the mixture was heated to 110°C for 20 hours. After allowing to cool to room temperature, the reaction mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by prep HPLC (TFA system) yielded ethyl 6-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate as a solid (37.1 mg, 26.3% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.60 (d, 1H), 7.34 (t, 1H), 7.24 (m, 1H), 7.12 (m, 1H), 6.84 (m, 4H), 6.73 (m, 2H), 6.51 (d, 1H), 6.44 (s, 1H), 5.12 (s, 2H), 4.41 (q, 2H), 2.27 (s, 3H), 2.00 (s, 3H), 1.42 (t, 3H). MS (ESI-) for $C_{33}H_{26}F_3N_3O_4$: 584 (M-H).

EXAMPLE 12

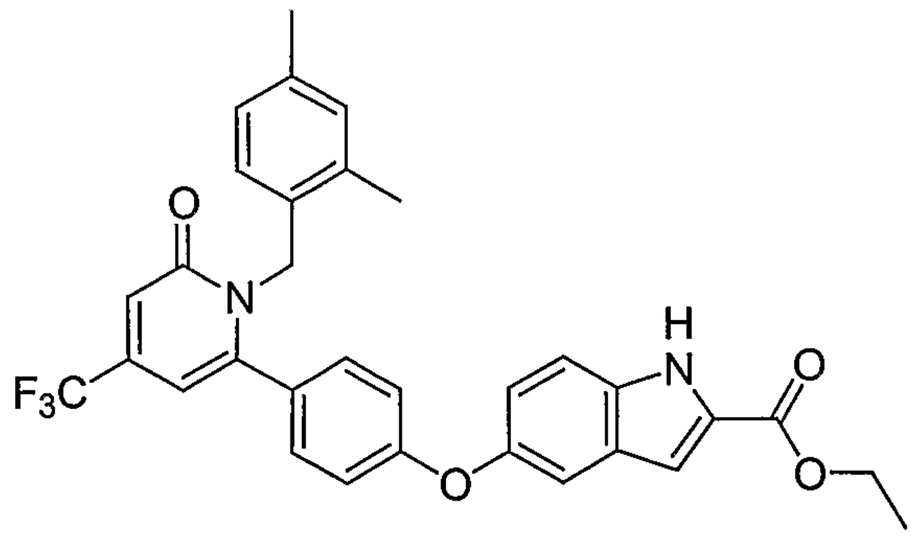
Ethyl 5-[(4-{5-cyano-1-[(2,6-dimethylpyridin-3-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate



In a seal tube was added 6-(4-bromo-phenyl)-1-(2,6-dimethyl-pyridin-3-ylmethyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (100 mg, 0.216 mmol), 5-hydroxy-1H-indole-2-carboxylic acid ethyl ester (49 mg, 0.238 mmol), Pd(II) acetate (7 mg, 0.022 mmol), racemic-2-(di-t-butylphosphino)-1,1'-binaphtyl (17 mg, 0.043 mmol), K_3PO_4 (92 mg, 0.432 mmol) and anhydrous toluene (2 mL). The mixture was heated at 115°C for 16 hours. The crude reaction mixture was diluted with ethyl acetate and acetonitrile, filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography with 50:50 EtOAc/hexanes to give ethyl 5-[(4-{5-cyano-1-[(2,6-dimethylpyridin-3-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (5.4 mg, 4.3%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.02 (s, 1H), 7.51 (d, 1H), 7.34 (m, 3H), 7.15 (m, 2H), 6.90 (m, 4H), 5.10 (s, 2H), 4.35 (q, 2H), 2.37 (s, 3H), 2.19 (s, 3H), 1.34 (t, 3H). MS (ESI+) for $C_{32}H_{25}F_3N_4O_4$: 587 (M+H).

EXAMPLE 13

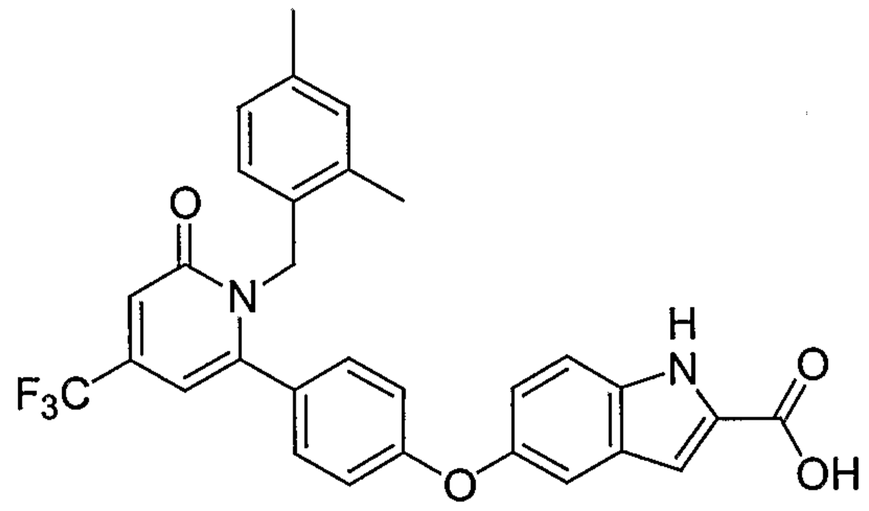
Ethyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate



6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-4-trifluoromethyl-1H-pyridin-2-one (179mgs, 0.41mmol), 5-hydroxy-1H-indole-2-carboxylic acid ethyl ester (103mgs, 0.50mmol), toluene (2.0mls), K_3PO_4 (170mgs, 0.80mmols), racemic-2-(Di-t-butylphospino)-1,1'-binaphthyl (20mgs), and palladium acetate (12mgs) were combined and heated at 115C overnight. The reaction mixture was concentrated in vacuo, redissolved in MeOH and insoluble material filtered. The filtrate was concentrated in vacuo and the resulting residue purified by flash chromatography (silica gel, 7:3 hexanes:EtOAc), followed by prep HPLC to give ethyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (12mgs, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.43 (d, 1H), 7.33 (d, 1H), 7.18 (m, 1H), 7.06 (m, 3H), 6.92 (m, 3H), 6.87 (d, 2H), 6.63 (d, 1H), 6.28 (d, 1H), 5.17 (s, 2H), 4.42 (q, 2H), 2.26 (s, 3H), 1.98 (s, 3H), 1.42 (t, 3H). MS (ESI+) for $C_{32}H_{27}F_3N_2O_4$: 561.3 (M+H).

EXAMPLE 14

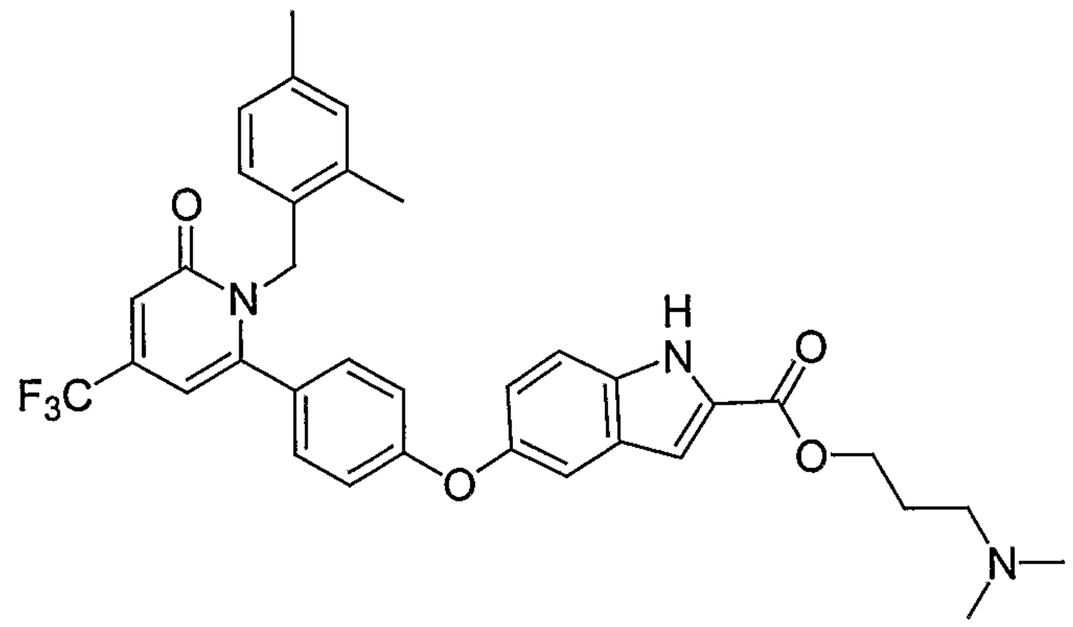
5-{4-[1-(2,4-Dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid



5-{4-[1-(2,4-Dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid. 5-{4-[1-(2,4-Dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid ethyl ester (80mgs, 0.14mmol) was dissolved in EtOH (2.0mls) and THF (2.0mls) to which was added 2M LiOH (1mls). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with H_2O, acidified with 1N HCl to pH 2-3 and extracted with EtOAc (3x). The combined EtOAc extractions were washed with saturated NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo to give 5-{4-[1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid (70mgs, 92%), which was used without further purification. MS (ESI-) for $C_{30}H_{23}F_3N_2O_4$: 531.2 (M-H).

EXAMPLE 15

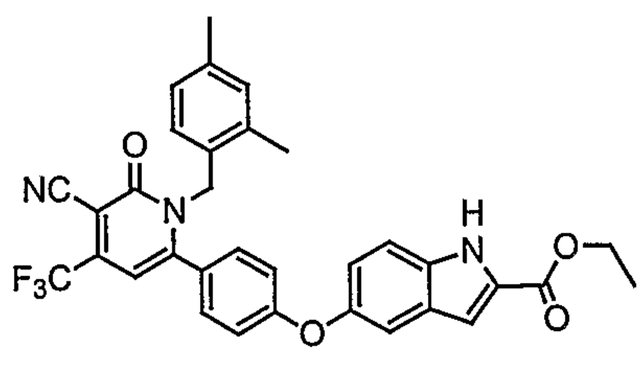
3-(Dimethylamino)propyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate



3-(Dimethylamino)propyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. 5-{4-[1-(2,4-Dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid (70mgs, 0.13mmol), CH_2Cl_2 (2.0mls), DMF (2 drops), and oxalyl chloride (35μl, 0.40mmol) were combined and stirred at room temperature for 3hrs. The reaction mixture was concentrated in vacuo and redissolved in CH_2Cl_2 (1.0mls) to which was added 3-dimethylamino-propan-1-ol (200μl). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and immediately purified by prep HPLC to give 3-(dimethylamino)propyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (30mgs, 37%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.01 (s, 1H), 7.51 (d, 1H), 7.33 (d, 1H), 7.24 (d, 2H), 7.13 (m, 1H), 6.93 (m, 2H), 6.88 (d, 2H), 6.52 (d, 1H), 6.42 (d, 1H), 5.01 (s, 2H), 4.32 (t, 2H), 2.35 (t, 2H), 2.20 (s, 3H), 2.14 (s, 6H), 1.98 (s, 3H), 1.85 (m, 2H). MS (ESI+) for $C_{35}H_{34}F_3N_3O_4$: 618.3 (M+H).

EXAMPLE 16

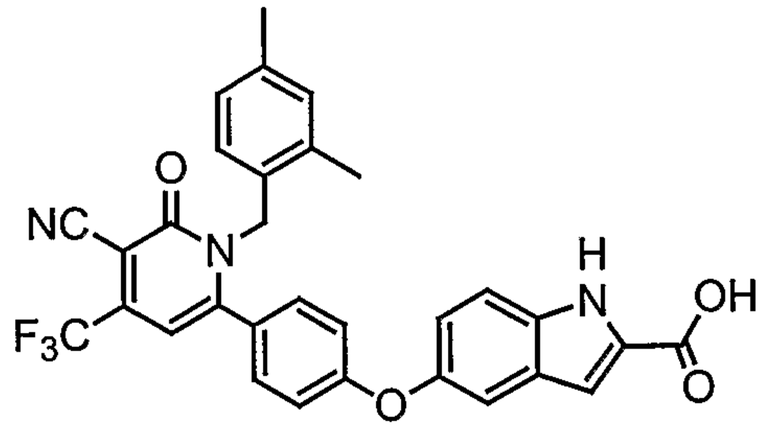
Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate



To a mixture of 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (1.26 g, 2.72 mmol), 5-hydroxy-1H-indole-2-carboxylic acid ethyl ester (0.44 g, 2.1 mmol) and potassium phosphate (1.11 g, 5.2 mmol) in toluene (10 mL) was added $Pd(OAc)_2$ (0.07 g, 0.24 mmol), followed by 2-(di-tertbutylphosphino) biphenyl (0.208 g, 0.52 mmol). After purged with N_2, the mixture was heated in a sealed tube at 110°C for 24 hours. After removal of solvent, the residue was dissolved in ethanol, and stirred for 10 minutes, then filtered. The filtrate was collected and concentrated in vacuo to dryness. The crude solid was impregnated on silica gel and purified by flash chromatography (1:4 EtOAc : hexanes). The obtained product was washed with aq. NaOH solution (2 x) to remove the trace amount of the starting hydroxyindole, affording ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate as a yellow solid (0.644g, 51% yield). MS (ESI-) for $C_{33}H_{26}F_3N_3O_4$: 584 (M-H).

EXAMPLE 17

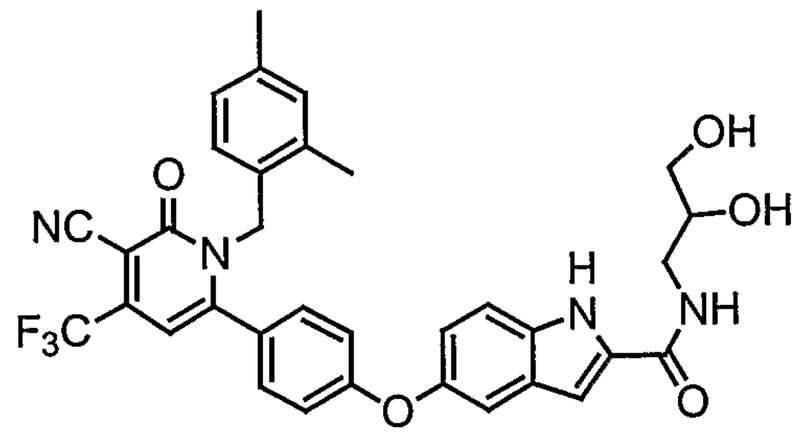
5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid



To a solution of ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate (130 mg, 0.22 mmol) in THF (2 mL) and ethanol (2 mL) was added 0.5 ml of a 2N LiOH solution. The resulting solution was stirred at RT for 14 hours. After removal of the organic solvents in vacuo, the remaining aqueous solution was adjusted to pH 2 using a 1N HCl solution. The product was then extracted using EtOAc (2 x). The combined organic layer was washed twice with brine, and dried (Na_2SO_4), and concentrated in vacuo to yield 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid as a pale yellow solid (130 mg, 92% yield). MS (ESI-) for $C_{31}H_{22}F_3N_3O_4$: 556 (M-H).

EXAMPLE 18

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2,3-dihydroxypropyl)-1H-indole-2-carboxamide

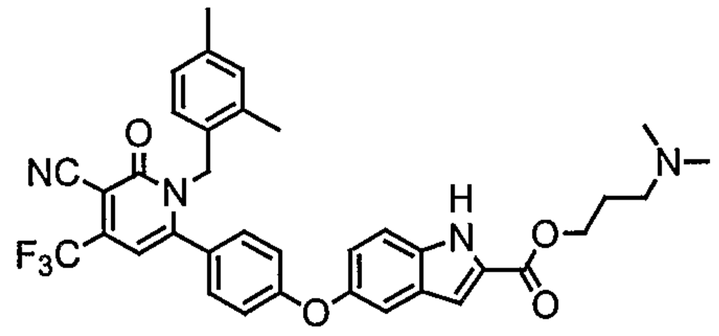


A. 5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2,3-dihydroxypropyl)-1H-indole-2-carboxamide. To a solution of 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid (56 mg, 0.1 mmol) and DCM (3 mL) was added EDCI (48mg, 0.25 mmol), HOBt (40 mg, 0.29 mmol) and TEA (0.041 ml, 0.3 mmol). After stirring for 15 minutes C-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methylamine (14.4 mg, 0.11 mmol) was added and the reaction mixture was stirred overnight. After the reaction is complete, the reaction mixture was diluted with EtOAc, washed sequentially with water, 1N aq. HCl, aq. $NaHCO_3$ and brine, and then dried over Na_2SO_4. After removal of solvent in vacuo, 5-{4-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid (2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-amide was obtained (50 mg, 75% yield). MS (ESI+) for $C_{37}H_{33}F_3N_4O_5$: 671 (M+H).

B. 5-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid (2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-amide (50 mg) was dissolved in THF (2 ml) after which a 1N HCl solution (0.1 ml) was added. Deprotection was complete in 3 hours and further purification by prep HPLC yielded a yellow 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2,3-dihydroxypropyl)-1H-indole-2-carboxamide ass a solid. (40 mg, 85% yield). ^1H NMR (400 MHz, d_6-DMSO) δ 11.73 (s, 1H), 8.47 (t, 1H), 7.48 (d, 1H), 7.34 (d, 3H), 7.14 (s, 1H), 6.94 (m, 5H), 6.76 (s, 1H), 6.68 (d, 1H), 5.07 (s, 2H), 4.87 (d, 1H), 4.61 (t, 1H), 3.65 (m, 1H), 3.47 (m, 2H), 3.18 (m, 2H), 2.21 (s, 3H), 2.02 (s, 3H). MS (ESI+) for $C_{34}H_{29}F_3N_4O_5$: 631 (M+H).

EXAMPLE 19

3-(Dimethylamino)propyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate hydrochloride

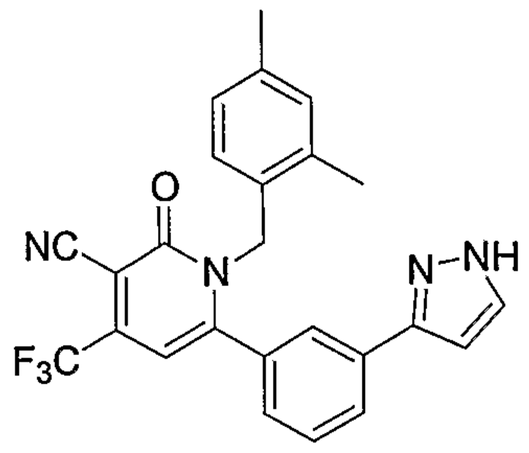


A. To a solution of 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid (400 mg, 0.70 mmol) in dry DCM (2 ml) and THF (1 ml) was added oxalyl chloride (0.7 ml, 0.7 mmol). The reaction was stirred at RT for two hours and was concentrated in vacuum to dryness. The acid chloride was obtained as a brownish solid in quantitative yield, and was used directly in the next reaction. MS (ESI) for $C_{31}H_{21}F_3N_3O_3$: 574 (M-H).

B. The acid chloride obtained above (400 mg, 0.69 mmol) was dissolved in dry DCM (2 ml) after which excess 3-dimethylamino-propan-1-ol was added. The reaction was complete in 10 minutes upon which the DCM was removed in vacuo. The crude was purified by prep HPLC to yield 3-(dimethylamino)propyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate as a yellow solid. Treatment of the product in MeCN with 1 equivalent of 1N HCl, followed by drying in high vacuum afforded 3-(dimethylamino)propyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate hydrochloride as a light yellow solid (0.277 g, 62% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.12 (s, 1H), 10.13 (bs, 1H), 7.55 (d, 1H), 7.36 (m, 3H), 7.33 (s, 1H), 6.95 (m, 4H), 6.75 (s, 1H), 6.69 (d, 1H), 5.07 (s, 2H), 4.37 (t, 2H), 3.22 (m, 2H), 2.51 (s, 6H), 2.21 (s, 3H), 2.15 (m, 2H), 2.01 (s, 3H). MS (ESI-) for $C_{36}H_{33}F_3N_4O_4$: 641 (M-H).

EXAMPLE 20

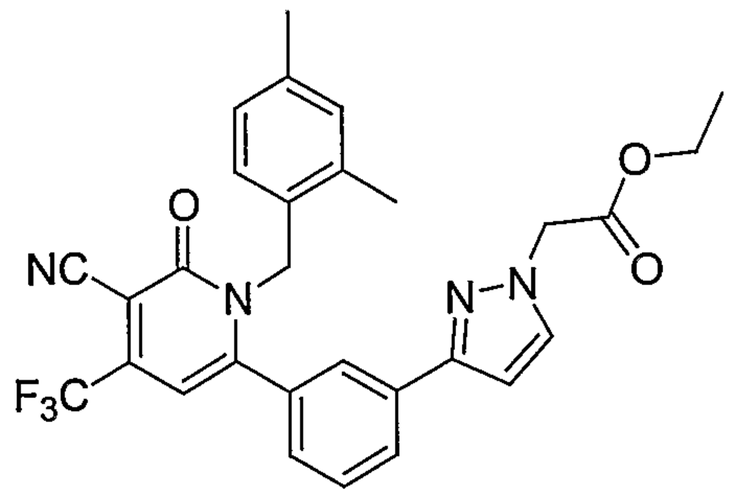
1-[(2,4-Dimethylphenyl)methyl]-2-oxo-6-[3-(1H-pyrazol-4-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



6-(3-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (535 mg, 1.16 mmol), K_2CO_3 (798 mg, 5.78 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazole-1-carboxylic acid tert-butyl ester (423 mg, 1.51 mmol), tetrakis(triphenylphosphine)palladium (169 mg, 0.14 mmol), DME (25.0ml), and H_2O (7.5 ml) were combined in a sealed tube under N_2 and heated to 80C for 2hrs. The reaction mixture was diluted with EtOAc and washed with H_2O (2x), saturated NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude material was purified by flash chromatography (silica gel, 4:1 hexanes:EtOAc, followed by 1:1 hexanes:EtOAc) to give both 4-{3-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-pyrazole-1-carboxylic acid tert-butyl ester (173 mg, 27%) and 1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-[3-(1H-pyrazol-4-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (301 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 10.2 (br s, 1H), 7.62 (d, 1H), 7.54 (s, 2H), 7.42 (t, 1H), 7.10 (m, 2H), 7.02 (d, 1H), 6.88 (s, 1H), 6.72 (d, 1H), 6.49 (s, 1H), 5.21 (br s, 2H), 2.30 (s, 3H), 1.77 (s, 3H). MS (ESI+) for $C_{25}H_{19}F_3N_4O$: 449.2 (M+H).

EXAMPLE 21

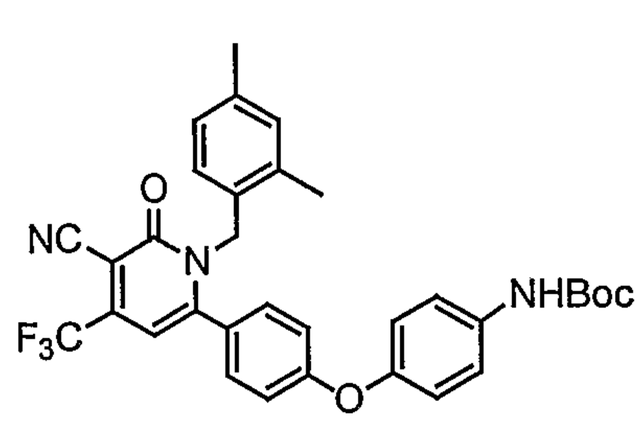
Ethyl [4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazol-1-yl]acetate



1-[(2,4-Dimethylphenyl)methyl]-2-oxo-6-[3-(1H-pyrazol-4-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (74 mg, 0.16 mmol), K_2CO_3 (84 mg, 0.61 mmol), ethyl bromoacetate (25μl, 0.22mmol) were combined in dry DMF (1.0 ml) and heated at 80°C overnight. The reaction mixture was allowed to cool to room temperature, diluted with H_2O and extracted with EtOAc (3x). The combined EtOAc extractions were washed with saturated NaCl (1x), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by flash chromatography (silica gel, 20% EtOAc in hexanes, followed by 50% EtOAc in hexanes) to give ethyl [4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazol-1-yl]acetate (32 mg, 36%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.51 (s, 1H), 7.41 (t, 1H), 7.33 (s, 1H), 7.08 (m, 2H), 7.02 (d, 1H), 6.90 (s, 1H), 6.72 (d, 1H), 6.49 (s, 1H), 5.20 (br s, 2H), 4.89 (s, 2H), 4.28 (q, 2H), 2.30 (s, 3H), 1.88 (s, 3H), 1.32 (t, 3H). MS (ESI+) for $C_{29}H_{25}F_3N_4O_3$: 535.3 (M+H).

EXAMPLE 22

1,1-Dimethylethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate

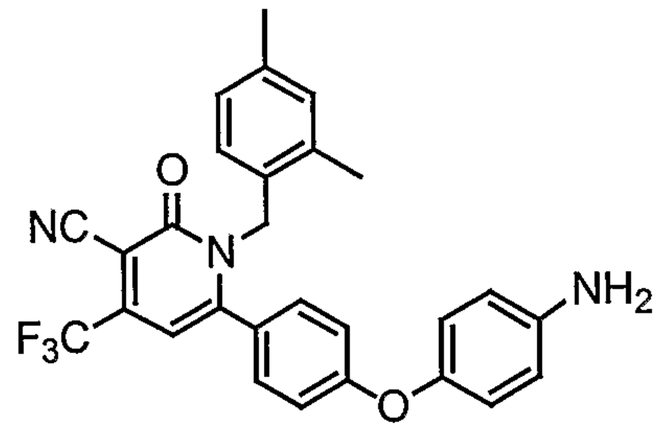


To a N_2-sparged mixture of (4-hydroxy-phenyl)-carbamic acid tert-butyl ester (1.20 g, 2.5 mmol), 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-

trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.54 g, 2.6 mmol) and potassium phosphate (1.11g, 5.2 mmol) in toluene (10 mL) $Pd(OAc)_2$ (0.07 g, 0.24 mmol), followed by 2-(di-tertbutylphosphino) biphenyl (0.208 g, 0.52 mmol). The resulting mixture was heated in a sealed tube to 110°C for 36 hours. Ahter removal of solvent in vacuo the residue was dissolved in ethanol. After stirring in ethanol for 10 minutes the solids were filtered away and the filtrate was collected and concentrated to dryness. The crude solids were impregnated on silica gel and purified by flash chromatography (1:4 EtOAc:hexanes) to yield 1,1-dimethylethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate as a yellow solid (1.05g, 70% yield). MS (ESI-) for $C_{33}H_{30}F_3N_3O_4$: 588 (M-H).

EXAMPLE 23

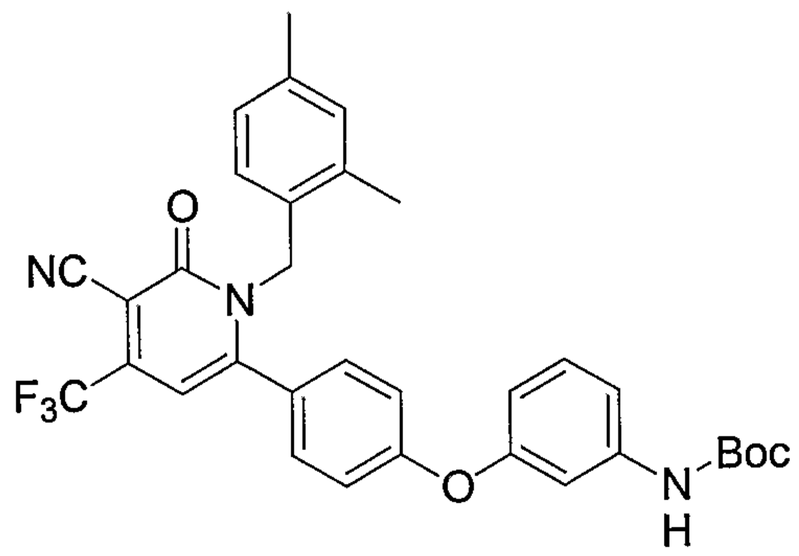
6-{4-[(4-Aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile hydrochloride



1,1-Dimethylethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate (1.02g, 1.73 mmol) was treated with 4M HCl/dioxane (15ml). After 10 hours the reactions was complete. After removal of solvent in vacuum the product was obtained as a cream solid (0.946g, 85%). ^1H NMR (400 MHz, d_6-DMSO) δ 7.53 (d, 2H), 7.16 (d, 2H), 7.14 (d, 2H), 6.96 (m, 4H), 6.61 (m, 1H), 6.45 (s, 1H), 5.13 (s, 2H), 3.68 (s, 1H), 2.29 (s, 3H), 2.10 (s, 3H). MS (ESI+) for $C_{28}H_{22}F_3N_3O_2$: 490 (M+H).

EXAMPLE 24

1,1-Dimethylethyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate

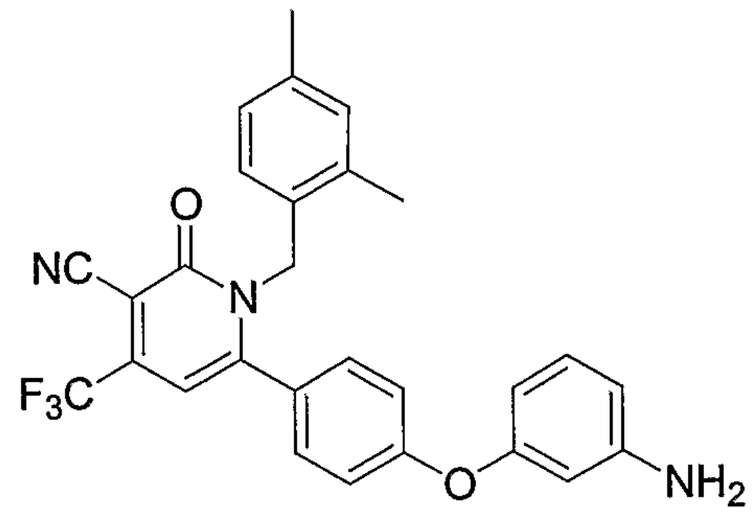


A. A solution containing 3-amino-phenol (5.0 g, 45.8 mmol) in dichloromethane (60 mL) was added DMAP (0.36 g, 2.95 mmol), triethylamine (8.11 g, 80.1 mmol) and Boc-anhydride (12.0 g, 55.0 mmol), then stirred at room temperature for 16 hours. After the reaction was complete, it was partitioned with dichloromethane and 1N HCl. The aqueous layer was found to contain pure product where the organic layer contained impurities. The aqueous layer was then basified with NaOH and re-extracted with EtOAc, washed with water, brine, dried with Na_2SO_4, filtered and concentrated in vacuo to yield (3-hydroxy-phenyl)-carbamic acid tert-butyl ester (0.931 g, 9.7%).

B. In a seal tube was added 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (1.157 g, 2.51 mmol), (3-hydroxy-phenyl)-carbamic acid tert-butyl ester (0.577 g, 2.76 mmol), Pd(II) acetate (0.056 g, 0.249 mmol), racemic-2-(di-t-butylphosphino)-1,1'-binaphtyl (0.200 g, 0.502 mmol), K_3PO_4 (1.065 g, 5.02 mmol) and anhydrous toluene (15 mL). The mixture was heated in the sealed tube at 105°C for 60 hours. The crude reaction mixture was diluted with ethyl acetate and acetonitrile, filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography with 20:80 EtOAc/hexanes to give 1,1-dimethylethyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate (1.241 g, 83.9%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.82 (s, 1H), 7.27 (m, 3H), 7.03 (m, 3H), 6.92 (m, 3H), 6.74 (s, 1H), 6.69 (m, 2H), 5.12 (s, 2H), 2.23 (s, 3H), 2.04 (s, 3H).

EXAMPLE 25

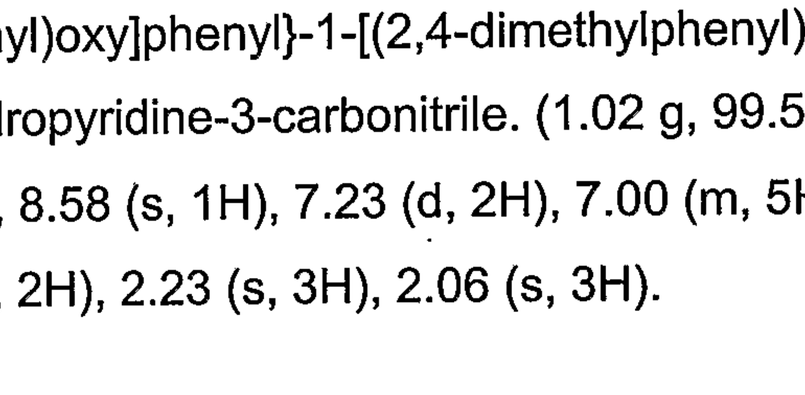
6-{4-[(3-Aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



A solution of 4M HCl in dioxane (10 mL) was slowly added to 1,1-dimethylethyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate (1.241 g, 2.10 mmol), and the mixture was stirred at room temperature for 16 hours. Upon completion, dioxane was removed in vacuo and the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ (x2), water, brine, dried with Na_2SO_4, filtered and concentrated in vacuo to afford 6-{4-[(3-aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. (1.02 g, 99.5%). ^1H NMR (400 MHz, d_6-DMSO) δ 9.37 (s, 1H), 8.58 (s, 1H), 7.23 (d, 2H), 7.00 (m, 5H), 6.68 (m, 2H), 6.55 (m, 2H), 6.35 (d, 1H), 5.12 (s, 2H), 2.23 (s, 3H), 2.06 (s, 3H).

EXAMPLE 26

3-Morpholin-4-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate

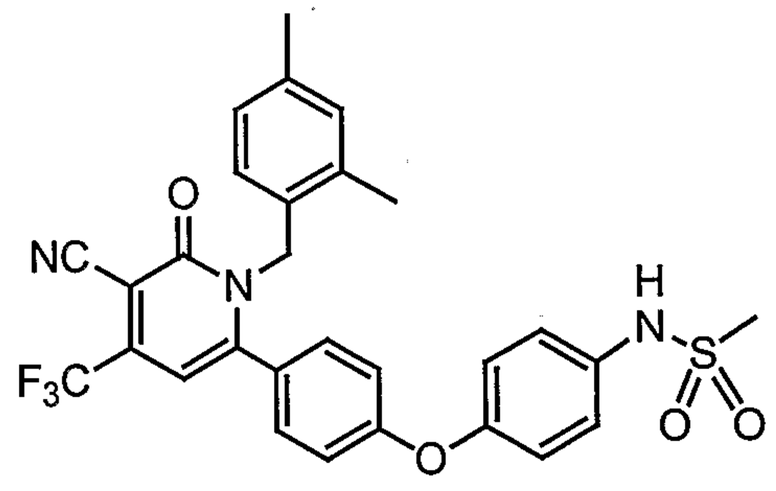


To a solution of 6-{4-[(3-Aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (1.0 g, 2.04 mmol) in anhydrous dichloromethane (40 mL) was added triphosgene (2.69 g, 8.17 mmol) slowly. The reaction mixture was stirred at room temperature for 16 hours. The

crude product 1-(2,4-Dimethyl-benzyl)-6-[4-(3-isocyanato-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile was carried on next step without further workup, and was divided up into 6 equal portions by volume. To one portion of this reaction mixture in a vial was added excess 3-morpholin-4-yl-propan-1-ol (0.5 mL) and DMAP (250 mg). The reaction was stirred at 30°C for 16 hours, and the crude product was purified by prep HPLC to yield 3-morpholin-4-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate (72.6 mg, 32.3%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.84 (s, 1H), 7.29 (m, 3H), 7.03 (m, 3H), 6.94 (m, 3H), 6.73 (m, 3H), 5.12 (s, 2H), 4.23 (t, 2H), 3.56 (t, 4H), 2.36 (m, 6H), 2.23 (s, 3H), 2.04 (s, 3H), 1.83 (m, 2H). MS (ESI) for $C_{36}H_{35}F_3N_4O_5$: 661.4 (M+H).

EXAMPLE 27

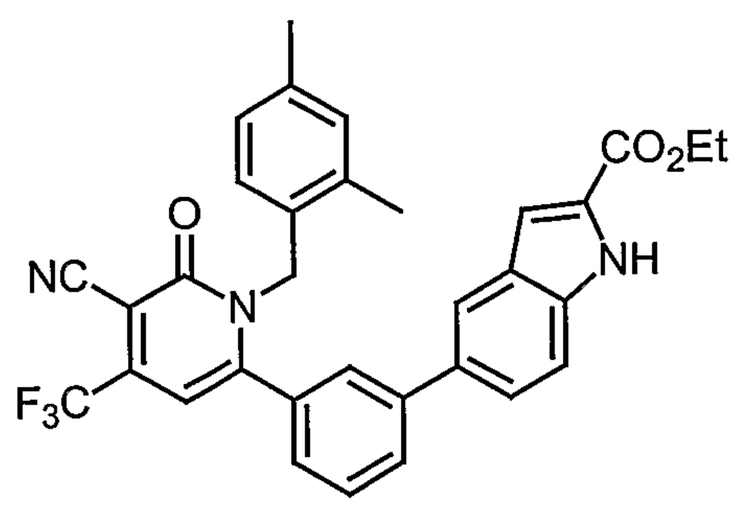
N-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}methanesulfonamide



To a solution of 6-{4-[(4-aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile hydrochloride (0.06 g, 0.13 mmol), TEA (0.05 ml, 0.39 mmol) and DCM (2 ml) was added methanesulfonyl chloride (0.015g, 0.14 mmol). The solution was stirred at RT for 20 min. After removal of solvent in vacuo, the crude product was purified by prep HPLC to yield N-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}methanesulfonamide as a yellow solid (0.028 g, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (bs, 1H), 7.37 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.96 (d, 2H), 6.92 (m, 2H), 6.76 (s, 1H), 6.67 (d, 1H), 5.07 (s, 2H), 2.98 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H). MS (ESI-) for $C_{29}H_{24}F_3N_3O_4S$: 566 (M-H).

EXAMPLE 28

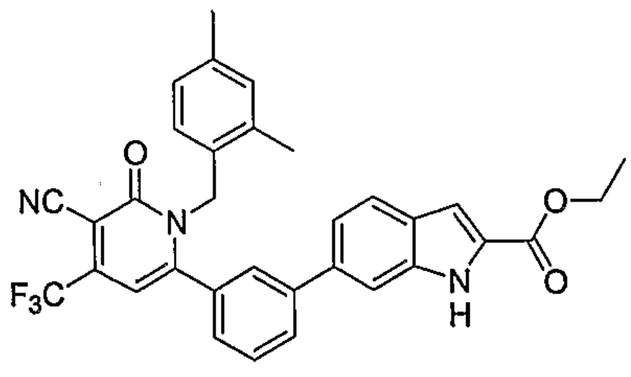
Ethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate



A solution containing 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (111 mg, 0.241 mmol), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester (76 mg, 0.241 mmol) and K_2CO_3 (166 mg, 1.20 mmol) in 1,2-Dimethoxyethane (5 mL) and water (1.5 mL) was inerted with N_2 and $Pd(PPh_3)_4$ (35.2 mg, 0.0305 mmol) was then added. The resulting mixture was heated to 80°C for 15 hours, then allowed to cool to room temperature before concentrating *in vacuo*. The resulting solids were partitioned between EtOAc and water. The organic phase was washed with $NaHCO_3$ (satd.) and brine, then dried over Na_2SO_4. The crude solids were impregnated on silica gel and purified by flash chromatography (silica gel, 1:4 EtOAc:Hexanes) to give ethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate as a yellow solid (85.2 mg, 62.2 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.74 (d, 1H), 7.48 (m, 3H), 7.20 (m, 4H), 7.01 (d, 1H), 6.90 (s, 1H), 6.71 (d, 1H), 6.52 (s, 1H), 5.17 (s, 2H), 4.44 (q, 2H), 2.31 (s, 3H), 1.90 (s, 3H), 1.44 (t, 3H). MS (ESI-) for $C_{33}H_{26}F_3N_3O_3$: 568 (M-H).

EXAMPLE 29

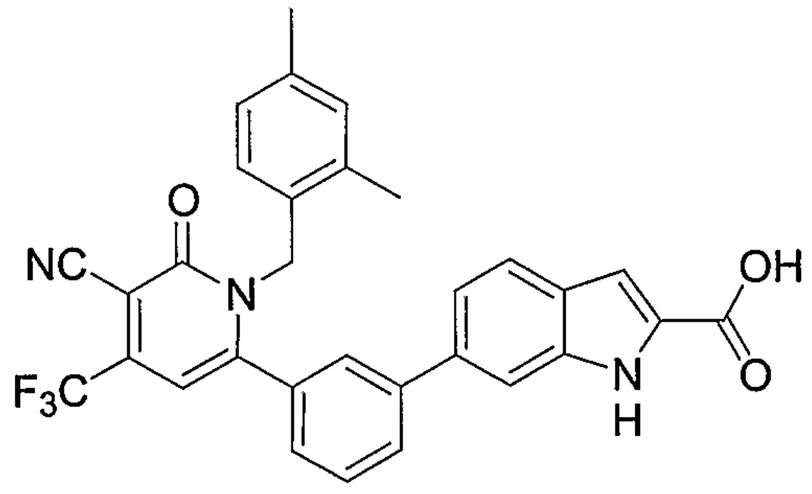
Ethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate



A solution containing 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.800 g, 1.73 mmol), 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester (0.547 g, 1.73 mmol), and K_2CO_3 (1.20 g, 8.67 mmol) in 1,2-Dimethoxyethane (40 mL) and water (10 mL) in a sealed tube was inerted with N_2 and $Pd(PPh_3)_4$ (0.200 g, 0.173 mmol) was added. The reaction mixture was heated at 80°C for 2.5 hours or until starting material was consumed. After cooling to room temperature, solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was washed again with water, $NaHCO_3$, 0.5M HCl, brine, then dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography with 30:70 EtOAc/hexanes to yield ethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate (0.82 g, 83.2%). MS (ESI-) for $C_{33}H_{26}F_3N_3O_3$: 568 (M-H).

EXAMPLE 30

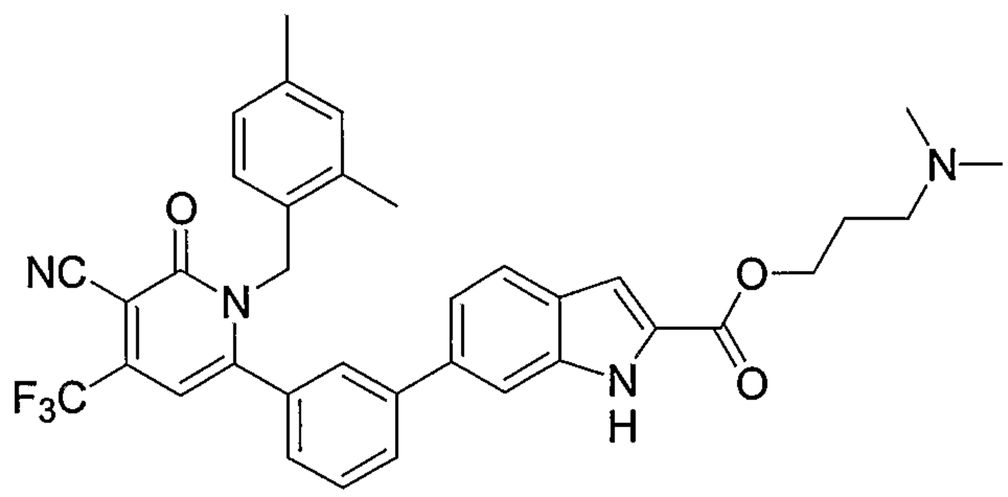
6-(3-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid



To a solution of ethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate (0.82 g, 1.44 mmol), ethanol (5 mL) and THF (6.5 mL) was added 2M LiOH (8 mL) dropwise. The reaction mixture was stirred at room temperature for 16 hours. After the reaction was complete, solvent was removed in vacuo to half the original volume and the residue was cooled in ice bath and then acidified with 1N HCl to pH 2. The mixture was extracted with ethyl acetate (X2), then washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo, dried under vacuum to yield 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid (0.741 g, 95.1%). MS (ESI-) for $C_{31}H_{22}F_3N_3O_3$: 540 (M-H).

EXAMPLE 31

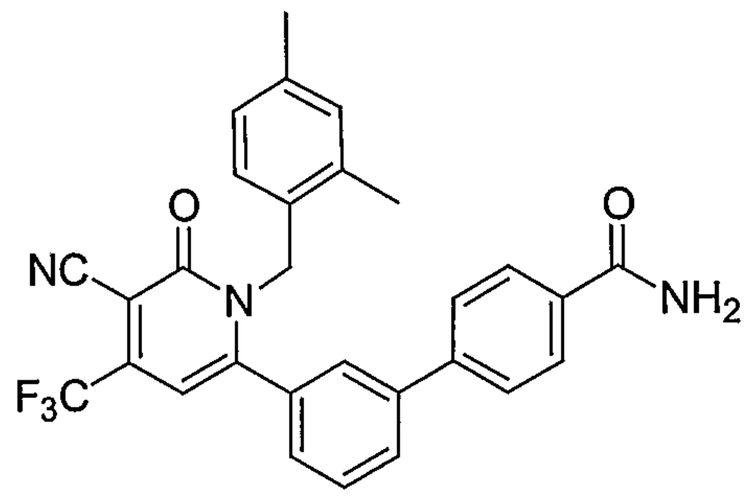
3-(Dimethylamino)propyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate



To a solution of 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid (105 mg, 0.194 mmol) in anhydrous dichloromethane (2 mL) was added 1 drop of DMF and oxalyl chloride (50 mg, 0.388 mmol). The reaction mixture was stirred at room temperature under N_2 for 1 hour. After the reaction was complete, solvent was removed and pumped under high vacuum for 1 hour to yield 6-{3-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-1H-indole-2-carbonyl chloride. This residue was subsequently dissolved in anhydrous dichloromethane (1 mL) and excess 3-dimethylamino-propan-1-ol (0.5 mL) was added. The reaction was complete after 5 minutes and solvent was removed. The crude product was purified by prep HPLC with NH_4OAc system to yield 3-(dimethylamino)propyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate (30.2 mg, 24.8%). ^1H NMR (400 MHz, d_6-DMSO) δ 12.02 (s, 1H), 7.80 (d, 1H), 7.66 (d, 1H), 7.53 (m, 3H), 7.36 (d, 1H), 7.18 (s, 1H), 6.98 (d, 2H), 6.89 (d, 2H), 6.78 (d, 1H), 5.08 (s, 2H), 4.33 (t, 2H), 2.37 (t, 2H), 2.20 (s, 3H), 2.15 (s, 5H), 1.89 (s, 6H). MS (ESI) for $C_{36}H_{33}F_3N_4O_3$: 627 (M+H).

EXAMPLE 32

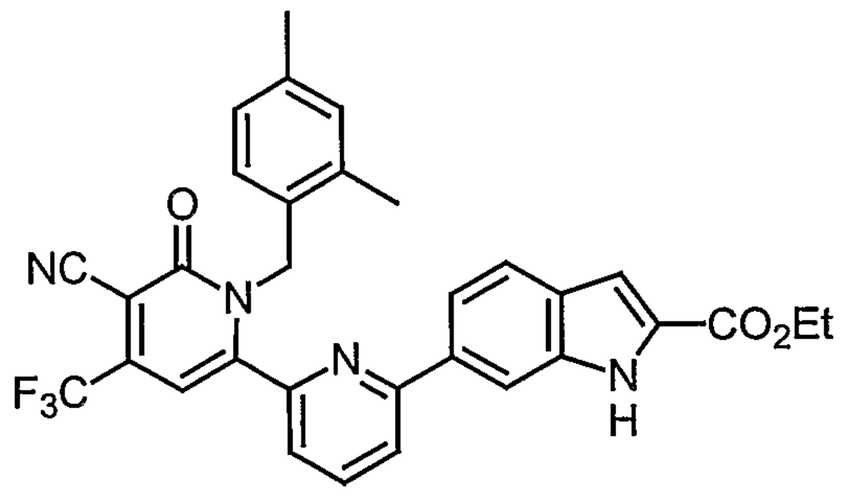
3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-carboxamide



6-(3-Bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (74.5mgs, 0.16mmol), K_2CO_3 (122 mg, 0.88 mmol), (4-aminocarbonylphenyl)boronic acid (35 mg, 0.21 mmol), tetrakis(triphenylphosphine)palladium (23 mg, 0.019 mmol), DME (4.0ml), and H_2O (1.2 ml) were combined in a sealed tube under N_2 and heated to 80°C for 2hrs. The reaction mixture was concentrated in vacuo and immediately purified by flash chromatography (silica gel, 1:1 hexanes:EtOAc) to give 3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-carboxamide (46 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H), 7.73 (m, 1H), 7.53 (t, 1H), 7.27 (m, 3H), 7.18 (m, 1H), 7.00 (d, 1H), 6.87 (s, 1H), 6.70 (d, 1H), 6.50 (s, 1H), 6.10 (br s, 1H), 5.67 (br s, 1H), 5.14 (br s, 2H), 2.28 (s, 3H), 1.85 (s, 3H). MS (ESI-) for $C_{29}H_{22}F_3N_3O_2$: 560.2 (M-H plus AcOH).

EXAMPLE 33

Ethyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate

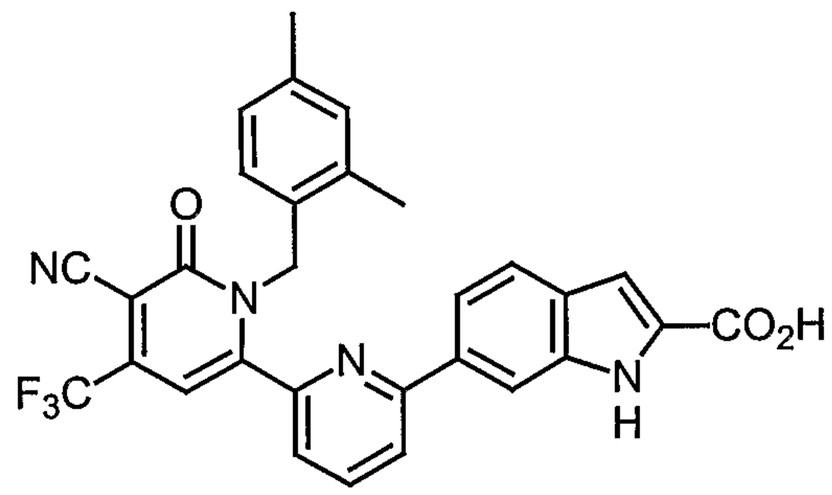


A solution containing 6'-bromo-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-[2,2']bipyridinyl-5-carbonitrile (199 mg, 0.430 mmol), 6-

(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester (140 mg, 0.444 mmol) and K_2CO_3 (297 mg, 2.14 mmol) in 1,2-Dimethoxyethane (18 mL) and water (4.5 mL) in a sealed tube was inerted with N_2 and $Pd(PPh_3)_4$ (50.0 mg, 0.043 mmol) was then added. The resulting mixture was heated to 90°C for 2.5 hours. After allowing to cool to room temperature, the mixture was diluted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solids were impregnated on silica gel and purified by flash chromatography (35:65 EtOAc:hexanes) to yield ethyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate as a yellow solid (146 mg, 59.6% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.91 (d, 1H), 7.83 (t, 1H), 7.71 (d, 1H), 7.63 (m, 1H), 7.56 (s, 1H), 7.20 (m, 2H), 6.96 (m, 2H), 6.72 (d, 1H), 6.23 (s, 1H), 5.42 (s, 2H), 4.44 (q, 2H), 2.37 (s, 3H), 2.00 (s, 3H), 1.44 (t, 3H). MS (ESI-) for $C_{32}H_{25}F_3N_4O_3$: 569 (M-H).

EXAMPLE 34

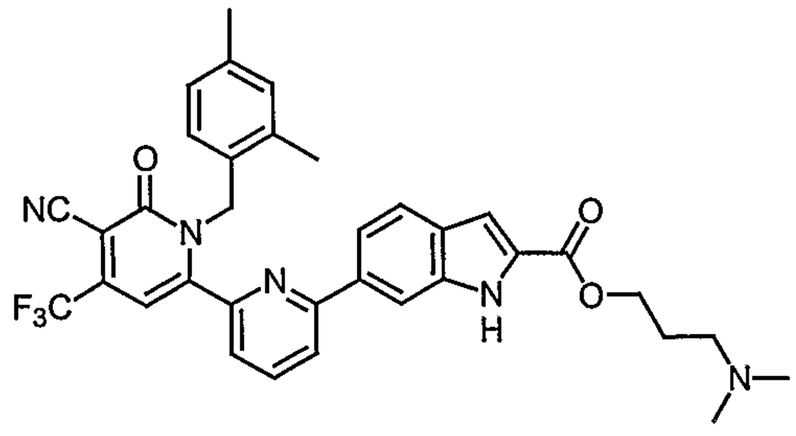
6-{5'-Cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid



To a mixture of ethyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate (89 mg, 0.156 mmol), THF (4 mL) and water (2 mL) was added lithium hydroxide monohydrate (21.8 mg, 0.520 mmol). The mixture was allowed to stir at room temperature for 17 hours. The mixture was then concentrated *in vacuo* and the crude solids were purified by prep HPLC to give 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid as a yellow solid (40.4 mg, 48.1% yield). MS (ESI-) for $C_{30}H_{21}F_3N_4O_3$: 541 (M-H).

EXAMPLE 35

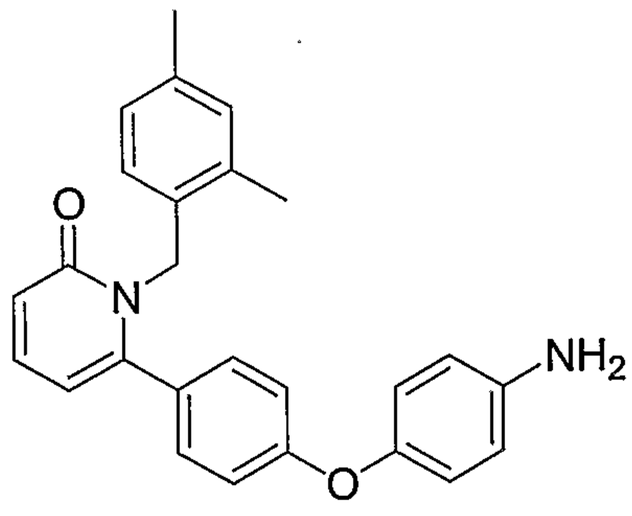
3-(Dimethylamino)propyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate



To a vacuum/heat gun dried RBF was added 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid (29.5 mg, 0.0544 mmol) and DMF (anhyd., 1 drop) in DCM (anhyd., 1.3 mL) under a N_2 atmosphere, followed by oxalyl chloride (14 μL, 0.163 mmol). The resulting solution was stirred at room temperature for 1.5 hours before concentrating to dryness and placing under high vacuum for 1 hour. The resulting solids were re-dissolved in DCM (anhyd., 1 mL) and N,N-dimethyl-3-amino-1-propanol (200 μL, 1.69 mmol) was then added. The resulting solution was stirred at room temperature for 30 minutes, concentrated to dryness and then purified by prep HPLC to yield 3-(dimethylamino)propyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate as a yellow solid (15.5 mg, 45.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (m, 1H), 7.90 (m, 1H), 7.83 (m, 1H), 7.77 (m, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.26 (m, 2H), 7.17 (m, 1H), 6.89 (m, 2H), 6.63 (m, 1H), 5.47 (s, 2H), 4.43 (t, 2H), 2.87 (m, 2H), 2.55 (d, 6H), 2.20 (m, 6H), 2.17 (m, 2H). MS (ESI+) for $C_{35}H_{32}F_3N_5O_3$: 628 (M+H).

EXAMPLE 36

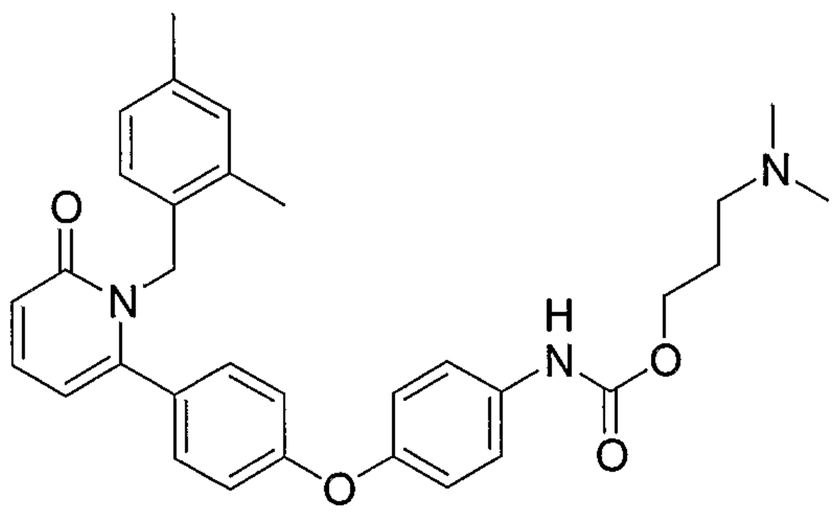
6-[4-(4-Amino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one



A mixture of 1-(2,4-Dimethyl-benzyl)-6-[4-(4-nitro-phenoxy)-phenyl]-1H-pyridin-2-one (4.93 mmol, 2.1 g), iron (2,5 g), ammonium formate (3 g), toluene (30 ml), and water (30 ml) was heated at reflux over night. The mixture was cooled to room temperature and diluted with ethyl acetate, and filtered through celite. The organic layer separated and concentrated to give 6-[4-(4-Amino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one (1.89 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (2H, d), 7.62-7.58 (1H, t), 7.35-7.33 (1H, d), 7.29-7.27 (1H, d), 7.05-6.99 (4H, m), 6.94-6.91 (2H, d), 6.72-6.70 (2H, d), 6.69-6.66 (1H, d), 5.44 (2H, s), 3.61 (2H, Br s), 2.39 (3H, s), 2.33 (3H, s); MS (ESI+) for $C_{26}H_{24}N_2O_2$: 397 (M+H).

EXAMPLE 37

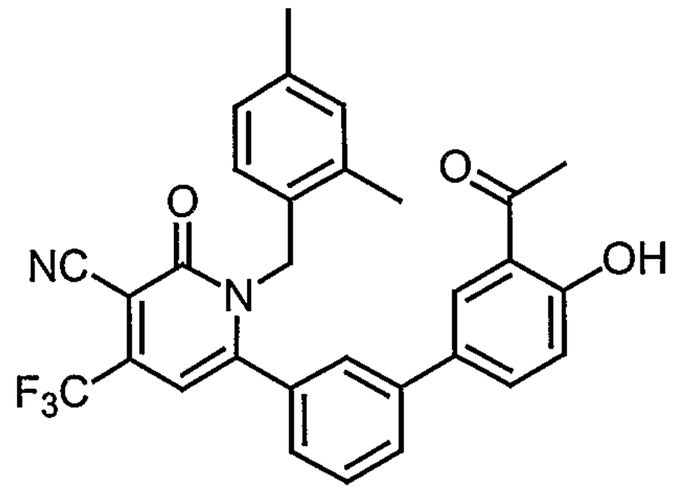
3-(Diethylamino)propyl {4-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate



Triphosgene (0.67 mmol, 0.2 g) was added to a cold solution of 6-[4-(4-amino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one (0.126 mmol, 0.05 g) and DCM (5 ml). The mixture was stirred at 0° C for 30 minutes, 3-diethylamino-1-propanol (1 ml) was added and stirred at room temperature for 1 hour. The crude material was purified by HPLC to give 3-(diethylamino)propyl {4-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-8.00 (2H, d), 7.63-7.59 (1H, t), 7.39-7.37 (1H, Br d), 7.35-7.33 (1H, d), 7.30-7.28 (1H, d), 7.06-7.01 (7H, m), 6.70-6.68 (1H, d), 5.44 (2H, s), 4.24-4.21 (2H, t), 2.61-2.59 (6H, m), 2.39 (3H, s), 2.32 (3H, s), 1.88-1.85 (2H, m), 1.08-1.04 (6H, t); MS (ESI+) for $C_{34}H_{39}N_3O_4$: 554 (M+H).

EXAMPLE 38

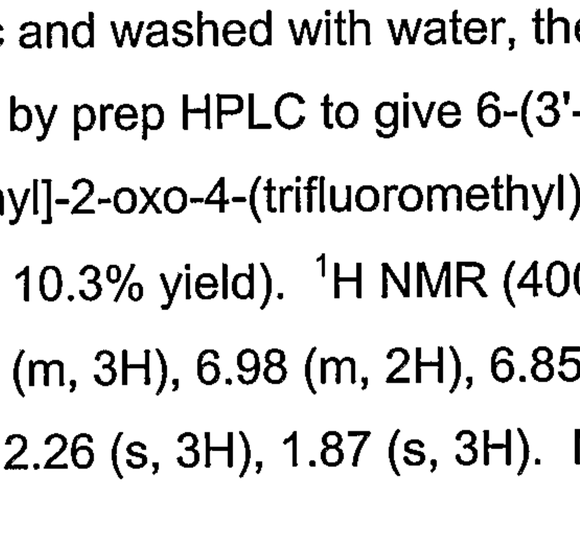
6-(3'-Acetyl-4'-hydroxybiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



A solution containing 1-(2,4-dimethyl-benzyl)-2-oxo-6-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (60.0 mg, 0.118 mmol), 1-(5-bromo-2-hydroxy-phenyl)-ethanone (25.4 mg, 0.118 mmol) and K_2CO_3 (81.5 mg, 0.59 mmol) in 1,2-dimethoxyethane (6 mL) and water (1.5 mL) in a sealed tube was inerted with N_2 and $Pd(PPh_3)_4$ (13.6 mg, 0.0118 mmol) was then added. The resulting mixture was heated to 90°C for 2.5 hours. After allowing to cool to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and washed with water, then dried over Na_2SO_4. The crude solids were then purified by prep HPLC to give 6-(3'-acetyl-4'-hydroxybiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile as a solid (6.3 mg, 10.3% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 12.3 (s, 1H), 7.68 (m, 2H), 7.51 (t, 1H), 7.21 (m, 3H), 6.98 (m, 2H), 6.85 (s, 1H), 6.70 (d, 1H), 6.50 (s, 1H), 5.13 (s, 2H), 2.64 (s, 3H), 2.26 (s, 3H), 1.87 (s, 3H). MS (ESI-) for $C_{30}H_{23}F_3N_2O_3$: 515 (M-H).

EXAMPLE 39

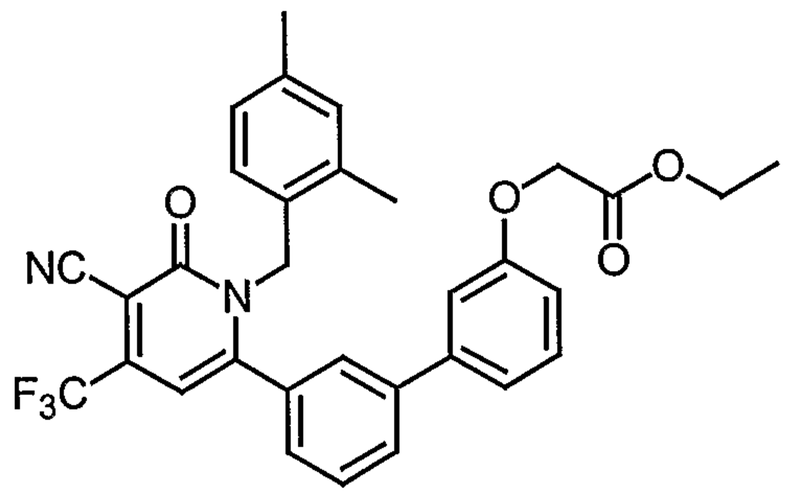
1-[(2,4-Dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



A solution containing 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (434 mg, 0.940 mmol), 3-hydroxyphenylboronic acid (131 mg, 0.954 mmol) and K_2CO_3 (650 mg, 4.70 mmol) in 1,2-Dimethoxyethane (15 mL) and water (3.8 mL) was inerted with N_2 and $Pd(PPh_3)_4$ (108 mg, 0.094 mmol) was then added. The resulting mixture was heated to 80°C for 2 hours, then allowed to cool to room temperature before concentrating *in vacuo*. The resulting solids were partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude solids were impregnated on silica gel and purified by flash chromatography (silica gel, 3:7 EtOAc:hexanes) to afford 1-[(2,4-dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile as a yellow solid (172 mg, 38.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.48 (t, 1H), 7.21 (m, 3H), 7.01 (d, 1H), 6.91 (s, 1H), 6.81 (m, 2H), 6.71 (d, 1H), 6.54 (t, 1H), 6.50 (s, 1H), 5.13 (s, 2H), 4.81 (s, 1H), 2.30 (s, 3H), 1.88 (s, 3H). MS (ESI-) for $C_{28}H_{21}F_3N_2O_2$: 473 (M-H).

EXAMPLE 40

Ethyl [(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate

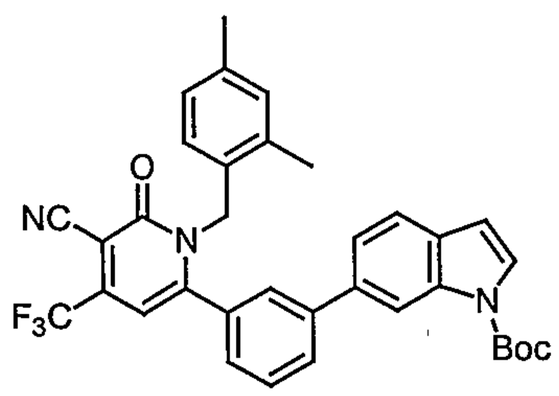


To a solution containing 1-[(2,4-dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (61.5 mg, 0.129 mmol) and ethyl bromoacetate (17 μL, 0.153 mmol) in acetonitrile (anhyd., 2 mL) was added Cs_2CO_3 (86.0 mg, 0.264 mmol) with stirring at room temperature. After stirring for 1 hour at room temperature, the reaction mixture was concentrated to dryness. The residue was diluted with EtOAc and washed with 0.5 N HCl, Na_2CO_3 (satd.) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in a minimal amount of acetonitrile and water and lyophilized to give ethyl [(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate as a solid (50.0 mg, 69.4% yield). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.67 (m, 1H), 7.47 (t, 1H), 7.29 (m, 1H), 7.18 (m, 2H), 6.99 (m, 1H), 6.91 (m, 1H), 6.86 (m, 2H), 6.81 (d, 1H), 6.67 (d, 1H), 6.48 (s, 1H), 5.14 (s, 2H), 4.64 (s, 2H), 4.12 (q, 2H), 2.27 (s, 3H), 1.86 (s, 3H), 1.26 (t, 3H). MS (ESI-) for $C_{32}H_{27}F_3N_2O_4$: 559 (M-H).

EXAMPLE 41

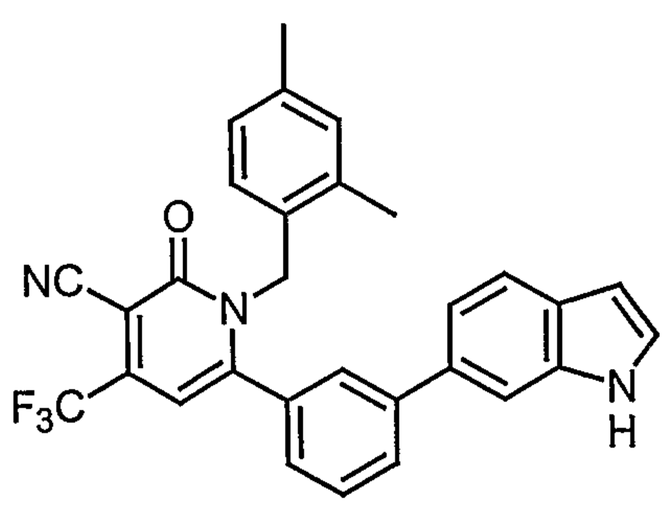
1,1-Dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate



A solution containing 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (150 mg, 0.325 mmol), 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert-butyl ester (112 mmol, 0.326 mmol) and K_2CO_3 (227 mg, 1.64 mmol) in 1,2-Dimethoxyethane (7.5 mL) and water (2 mL) was inerted with N_2 and $Pd(PPh_3)_4$ (39.2 mg, 0.0339 mmol) was then added. The resulting mixture was heated to 80°C for 1 hour, then allowed to cool to room temperature before concentrating *in vacuo*. The crude solids were impregnated on silica gel and purified by flash chromatography (15:85 EtOAc:Hexanes) to give 1,1-dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate as a yellow solid (179 mg, 92.3 % yield). MS (ESI-) for $C_{35}H_{30}F_3N_3O_3$: 596 (M-H).

EXAMPLE 42

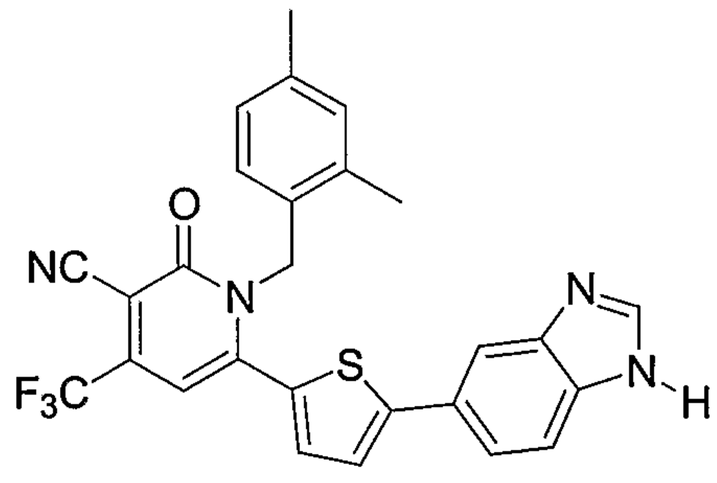
1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



To a solution containing 1,1-dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate (160 mg, 0.268 mmol) in DCM (4 mL) was added TFA (4 mL) with stirring at room temperature. After stirring for 1.5 hours at room temperature, the reaction mixture was concentrated to dryness. The resulting solid was dissolved in EtOAc and washed with $NaHCO_3$ (satd.), water and brine, dried over Na_2SO_4 and concentrated to dryness, affording 1-[(2,4-dimethylphenyl)methyl]-6-[3-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile as a yellow solid (121 mg, 91.0% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.76 (d, 1H), 7.62 (d, 1H), 7.47 (t, 1H), 7.29 (m, 2H), 7.13 (d, 1H), 7.00 (m, 2H), 6.89 (s, 1H), 6.72 (d, 1H), 6.56 (m, 2H), 5.17 (s, 2H), 2.30 (s, 3H), 1.90 (s, 3H). MS (ESI+) for $C_{30}H_{22}F_3N_3O$: 498 (M+H).

EXAMPLE 43

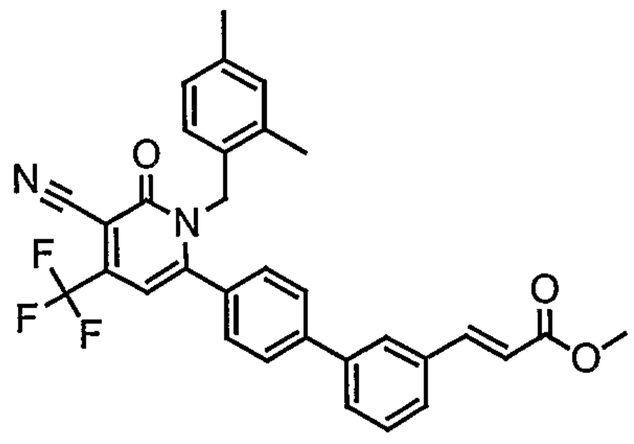
6-[5-(1H-Benzimidazol-5-yl)-2-thienyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



To a solution containing 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester (172 mg, 0.5 mmol) in1,2-dimethoxyethane (7.50 mL) was added 6-(5-bromo-thiophen-2-yl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (231 mg, 0.5 mmol)) , K_2CO_3 (345 mg, 2.5 mmol), water (2.0 mL) in a sealed tube was inerted with N_2, and $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) was then added. The resulting mixture was heated to 90°C for 16 hours. The crude product was treated with 50% TFA:DCM for 1h and concentrated. 6-[5-(1H-benzimidazol-5-yl)-2-thienyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile was obtained on purification by prep-HPLC (41 mg, 20% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.25 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 7.7 (d, 1H), 7.60 (s, 1H), 7.5 (m, 1H), 7.25 (d, 1H), 7.08 (s, 1H), 7.0 (m, 2H), 6.75 (m, 1H), 5.25 (s, 2H), 2.20 (s, 3H), 2.30 (s, 3H). MS (ESI+) for $C_{27}H_{19}BF_3N_4OS$: 505 (M+H).

EXAMPLE 44

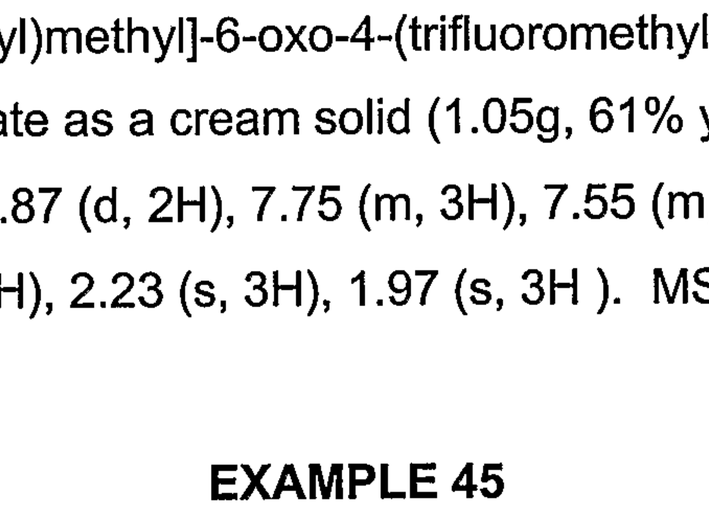
Methyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate



A mixture containing 6-(4-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (0.075 g, 0.17 mmol), [3-(E-3-methoxy-3-oxo-1-propen-1-yl)phenyl]boronic acid (0.031 g, 0.18 mmol), potassium carbonate (0.11g, 0.81 mmol) and $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol) in DMF/DME 4:1 ratio (4 mL) was sparged with N_2 in a sealed tube. The mixture was heated to 80°C for 2 hours. After the reaction was complete the crude reaction was impregnated on silica gel and purified by flash chromatography (1:4 EtOAc:hexanes) to give methyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate as a cream solid (1.05g, 61% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.10 (s, 1H), 7.87 (d, 2H), 7.75 (m, 3H), 7.55 (m, 3H), 6.94 (d, 2H), 6.74 (m, 3H), 5.08 (s, 2H), 3.74 (s, 3H), 2.23 (s, 3H), 1.97 (s, 3H). MS (ESI) for $C_{33}H_{25}F_3N_2O_3$: 541 (M-H).

EXAMPLE 45

Methyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate

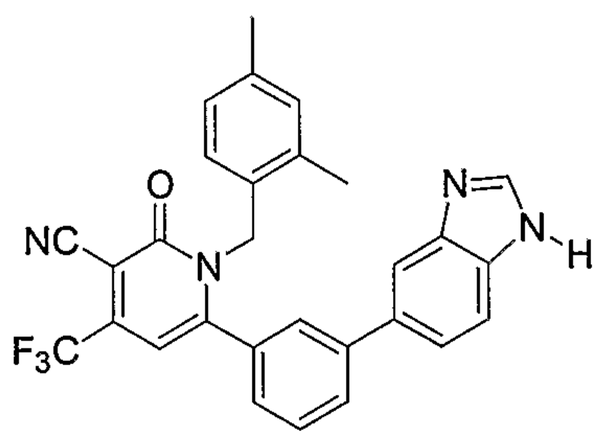


Methyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate (0.017g, 0.03 mmol)

was dissolved in EtOH (3 ml) to which Pd/C (5 mg) was added. A hydrogen ballon was attached to the reaction and the vessel was evacuated and filled with hydrogen twice. The reaction was allowed to stir under hydrogen for 45 minutes upon which time it was filtered thru celite. After removal of the solvent methyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate was obtained as a cream colored solid (12 mg, 70%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.76 (d, 2H), 7.74 (s, 1H), 7.63 (d, 1H), 7.51 (d, 2H), 7.36 (t, 1H), 7.27 (d, 1H), 6.95 (d, 2H), 6.84 (s, 1H), 6.74 (d, 1H), 5.07 (s, 2H), 3.58 (s, 3H), 2.91 (t, 2H), 2.71 (t, 2H), 2.22 (s, 3H), 1.96 (s, 3H). MS (ESI-) for $C_{32}H_{27}F_3N_2O_3$: 543 (M-H).

EXAMPLE 46

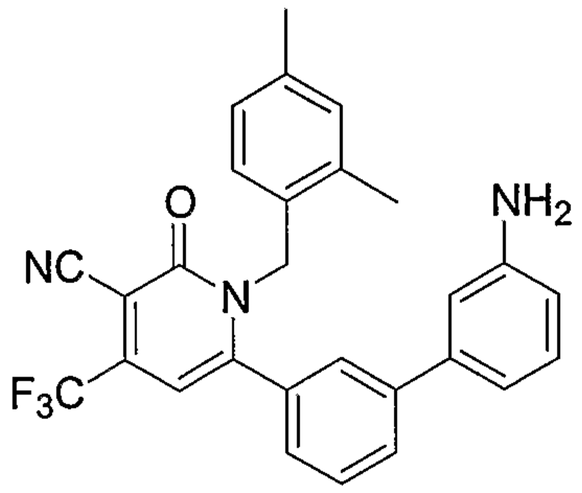
6-[3-(1H-Benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile



To a solution of 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoimidazole-1-carboxylic acid tert-butyl ester (172 mg, 0.5 mmol) in1,2-dimethoxyethane (7.50 mL) was added 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (230 mg, 0.5 mmol)), K_2CO_3 (345 mg, 2.5 mmol), water (2.0 mL). The mixture was inerted with N_2 and $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) was then added. The resulting mixture was heated in a sealed tube at 90°C for 16 hours. The desired coupling product obtained was isolated on flash chromatography purification, and subsequently treated with 75% TFA:DCM for 1h and then concentrated in vacuo. The crude product was purified by prep-HPLC to give 6-[3-(1H-benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (135 mg, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.85 (d, 1H), 7.65 (s, 1H), 7.50 (m, 3H), 7.35 (d, 1H), 7.15 (br, 1H), 7.0 (d,1H), 6.9 (s, 2H), 6.8 (d, 1H), 7.0 (m, 2H), 6.75 (m, 1H), 5.10 (s, 2H), 1.9 (d, 6H). MS (ESI-) for $C_{29}H_{21}F_3N_4O$: 497 (M-H).

EXAMPLE 47

6-(3'-Amino-biphenyl-3-yl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile



To a solution containing 3-aminophenylboronic acid (293 mg, 2.16 mmol) in1,2-dimethoxyethane (15 mL) was added 6-(3-bromo-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile (1g, 2.16 mmol)), followed by K_2CO_3 (1.49 g, 10.8 mmol), water (2.0 mL) and $Pd(PPh_3)_4$ (249 mg, 0.216 mmol). The mixture was purged with N_2, and heated in a sealed tube at 96°C for 16 hours. The desired product was obtained on flash chromatography purification (700mg, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, 1H), 7.20 (m, 3H), 7.0 (d, 1H), 6.95 (s, 1H), 6.65 (m, 3H), 6.40 (s, 1H), 5.20 (br,1H), 3.75 (br, 2H), 2.30 (s, 3H), 1.90 (s, 3H). MS (ESI) for $C_{28}H_{22}F_3N_3O$: 474 (M+H).

EXAMPLE 48

Compounds of the Invention

Following the procedures set forth above in the foregoing preparations and examples and in U.S. patent application Ser. No. 10/327,813 and Ser. No. 10/899,453, the following compounds of the invention were or may be prepared:

1-{3-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea. MS (ESI+) for $C_{35}H_{36}F_3N_5O_3$: 632.1 (M+H);

3-Piperidin-1-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for $C_{37}H_{37}F_3N_4O_4$: 659.4 (M+H);

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea. ^1H NMR (400 MHz, d_6-DMSO) δ 8.52 (s, 1H), 7.43 (m, 2H), 7.33 (m, 2H), 6.93 (bs, 6H), 6.75 (s, 1H),

6.67 (m, 1H), 6.18 (bs, 1H), 5.06 (s, 2H), 3.07 (bs, 2H), 2.21 (d, 4H), 2.10 (s, 6H), 2.00 (s (3H), 1.41 (bs, 4H). MS (ESI+) for $C_{35}H_{36}F_3N_5O_3$: 632 (M+H);

3-Morpholin-4-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.4 (br, 2H), 7.50 (d, 2H), 7.35 (d, 2H), 7.0 (d, 2H), 6.9(m, 4H), 6.8 (s, 1H), 6.65(d, 1H), 5.10 (s, 2H), 4.20 (t, 2H), 3.1-3.7(m, 14H), 2.2(s, 3H), 2.1 (m, 2H), 1.9(s, 3H). MS (ESI+) for $C_{36}H_{36}F_3N_5O_4$: 660(M+H);

3-Piperazin-1-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for C36H36F3N5O4: 660 (M+H);

4-(Dimethylamino)butyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.69 (s, 1H), 7.50 (d, 2H), 7.34 (d, 2H), 7.00 (d, 2H), 6.93 (m, 4H), 6.75 (s, 1H), 6.67 (s, 1H), 5.06 (s, 2H), 4.08 (m, 2H), 2.21 (m, 5H), 2.10 (s, 6H), 2.00 (s, 3H), 1.61 (m, 2H), 1.48 (m, 2H). MS (ESI+) for $C_{35}H_{35}F_3N_4O_4$: 633 (M+H);

Methyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for $C_{30}H_{24}F_3N_3O_4$: 546 (M-H);

3-(Dimethylamino)propyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for $C_{34}H_{33}F_3N_4O_4$: 619 (M+H);

2-{[2-(Dimethylamino)ethyl]oxy}ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI) for $C_{35}H_{35}F_3N_4O_5$: 649 (M+H);

2-(Dimethylamino)ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for $C_{33}H_{31}F_3N_4O_4$: 605 (M+H);

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2-hydroxyethyl)urea. MS (ESI+) for $C_{31}H_{27}F_3N_4O_4$: 577 (M+H);

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}urea. MS (ESI+) for $C_{29}H_{23}F_3N_4O_4$: 533 (M+H);

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[(2,3-dihydroxypropyl)oxy]urea. MS (ESI) for $C_{32}H_{29}F_3N_4O_6$: 623 (M+H);

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2,3-dihydroxypropyl)urea. MS (ESI) for $C_{32}H_{29}F_3N_4O_5$: 607 (M+H);

N-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}ethanediamide. MS (ESI-) for $C_{30}H_{23}F_3N_4O_4$: 559 (M-H);

Ethyl ({4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}amino)(oxo)acetate. MS (ESI-) for $C_{32}H_{26}F_3N_3O_5$: 588 (M-H);

Methyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.70 (m, 2H), 7.5 (t, 1H), 7.4 (m, 3H), 7.25 (t, 1H), 6.9 (d, 1H), 6.85 (m, 3H), 6.8 (d, 1H), 5.10 (s, 2H), 3.70(s, 3H), 2.20 (s, 3H), 1.90 (s, 3H). MS (ESI) for $C_{30}H_{24}F_3N_3O_3$: 530 (M-H);

3-(Dimethylamino)propyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate. MS (ESI+) for $C_{34}H_{33}F_3N_4O_3$: 603 (M+H);

1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-ethylurea. MS (ESI+) for $C_{31}H_{27}F_3N_4O_2$: 545 (M+H);

3-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-1,1-dimethylurea. MS (ESI+) for $C_{31}H_{27}F_3N_4O_2$: 545 (M+H);

2-(Dimethylamino)ethyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate. MS (ESI+) for $C_{33}H_{31}F_3N_4O_3$: 589 (M+H);

Ethyl N-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)glycinate. MS (ESI+) for $C_{32}H_{28}F_3N3O_3$: 560 (M+H);

1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[3-(dimethylamino)propyl]urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.80 (s, 1H), 7.70 (m, 2H), 7.5 (t, 1H), 7.4 (s, 1H), 7.3(m, 1H), 7.20 (t, 2H), 7.0(d, 1H), 6.9 (s, 1H), 6.85 (m, 2H), 6.40 (t, 1H), 5.10 (s, 2H), 3.20 (m, 2H), 3.0(m, 3H), 2.8(d, 6H), 2.2 (s, 3H), 1.9(s, 3H), 1.8 (m, 2H). MS (ESI+) for $C_{34}H_{34}F_3N_5O_2$: 602 (M+H);

1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[2-(dimethylamino)ethyl]urea. MS (ESI+) for $C_{33}H_{32}F_3N_5O_2$: 588 (M+H);

Ethyl 5-[(4-{5-cyano-1-[(2,4-dichlorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI-) for $C_{31}H_{20}Cl_2F_3N_3O_4$: 624 (M-H);

Ethyl 5-({4-[5-cyano-1-{[2-methyl-4-(methyloxy)phenyl]methyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl]phenyl}oxy)-1H-indole-2-carboxylate. MS (ESI-) for $C_{33}H_{26}F_3N_3O_5$: 600 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{28}H_{21}F_3N_2O_2$: 473 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{30}H_{22}F_3N_3O$: 498 (M+H);

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1-methyl-1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{31}H_{24}F_3N_3O$: 512 (M+H);

1,1-Dimethylethyl 4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazole-1-carboxylate. MS (ESI+) for $C_{30}H_{27}F_3N_4O_3$: 449.2 (M+H minus Boc);

Ethyl 5-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI-) for $C_{33}H_{26}F_3N_3O_4$: 584.2 (M-H);

1,1-Dimethylethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate. MS (ESI-) for $C_{35}H_{30}F_3N_3O_3$: 596 (M-H);

6-{5'-Cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid. MS (ESI-) for $C_{30}H_{21}F_3N_4O_3$: 541 (M-H);

Ethyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate. MS (ESI-) for $C_{33}H_{27}F_3N_2O_3$: 555 (M-H);

6-[4-(1H-Benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{29}H_{21}F_3N_4O$: 499 (M+H);

Methyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.90 (d, 1H), 7.74 (m, 2H), 7.58 (m, 2H), 7.42 (m, 4H), 6.98 (d, 1H), 6.89 (d, 2H), 6.79 (m, 2H), 5.07 (s, 2H), 3.75 (s, 3H), 2.19 (s, 3H), 1.88 (s, 3H). MS (ESI) for $C_{32}H_{25}F_3N_2O_3$: 541 (M-H);

6-(4'-Acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{30}H_{23}F_3N_2O_2$: 499 (M-H);

6-[3-(2,3-Dihydro-1,4-benzodioxin-6-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{30}H_{23}F_3N_2O_3$: 515 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{26}H_{21}F_3N_4O$: 463 (M+H);

6-(3'-Acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{30}H_{23}F_3N_2O_2$: 499 (M-H);

6-[3',4'-Bis(methyloxy)biphenyl-3-yl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{29}H_{23}F_3N_2O_3S$: 517 (M-H);

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N,N-dimethylbiphenyl-3-carboxamide. MS (ESI+) for $C_{31}H_{26}F_3N_3O_2$: 530 (M+H);

Methyl 4-amino-3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate. MS (ESI+) for $C_{30}H_{24}F_3N_3O_3$: 532 (M+H);

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxamide. MS (ESI-) for $C_{29}H_{22}F_3N_3O_2$: 560.2 (M-H plus AcOH);

1-[(2,4-Dimethylphenyl)methyl]-6-[4'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{29}H_{23}F_3N_2O_3S$: 535 (M-H);

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-3-carboxamide. MS (ESI+) for $C_{31}H_{26}F_3N_3O_2$: 530.1 (M+H);

Methyl 3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate. MS (ESI-) for $C_{30}H_{23}F_3N_2O_3$: 515 (M-H);

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-methylbiphenyl-3-carboxamide. MS (ESI+) for $C_{30}H_{24}F_3N_3O_2$: 516 (M+H);

1-[(2,4-Dimethylphenyl)methyl]-6-[3'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{29}H_{23}F_3N_2O_3S$: 535 (M-H);

Ethyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate. MS (ESI-) for $C_{33}H_{27}F_3N_2O_3$: 555 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-2-oxo-6-{3-[1-(phenylmethyl)-1H-pyrazol-4-yl]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{32}H_{25}F_3N_4O$: 537 (M-H);

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-4-carboxamide. MS (ESI+) for $C_{31}H_{26}F_3N_3O_2$: 530.1 (M+H);

Methyl 3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.80 (d, 1H), 7.57 (t, 1H), 7.44 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.22 (d, 2H), 7.15 (d, 1H), 6.99 (d, 1H), 6.90 (d, 2H), 6.80 (d, 1H), 5.05 (s, 2H), 3.59 (s, 3H), 2.87 (t, 2H), 2.67 (t, 2H), 2.21 (s, 3H), 2.08 (s, 3H), 1.88 (s, 3H). MS (ESI-) for $C_{32}H_{27}F_3N_2O_3$: 543 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-{3-[1-(3-methylbutyl)-1H-pyrazol-4-yl]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for C30H29F3N4O: 519 (M+H);

Ethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate. MS (ESI-) for $C_{31}H_{24}F_3N_3O_3S$: 574 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-[5-(1H-indol-6-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{28}H_{20}F_3N_3OS$: 504 (M+H);

Ethyl 5-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.88 (s, 1H), 7.49 (m, 2H), 7.20 (m, 2H), 7.05 (s, 1H),

7.00 (m, 2H), 6.74 (s, 1H), 6.65 (d, 1H), 5.36 (s, 2H), 4.43 (q, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 1.43 (t, 3H). MS (ESI-) for $C_{31}H_{24}F_3N_3O_3S$: 574 (M-H);

1,1-Dimethylethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-1-carboxylate. MS (ESI-) for $C_{33}H_{28}F_3N_3O_3S$: 602 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{28}H_{21}F_3N_2O_2$: 473 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI-) for $C_{28}H_{21}F_3N_2O_2$: 473 (M-H);

Ethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate. MS (ESI-) for $C_{33}H_{26}F_3N_3O_3$: 568 (M-H);

1-[(2,4-Dimethylphenyl)methyl]-6-[4-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{30}H_{22}F_3N_3O$: 498 (M+H);

1-[(2,4-Dimethylphenyl)methyl]-6-[4-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile. MS (ESI+) for $C_{30}H_{22}F_3N_3O$: 498 (M+H);

Ethyl 5-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate. MS (ESI-) for $C_{33}H_{26}F_3N_3O_3$: 568 (M-H);

Ethyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)propanoate. MS (ESI-) for $C_{33}H_{29}F_3N_2O_3$: 557 (M-H);

5-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-1H-indole-2-carboxylic acid. MS (ESI-) for $C_{31}H_{22}F_3N_3O_3$: 540 (M-H);

1,1-Dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate. MS (ESI-) for $C_{35}H_{30}F_3N_3O_3$: 596 (M-H);

Ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)oxy]acetate. MS (ESI-) for $C_{32}H_{27}F_3N_2O_4$: 559 (M-H);

Ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate. MS (ESI-) for $C_{32}H_{27}F_3N_2O_4$: 559 (M-H);

1,1-Dimethylethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate. MS (ESI+) for $C_{35}H_{30}F_3N_3O_3$: 598 (M+H);

3-Morpholin-4-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate hydrochloride. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.13 (s, 1H), 10.60 (bs, 1H), 7.55 (d, 1H), 7.36 (d, 3H), 7.20 (s, 1H), 7.05 (d, 1H), 6.93 (m, 4H), 6.75 (s, 1H), 6.67 (d, 1H), 5.07 (s, 2H), 4.38 (t, 2H), 3.99 (d, 2H), 3.75 (t, 2H), 3.49 (d, 2H), 3.30 (s, 2H), 3.10 (q, 2H), 2.21 (m, 5H), 2.01 (s, 3H). MS (ESI+) for $C_{38}H_{35}F_3N_4O_5$: 685 (M+H);

4-(Dimethylamino)butyl 5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for $C_{37}H_{35}F_3N_4O_4$: 657 (M+H);

3-Piperazin-1-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[(2,3-dihydroxypropyl)oxy]-1H-indole-2-carboxamide. MS (ESI+) for $C_{34}H_{29}F_3N_4O_6$: 647 (M+H);

3-Piperidin-1-ylpropyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate. MS (ESI+) for $C_{39}H_{37}F_3N_4O_3$: 667 (M+H);

3-Piperazin-1-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for $C_{38}H_{36}F_3N_5O_4$: 684 (M+H);

2-{[2-(dimethylamino)ethyl]oxy}ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for C37H35F3N4O5: 673 (M+H);

1-Methylethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI-) for $C_{34}H_{28}F_3N_3O_4$: 598 (M-H);

3-(Dimethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for $C_{38}H_{37}F_3N_4O_4$: 671 (M+H);

1-Methylpiperidin-4-yl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for $C_{37}H_{33}F_3N_4O_4$: 655 (M+H);

3-(Diethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI+) for $C_{40}H_{41}F3N_4O_4$: 699 (M+H);

2-(dimethylamino)ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI-) for $C_{35}H_{31}F_3N_4O_4$: 627 (M-H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-propyl-1H-indole-2-carboxamide. MS (ESI+) for C34H29F3N4O3: 599 (M+H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethyl-1H-indole-2-carboxamide. MS (ESI-) for $C_{33}H_{27}F_3N_4O_3$: 583 (M-H);

2-[(2-Hydroxyethyl)oxy]ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate. MS (ESI+) for $C_{33}H_{30}F_3N_3O_6$: 621 (M+H);

2,3-Dihydroxypropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. MS (ESI-) for $C_{34}H_{28}F_3N_3O_6$: 630 (M-H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(1-methylethyl)-1H-indole-2-carboxamide. MS (ESI+) for $C_{34}H_{29}F_3N_4O_3$: 599 (M+H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-methylpropyl)-1H-indole-2-carboxamide. MS (ESI+) for $C_{35}H_{31}F_3N_4O_3$: 613 (M+H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[3-(dimethylamino)propyl]-1H-indole-2-carboxamide. MS (ESI) for $C_{36}H_{34}F_3N_5O_3$: 642 (M+H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-ethyl-1H-indole-2-carboxamide. MS (ESI+) for $C_{33}H_{27}F_3N_4O_3$: 585 (M+H);

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-hydroxyethyl)-1H-indole-2-carboxamide. MS (ESI+) for $C_{33}H_{27}F_3N_4O_4$: 601 (M+H);

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(difluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.51 (d, 1H), 7.35 (d, 1H), 7.32 (d, 2H), 7.20 (t, 1H), 7.13 (d, 1H), 7.03 (dd, 1H), 6.95-6.91 (m, 4H), 6.59 (s, 1H), 6.58 (d, 1H), 5.07 (s, 2H), 4.35 (q, 2H), 2.21 (s, 3H), 2.01 (s, 3H), 1.34 (t, 3H). MS (ESI-) for $C_{33}H_{27}F_2N_3O_4$: 566.1 (M-H);

Ethyl 5-[(4-{5- carbamoyl-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-carboxy-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2-amino-6-methylpyridin-5-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate.

The biological assays disclosed in the following Examples are directed to the ability of the compounds of the invention to modulate LXRα and LXRβ activity, as well as FXR activity. It is understood, that one of ordinary skill in the art would recognize that the following assays could be used to test the ability of the compounds of the invention to modulate FXR activity.

EXAMPLE 49

FRET Coactivator Assay

The FRET coactivator assay measures the ability of LXR ligands to promote protein-protein interactions between the ligand binding domain (LBD) of LXR and transcriptional coactivator proteins. The assay involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at

665 nm. If the europium chelate is not brought into close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction.

Required Materials:

1. Partially purified recombinant protein comprising glutathione-S-transferase fused in frame to the LXR-ligand binding domain (comprising amino acids 188-447 of human LXRα, or amino acids 198-461 of human LXRβ).
2. Biotinylated peptide containing a SRC-1 LXXLL receptor interaction motif (B-SRC-1)
3. Anti-GST antibody conjugated to an Europium chelate (αGST-K) (From Wallac/PE Life Sciences Cat# AD0064)
4. Streptavidin linked allophycocyanin (SA-APC) (From Wallac/PE Life Sciences CAT# AD0059A)
5. 1x FRET Buffer: (20 mM KH_2PO_4/K_2HPO_4 pH 7.3, 150 mM NaCl, 2.5 mM CHAPS, 2 mM EDTA, 1 mM DTT (add fresh))
6. 96 well or 384 well black multiwell plates (from LJL)

Stock Solutions:

0.5 M KH_2PO_4/K_2HPO_4: pH 7.3

5 M NaCl

80 mM (5%) CHAPS

0.5 M EDTA pH 8.0

1 M DTT (keep at –20°C)

Preparation of Screening Reagents:

Prepare reaction mixture for the appropriate number of wells by combining the following reagents 5 nM/well GST-hLXRαLBD, 5 nM/well GST-hLXRβLBD, 5 nM/well Anti-GST antibody (Eu), 12 nM/well biotin-SRC-1 peptide, 12 nM/well APC-SA adjust the volume to 10 µL/well with 1x-FRET buffer.

Procedure:

Add 0.5 µL of a 1 mM stock compound (for approx. 10 µM final concentration) or solvent to each well in a 96 well or 384 well black plate (LJL).

Add 10 µl reaction mixture (prepared above) to each well of the multiwell plate.

Incubate covered or in the dark (the APC is light sensitive) at ambient temperature for 1-4 hours. After this time if reactions are not read they can be stored at 4°C for several more hours without too much loss of signal.

Read the plate using an LJL Analyst, or similar instrument, using the following conditions:

Channel 1: Excitation is 330 nm and emission is 615. This is for Eu chelate

Channel 2: Excitation is 330 nm and emission is 665. This is for APC

For channel 1: Flashes per well = 100; Integration time = 1000 µs; interval between flashes = 1x10 ms; Delay after flash = 200 µs

For channel 2: Flashes per well = 100; Integration time = 100 µs; interval between flashes = 1x10 ms; Delay after flashes = 65 µs.

EXAMPLE 50

Scintillation proximity assay (SPA):

The SPA assay measures the radioactive signal generated by the binding of ^{3}H-24,25-epoxycholesterol to LXRα or LXRβ. The basis of the assay is the use of SPA beads containing a scintillant, such that when binding to the receptor brings the labeled ligand into proximity with the bead, the energy from the label stimulates the scintillant to emit light. The light is measured using a standard microplate scintillation reader. The ability of a ligand to bind to a receptor can be measured by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor.

<u>Required Materials:</u>

1. Label: ^{3}H-24,25-epoxy-cholesterol (Amersham)
2. LXRα lysate: Baculovirus expressed LXRα/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate
3. LXRβ lysate: Baculovirus expressed LXRβ/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate
4. SPA beads: Ysi copper His-tag SPA beads (Amersham)
5. Plates: Non-binding surface 96-well plate (Corning)
6. Protein lysate dilution buffer: (20 mM Tris-HCl pH 7.9, 500 mM NaCl, 5 mM Imidazole).

7. 2x SPA Buffer: (40 mM K_2HPO_4/KH_2PO_4 pH7.3, 100 mM NaCl, 0.05% Tween 20, 20% Glycerol, 4 mM EDTA)

8. 2x SPA Buffer w/o EDTA: (40 mM K_2HPO_4/KH_2PO_4 pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol)

Stock Solutions

0.5 M K_2HPO_4/KH_2PO_4 pH 7.3

0.5 M EDTA pH 8.0

5 M NaCl

10% Tween-20

Glycerol

Preparation of protein lysates

Baculovirus expression plasmids for human RXR α (accession No NM_002957), LXRα (accession No U22662), LXRβ (accession No U07132) were made by cloning the appropriate full-length cDNAs into the pBacPakhis1 vector (Clontech, CA) following standard procedures. Insertion of the cDNAs into the pBAcPakhis1 vector polylinker created an in frame fusion to the cDNA to an N-terminal poly-His tag present in pBacPakhis1. Correct cloning was confirmed by restriction mapping, and /or sequencing.

Cell lysates were prepared by infecting healthy, Sf9 insect cells at a density of approximately $1.25x10^6$ /ml at 27°C, in a total volume of 500 mL per 1L sized spinner flasks, cultured under standard conditions. To prepare LXRα lysate, insect cells were co-transfected with the LXRα expression cassette at an M.O.I of 0.5 to 0.8 and with the RXR expression cassette at a M.O.I. of approximately 1.6. To prepare LXRβ lysate, insect cells were co-transfected with the LXRβ expression cassette at an M.O.I of approximately 1.6 and with the RXR expression cassette at a M.O.I. of approximately 1.6. In both cases cells were incubated for 48 hours at 27°C with constant shaking prior to harvesting.

After incubation, cells were harvested by centrifugation and pelleted. Cell pellets were resuspended in two volumes of ice-cold freshly prepared extraction buffer (20mM Tris pH 8.0, 10mM Imidazole, 400mM NaCl, containing one EDTA free protease inhibitor tablet (Roche Catalog No: 1836170) per 10 ml of extraction buffer).

Cells were homogenized slowly on ice using a Douncer to achieve 80-90% cell lysis. The homogenate was centrifuged in a pre-chilled rotor (Ti50 or Ti70, or equivalent) at 45,000 rpm for 30 minutes at 4°C. Aliquots of the supernatant were frozen

on dry ice and stored frozen at –80°C until quantification and quality control. Aliquots of the lysates were tested in the SPA assay to ensure lot to lot consistency, and via SDS-PAGE analysis after purification using Ni-NTA Resin (Qiagen) and adjusted for protein concentration and expression level prior to use in screening assays.

Preparation of Screening Reagents

[^{3}H] 24,25 Epoxycholesterol (EC) solution: For a single 384-well plate (or 400 wells), 21 µL of [^{3}H] EC (specific activity 76.5 Ci/mmol, concentration 3.2 mCi/mL) was added to 4.4 mL of 2x SPA buffer to provide for a final concentration of 200 nM. For each additional 384-well plate, an additional 19.1 µL of [^{3}H] EC was added to 4.0 mL of additional 2x SPA buffer. The final concentration of [^{3}H] EC in the well was 50 nM.

LXRα lysate (prepared as above) was diluted with protein lysate dilution buffer. 1400 µL of diluted LXRα lysate was prepared per 384-well plate, (or 200 wells) and 1120 µL of diluted LXRα lysate was prepared for each additional 384-well plate.

LXRβ lysate (prepared as above) was diluted with protein lysate dilution buffer. 1400 µL of diluted LXRβ lysate was prepared per 384-well plate, (or 200 wells) and 1120 µL of diluted LXRβ lysate was prepared for each additional 384-well plate.

SPA bead solution: For a 384-well plate (or 400 wells), 3.75 mL of 2x SPA buffer w/o EDTA, 2.25 mL of H_2O, and 1.5 mL of Ysi His-tag SPA beads (vortex well before taking) were mixed together. For each additional 384-well plate, an additional 3.5 mL of 2x SPA buffer w/o EDTA, 2.1 mL of H_2O, and 1.4 mL of Ysi His-tag SPA beads were mixed together.

Procedure:

Appropriate dilutions of each compound were prepared and pipetted into the appropriate wells of a multiwell plate.

9.1 µL of [^{3}H] EC was added to each well of column 2-23 of the multiwell plate.

5 µl of diluted LXRα lysate was added to each well of column 2-23 on odd rows of the multiwell plate.

5 µL of diluted LXRβ lysate was added to each well of column 2-23 on even rows of the multiwell plate.

17.5 µL of SPA bead solution was added to each well of column 2-23 of the multiwell plate.

The plates were covered with clear sealer and placed in an incubator at ambient temperature for 1 hour.

After incubation plates were analyzed using a luminescent plate reader (MicroBeta, Wallac) using the program n ABASE 3H_384DPM. The setting for n ABASE 3H_384DPM was:

Counting Mode: DPM

Sample Type: SPA

ParaLux Mode: low background

Count time: 30 sec.

Assays for LXRα and LXRβ were performed in the identical manner. The determined Ki represents the average of at least two independent dose response experiments. The binding affinity for each compound may be determined by non-linear regression analysis using the one site competition formula to determine the IC_{50} where:

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{(1+10^{X-\log IC50})}$$

The Ki is than calculated using the Cheng and Prusoff equation where:

$$Ki = IC_{50}/(1 + [\text{Concentration of Ligand}]/Kd \text{ of Ligand})$$

For this assay, typically the Concentration of Ligand = 50 nM and the Kd of EC for the receptor is 200 nM as determined by saturation binding.

The compounds of the invention demonstrated the ability to bind to LXRα and/or LXRβ, as well as FXR when tested in this assay. Preferably, the compound binds to the LXR, as well as FXR with a binding affinity, for example, of about 50μM or less, 20μM or less, 10μM or less, 5μM or less, 2.5μM or less or 1μM or less. In an advantageous embodiment, the IC50 of the binding compounds is about 0.5μM or less, about 0.3μM or less, about 0.1μM or less, about 0.08μM or less, about 0.06μM or less, about 0.05μM or less, about 0.04μM or less, 0.03μM or less, preferably, about 0.03μM or less.

EXAMPLE 50A

TIME RESOLVED FLUORESCENCE RESONANCE ENERGY TRANSFER (TR-FRET) ASSAY

The TR-FRET assay was performed by incubating 8 nM of GST-

farnesoid X receptor -LBD (comprising glutathione-S-transferase fused in frame to the farnesoid X receptor ligand binding domain , (amino acids 244-471 of the human farnesoid X receptor)), 8 nM of Europium-labeled anti-GST antibody (Wallac/PE Life Sciences Cat#AD0064), 16 nM biotin-SRC-1 peptide [5'-biotin-CPSSHSSLTERHKILHRLLQEGSPS-CONH2], 20 nM APC-SA [allophycocyanin conjugated streptavidin] (Wallac/PE Life Sciences, Cat# AD0059A) in FRET assay buffer (20 mM KH_2PO_4/K_2HPO_4 (pH 7.3), 150 mM NaCl, 2 mM CHAPS, 2 mM EDTA, 1 mM DTT) in the presence of the test compound(s) for 2-4 hours at room temperature in a 384 well assay plate. Data was collected using an LJL Analyst using the standard operating instructions and conditions with readings at emission wavelengths of 615 nm and 665 nm after a delay of 65 μs and an excitation wavelength of 330 nm.

EXAMPLE 50B

FXR CO-TRANSFECTION ASSAY

The basic co-transfection protocol for measuring the farnesoid X receptor activity is as follows. CV-1 African Green Monkey Kidney cells were plated 24 hours before transfection to achieve approximately 70-80 percent confluency. Cells were transfected with the following expression vectors, CMX- farnesoid X receptor (full length human farnesoid X receptor), CMX-RXRα (full length human RXR), Luc12 ((ECREx7-Tk-Luciferase) luciferase reporter gene construct. (See WO 00/76523, Venkateswaran et al., (2000) J. Biol. Chem. **275** 14700-14707). A CMX-β-Galactosidase expression vector was used as a transfection control. The transfection reagent used was DOTAP (Boehringer Mannheim). Cells were incubated with the DOTAP/DNA mixture for 5 hours after which the cells were harvested and plated onto either 96 well or 384 well plates containing the appropriate concentration of test compound. The assay was allowed to continue for an additional 18-20 hours, after which the cells were lysed, with lysis buffer (1 % triton X 100, 10 % glycerol, 5 mM Dithiothreitol, 1 mM EGTA, 25 mM Tricine, pH 7.8) and the luciferase activity measured in the presence of Luciferase assay buffer (0.73 mM ATP, 22.3 mM Tricine, 0.11 mM EGTA, 0.55 mM Luciferin, 0.15 mM Coenzyme A, 0.5 mM HEPES, 10 mM Magnesium sulphate) on a standard luminomter plate reader (PE Biosystems, NorthStar Reader), using recommended operating instructions and conditions.

RESULTS OF EXAMPLE 50A AND 50B

Both the farnesoid X receptor /ECREx7 co-transfection assay (Example 50B) and the TR-FRET assay (Example 50A) can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control (chenodeoxycholic acid, CDCA) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. The curve for the data is generated by using the equation:

Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by chenodeoxycholic acid that is measured individually in each dose response experiment.

For the antagonist assay, CDCA is added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of CDCA. In this example, 100% inhibition would indicate that the activity of CDCA has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays (EC_{50} or IC_{50} less than 10 μM). Most compounds showed activity at or below 1 μM. Moreover, the compounds exhibited agonist activity at or less than 1μM EC_{50} with greater than 100 % efficacy as measured via the co-transfection assay:

EXAMPLE 51

LXR Co-Transfection Assay

To measure the ability of compounds to activate or inhibit the transcriptional activity of LXR in a cell based assay, the co-transfection assay was used. It has been shown that LXR functions as a heterodimer with RXR. For the co-transfection assay, expression plasmids for LXR and RXR are introduced via transient transfection into mammalian cells along with a luciferase reporter plasmid that contains

one copy of a DNA sequence that is bound by LXR-RXR heterodimers (*LXRE*; Willy, P. *et.al.* 1995). Treatment of transfected cells with an LXR agonist increases the transcriptional activity of LXR, which is measured by an increase in luciferase activity. Similarly, LXR antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of a LXR agonist.

Required Materials

1. CV-1 African Green Monkey Kidney Cells
2. Co-transfection expression plasmids, comprising full- length LXRα (pCMX-hLXR α), LXRβ (pCMX-hLXR β), or RXRα (pCMX-RXR), reporter plasmid (LXREx1-Tk-Luciferase), and control (pCMX-Galactosidase expression vector) (Willey et al. Genes & Development 9 1033-1045 (1995)).
3. Transfection reagent such as FuGENE6 (Roche).
4. 1x Cell lysis buffer (1 % Triton X 100 (JT Baker X200-07), 10% Glycerol (JT Baker M778-07), 5 mM Ditriotreitol (Quantum Bioprobe DTT03; add fresh before lysing), 1 mM EGTA (Ethylene Glycol-bis (B-Amino ethyl ether)-N,N,N',N'-Tetracetic Acid) (Sigma E-4378), 25 mM Tricine (ICN 807420) pH 7.8)
5. 1x Luciferase assay buffer (pH at 7.8) (0.73 mM ATP , 22.3 mM Tricine, 0.11 mM EDTA, 33.3 mM DTT)
6. 1x Luciferrin/CoA (11 mM Luciferin, 3.05 mM Coenzyme A, 10 mM HEPES)

Preparation of Screening Reagents

CV-1 cells were prepared 24 hours prior to the experiment by plating them into T-175 flasks or 500 cm^2 dishes in order to achieve 70-80% confluency on the day of the transfection. The number of cells to be transfected was determined by the number of plates to be screened. Each 384 well plate requires 1.92x106 cells or 5000 cells per well. DNA Transfection Reagent was prepared by mixing the required plasmid DNAs with a cationic lipid transfection reagent FuGENE6 (Roche) by following the instructions provided with the reagents. Optimal DNA amounts were determined empirically per cell line and size of vessel to be transfected. 10-12 mL of media was added to the DNA Transfection Reagent and this mixture was added to the cells after aspirating media from the T175 cm^2 flask. Cells were then incubated at least 5 hours at 37°C to prepare screening cells.

Luciferase assay reagent was prepared by combining before use (per 10 mL):

10 mL 1x Luciferase assay buffer

0.54 mL of 1x Luciferrin/CoA

0.54 mL of 0.2 M Magnesium sulfate

Procedure

Assay plates were prepared by dispensing 5 µL of compound per well of a 384 well plate to achieve final compound concentration of 10 µM and no more than 1% DMSO. Media was removed from the screening cells, the cells trypsinized, harvested cells by centrifugation, counted, and plated at a density of approximately 5000 cells per well in the 384 well assay plate prepared above in a volume of about 45 µL. Assay plates containing both compounds and screening cells (50 µL in total volume) were incubated for 20 hours at 37°C.

After incubation with compounds, media was removed from the cells and lysis buffer (30 µL/well) added. After 30 minutes at ambient temperature, luciferase assay buffer (30 µL/well) was added and the assay plates read on a luminometer (PE Biosystems Northstar reader with on-board injectors, or equivalent). Plates were read immediately after addition of luciferase assay buffer.

The LXR/LXRE co-transfection assay can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control ((*N*-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)amino)propyl)-2,2-dimethylpropionamide)) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate.

The data from this assay is fitted to the following equation, from the EC_{50} value may be solved:

$$Y = Bottom + (Top-Bottom)/(1+10^{((logEC50-X)*HillSlope)})$$

The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by ((*N*-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) that is measured individually in each dose response experiment.

For the antagonist assay, a LXR agonist can be added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of the agonist. In this example, 100% inhibition would indicate that the activity of a specific concentration of LXR agonist has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only. Compounds of the invention, when tested in this assay, demonstrated the ability to modulate the activity of LXRα and/or LXRβ.

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays (EC_{50} or IC_{50} less than 10 μM). Most compounds showed activity at or below 1 μM. Moreover, the compounds exhibited agonist activity at or less than 1μM EC_{50} with greater than 100 % efficacy as measured via the co-transfection assay

EXAMPLE 52

In Vivo Assays

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for a lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice (LXRα-/- or LXRβ -/-) and C57BL/6 wild-type controls are used in this same protocol.

<u>Plasma Lipid Evaluation:</u>

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day –1 (in order to group animals), day 1, 3, and 7. Samples are collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and

triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice (LXRα-/- or LXRβ-/-) and C57BL/6 wild-type controls are used in this same protocol.

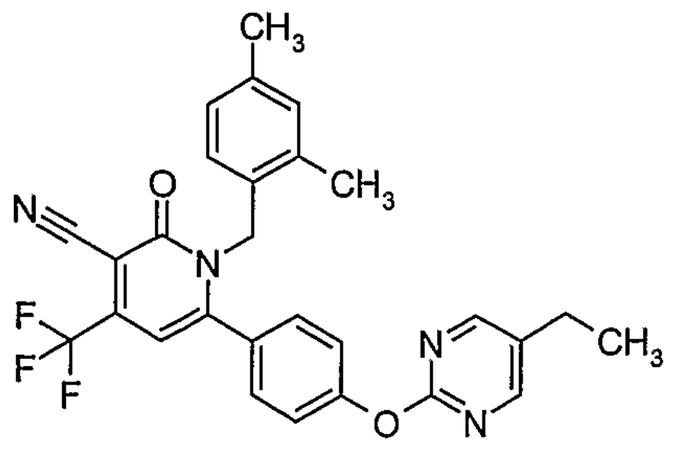
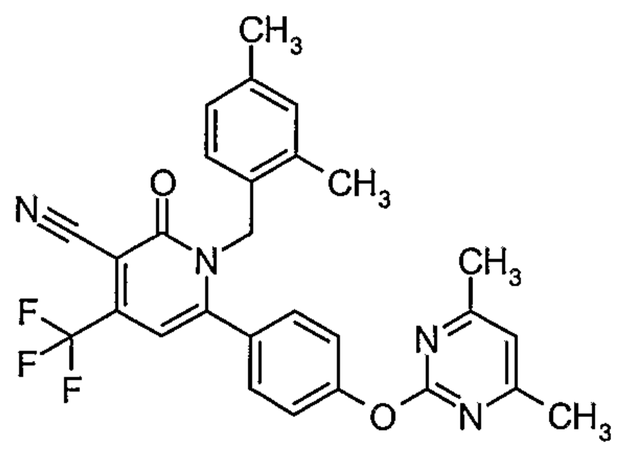
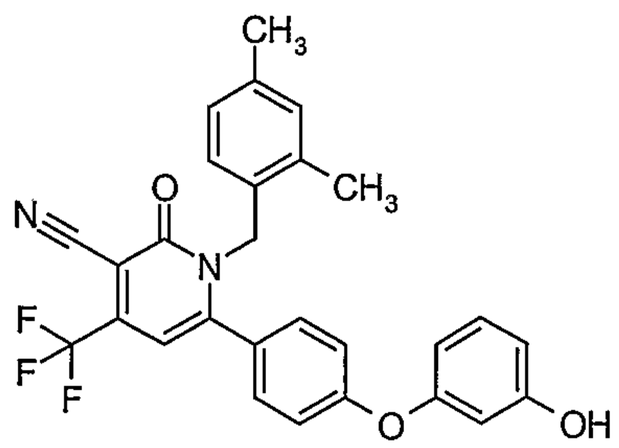
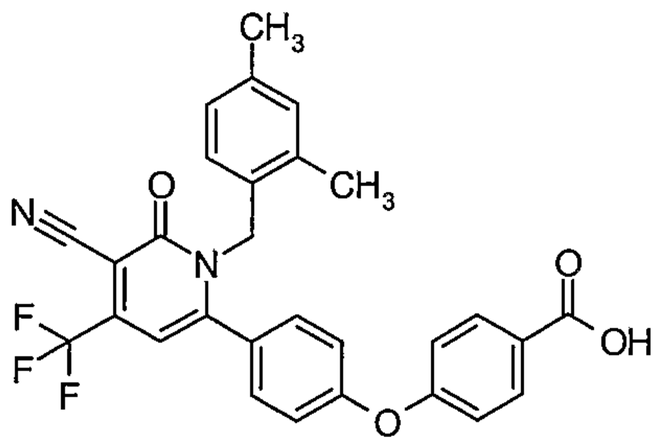
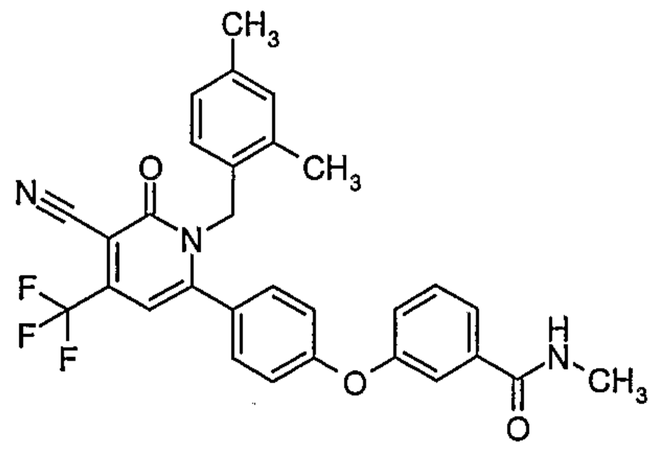
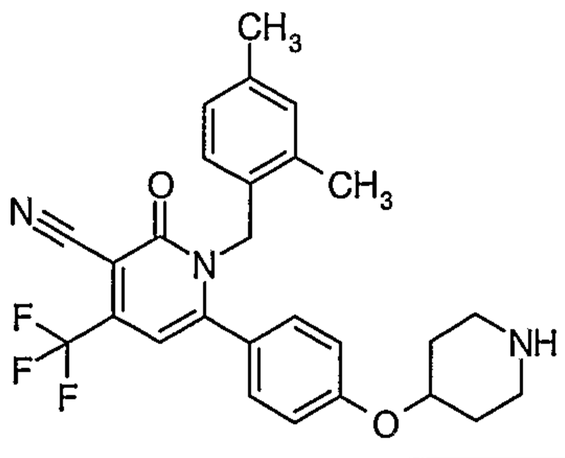
Cholesterol Absorption:

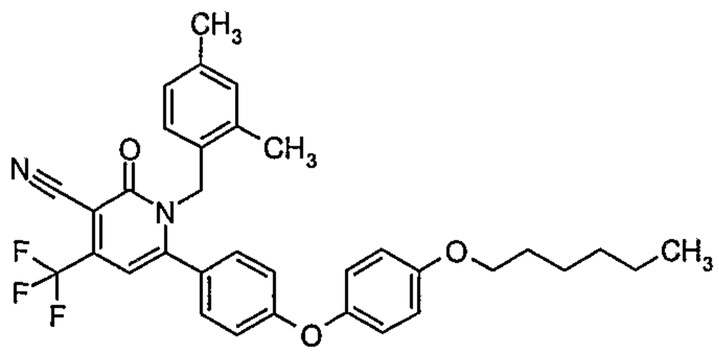
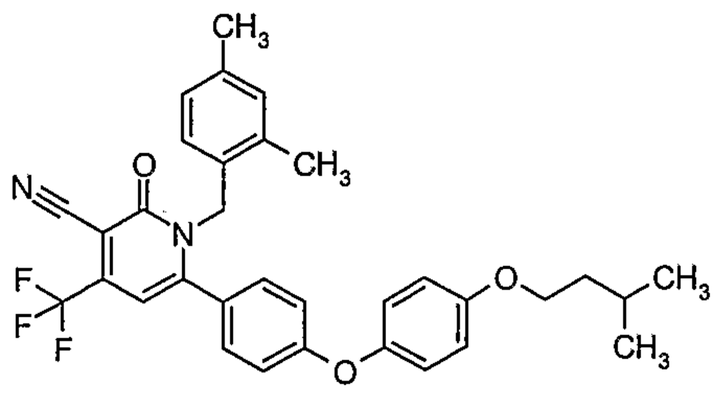
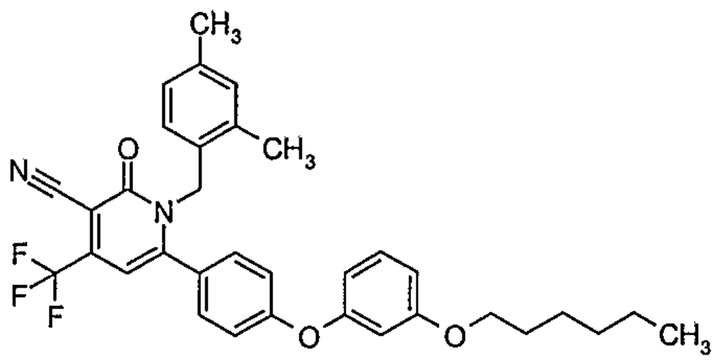
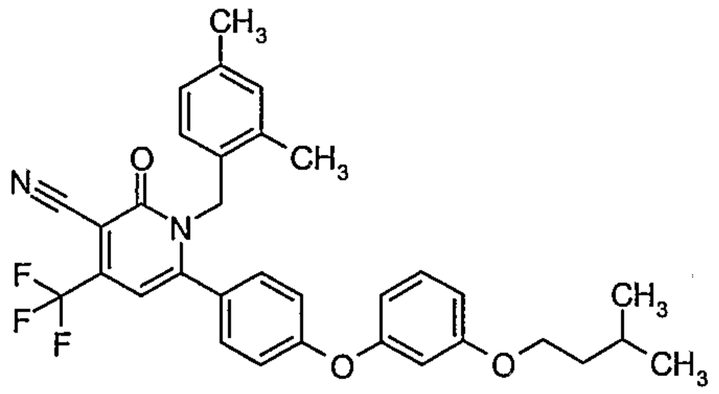
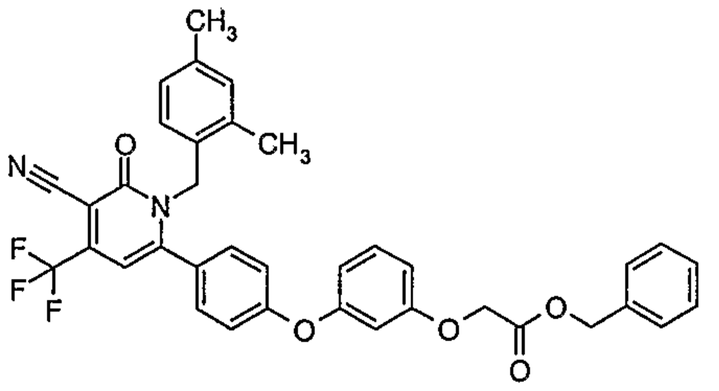
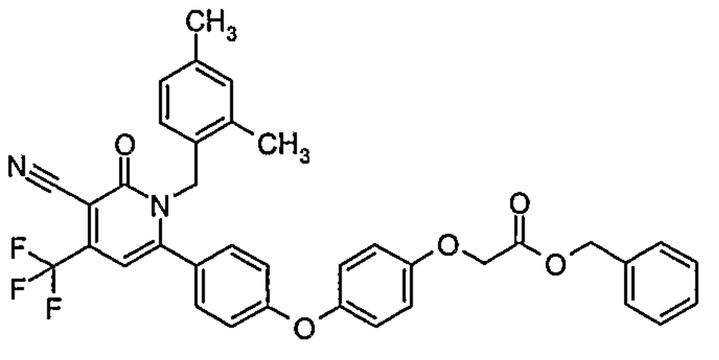
Evaluation of compounds to inhibit cholesterol absorption is done via measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of the study, animals are administered [^{14}C]-cholesterol and [^{3}H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to evaluate the amount of cholesterol absorbed by the individual animal.

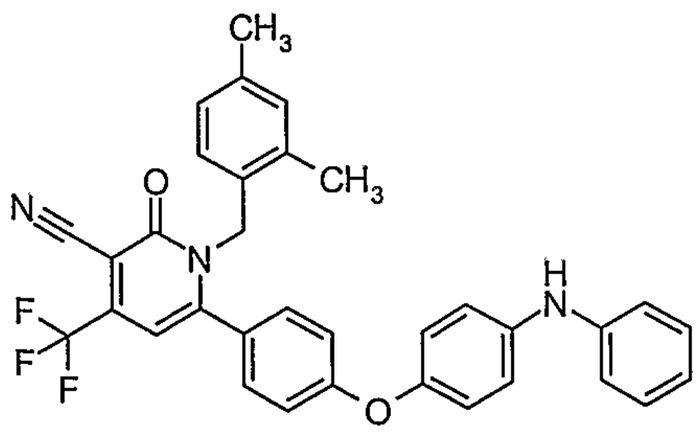
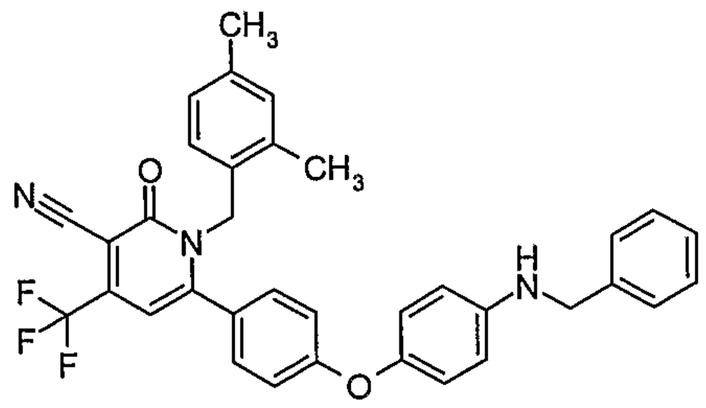
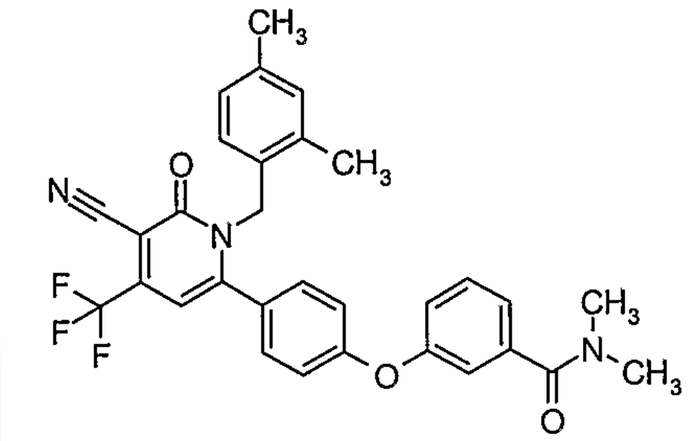
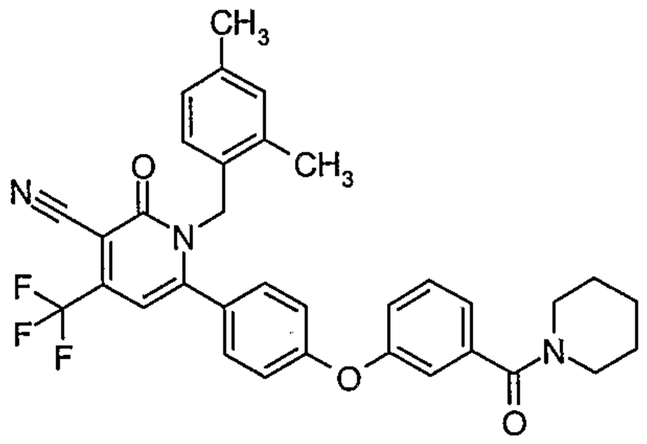
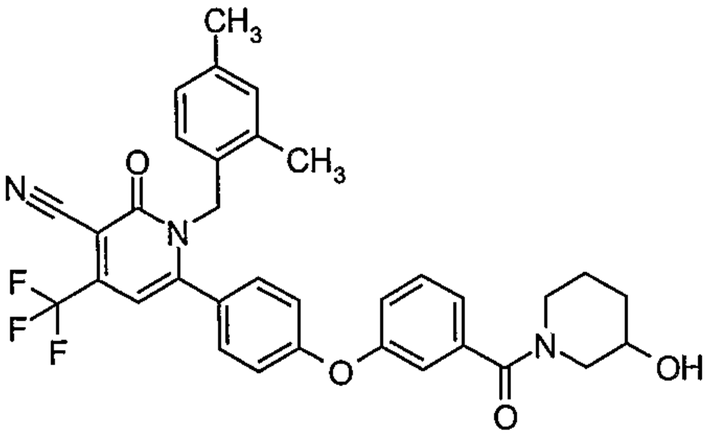
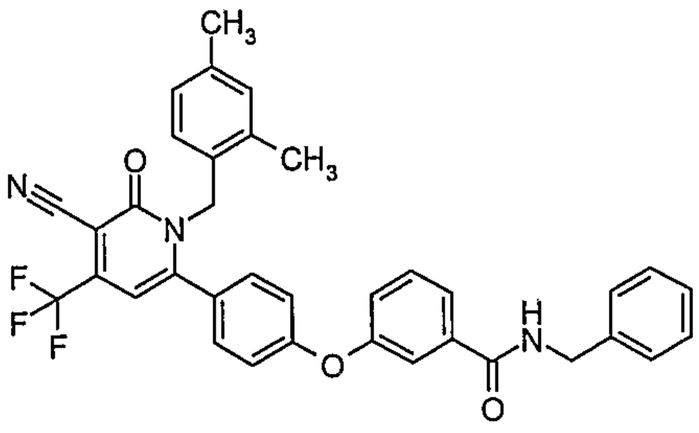
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety.

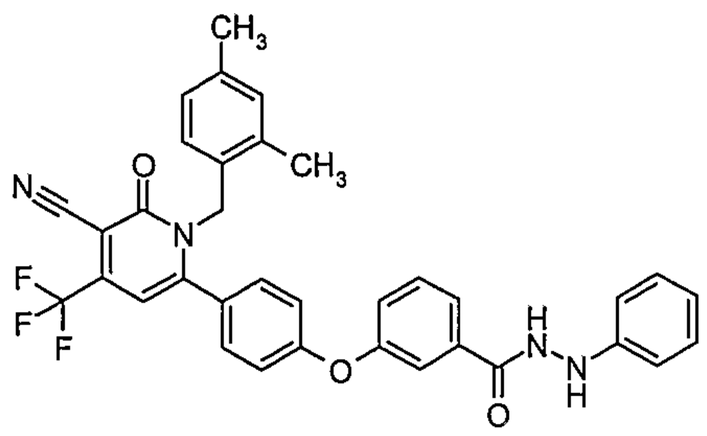
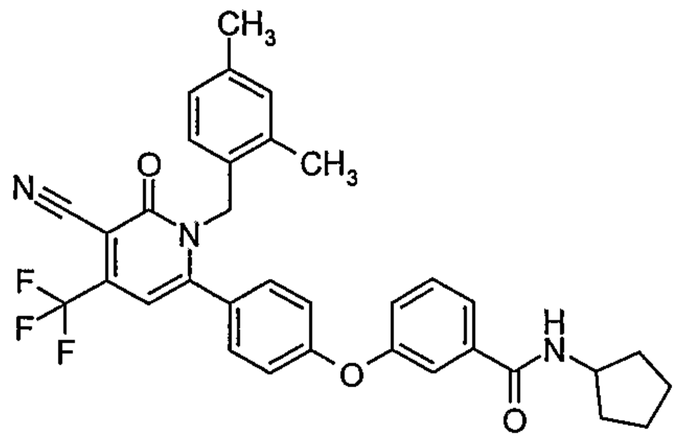
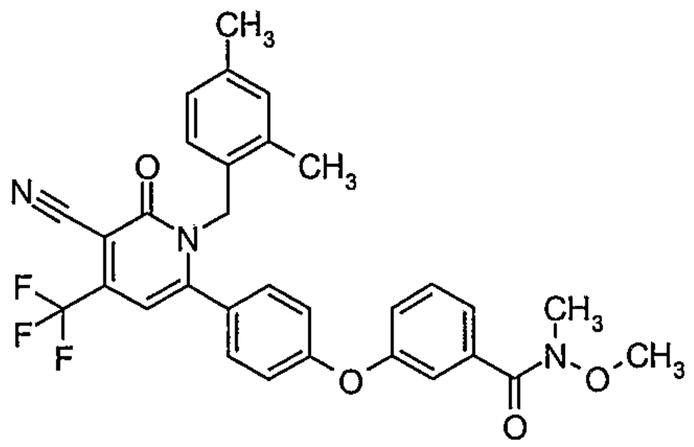
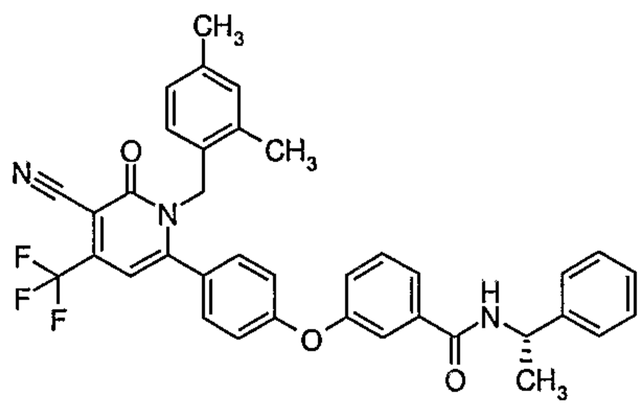
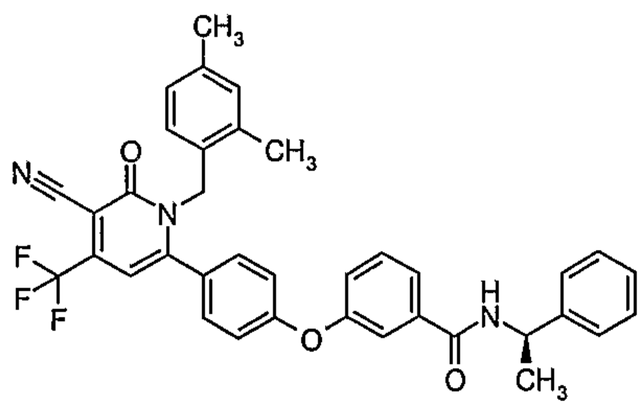
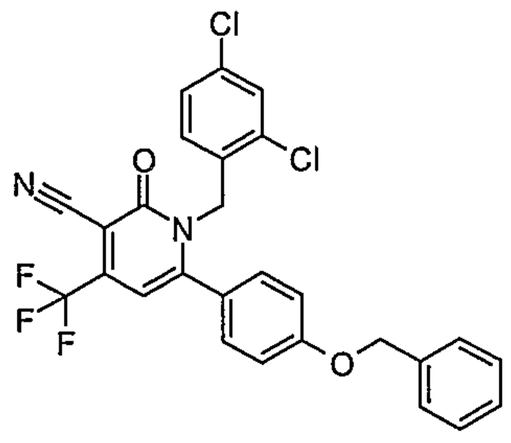
From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

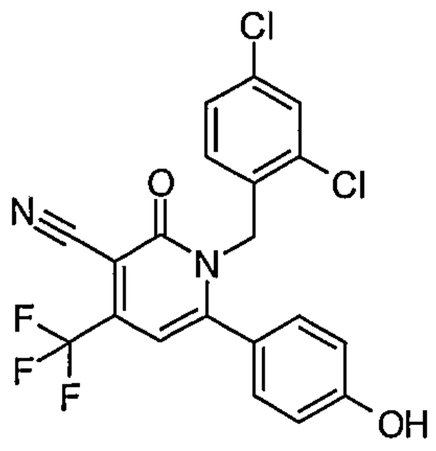
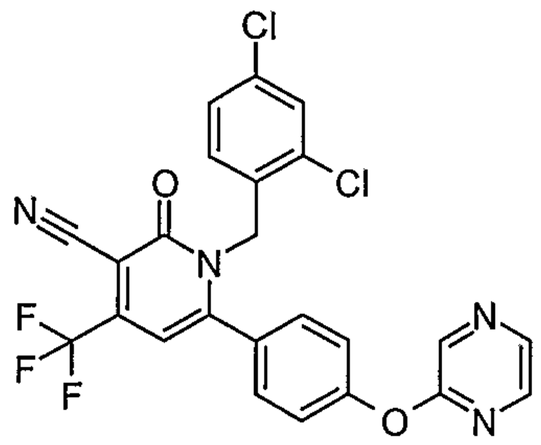
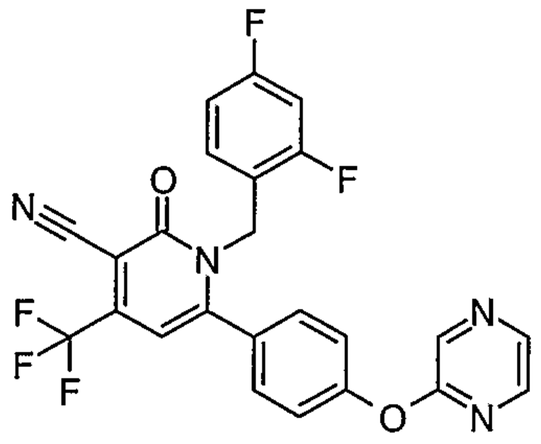
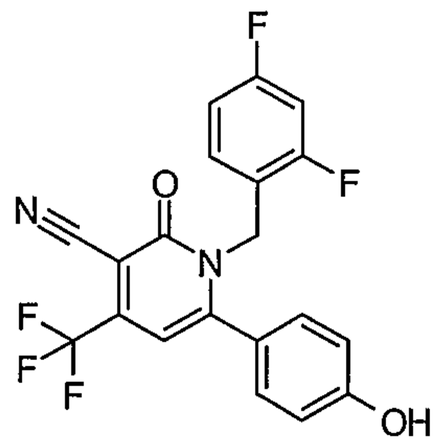
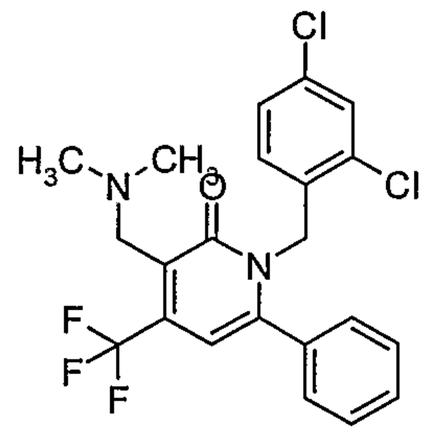
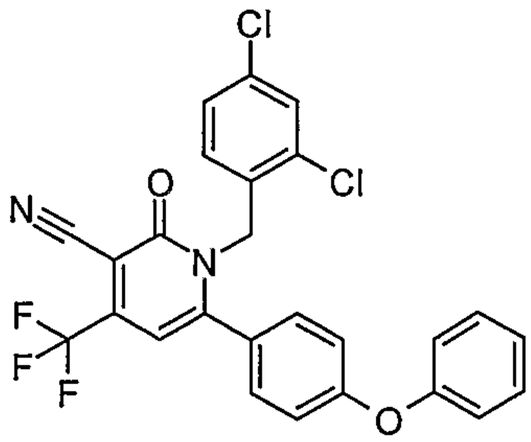
Table 1

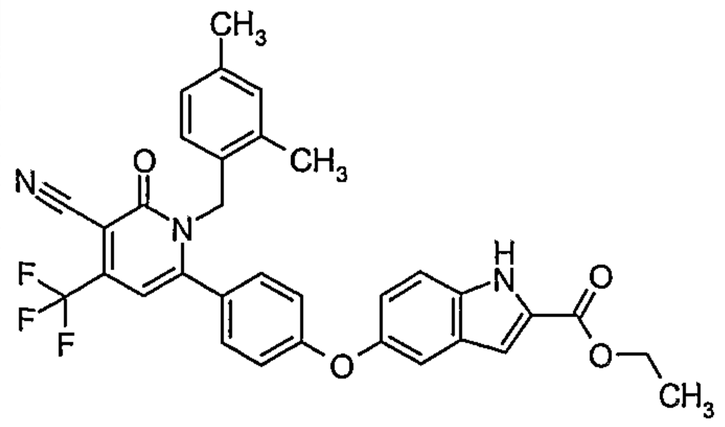
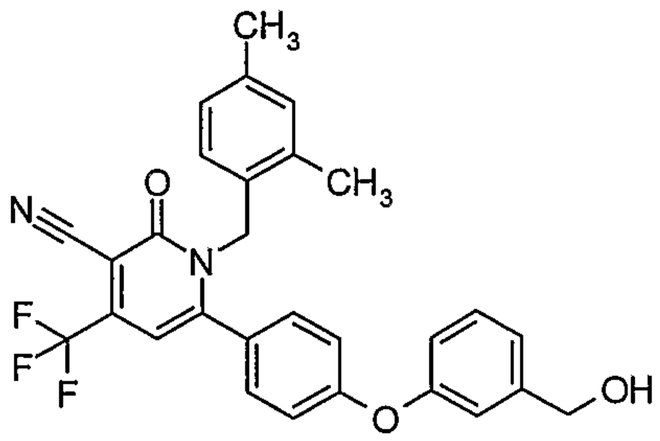
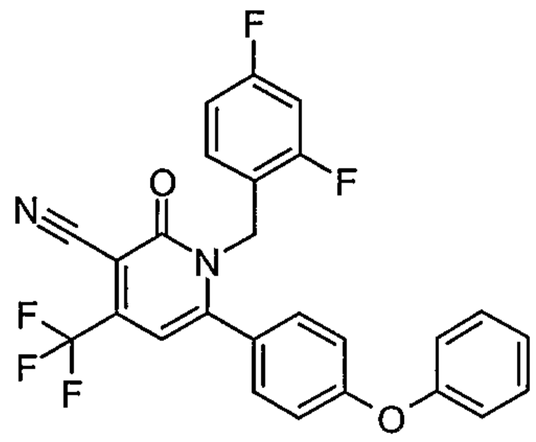
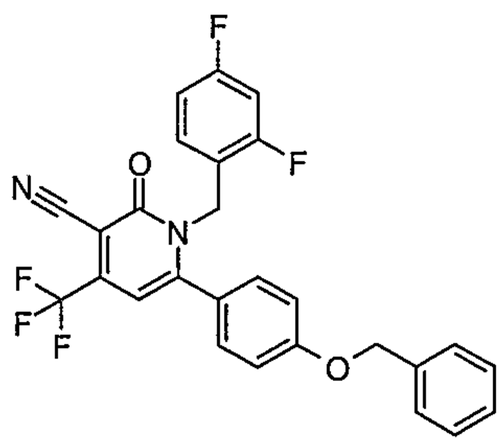
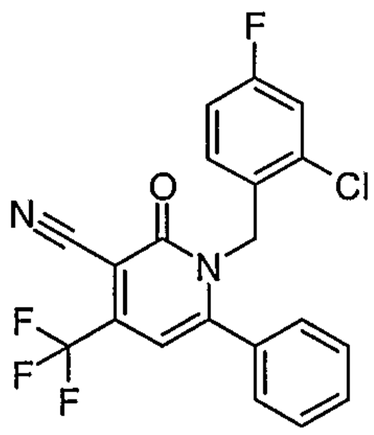
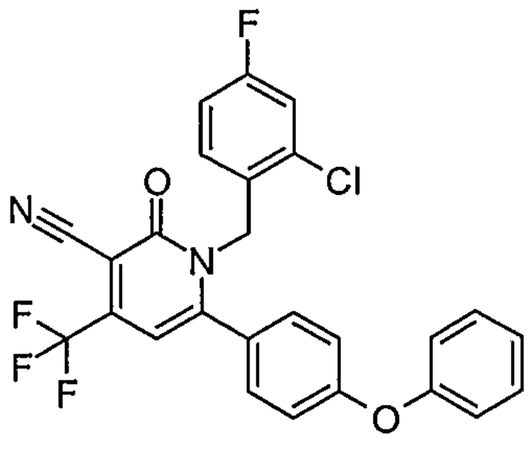
1		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(5-ethylpyrimidin-2-yl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
2		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(4,6-dimethylpyrimidin-2-yl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
3		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(3-hydroxyphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
4		4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]benzoic acid
5		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-methylbenzamide
6		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-[4-(piperidin-4-yloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

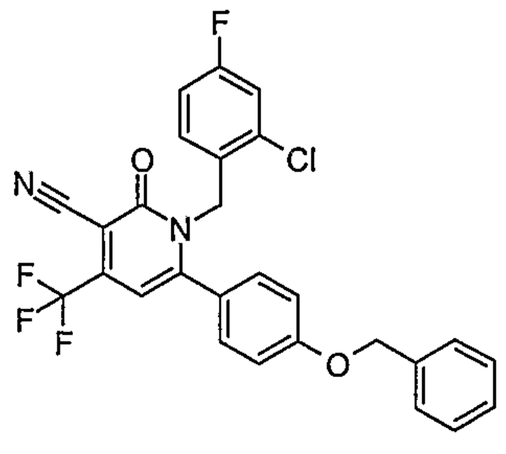
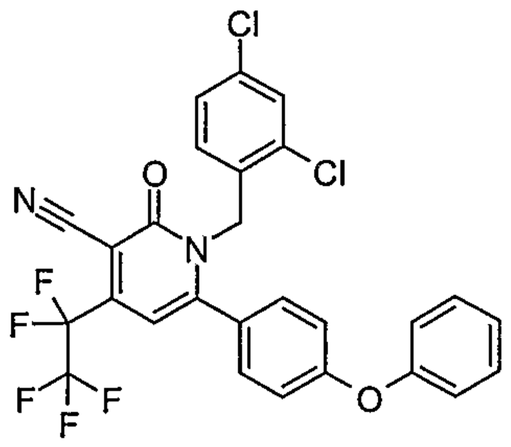
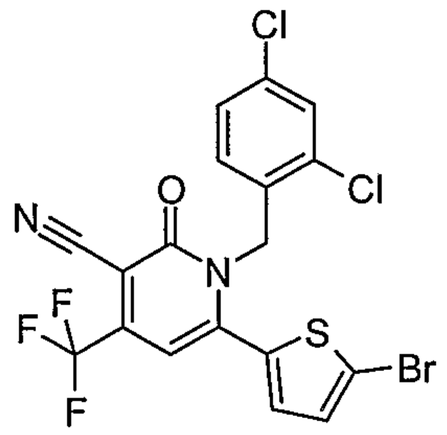
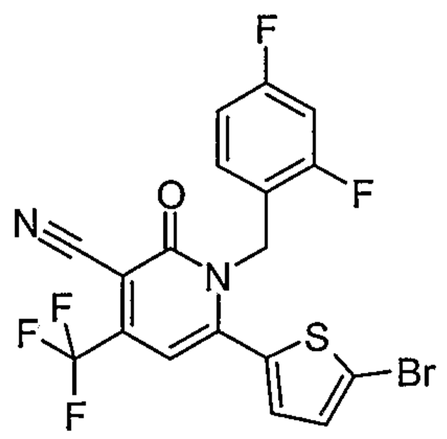
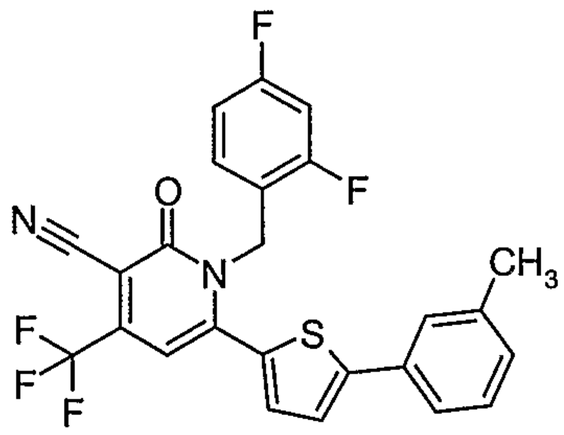
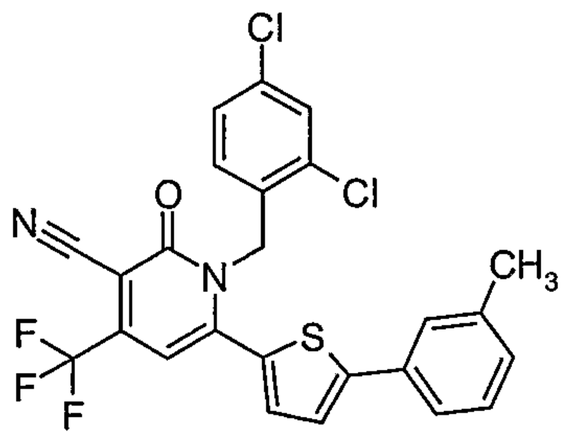
7		1-[(2,4-dimethylphenyl)methyl]-6-(4-{[4-(hexyloxy)phenyl]oxy}phenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
8		1-[(2,4-dimethylphenyl)methyl]-6-[4-({4-[(3-methylbutyl)oxy]phenyl}oxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
9		1-[(2,4-dimethylphenyl)methyl]-6-(4-{[3-(hexyloxy)phenyl]oxy}phenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
10		1-[(2,4-dimethylphenyl)methyl]-6-[4-({3-[(3-methylbutyl)oxy]phenyl}oxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
11		phenylmethyl ({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}oxy)acetate
12		phenylmethyl ({4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}oxy)acetate

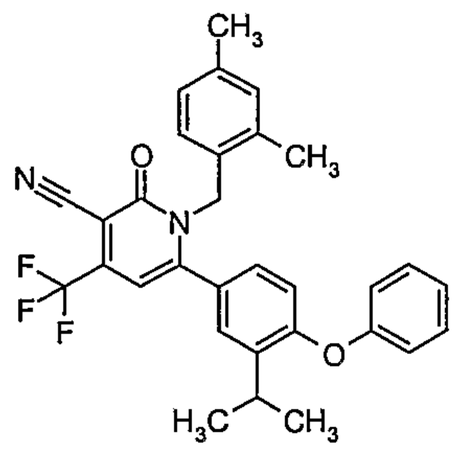
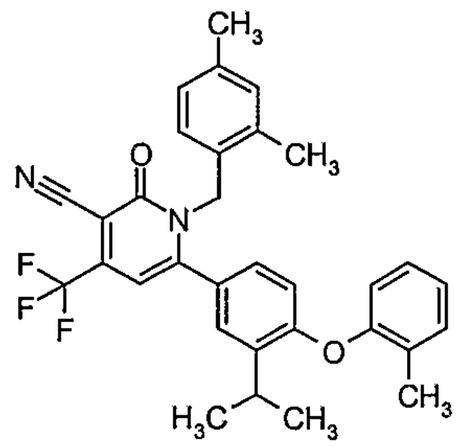
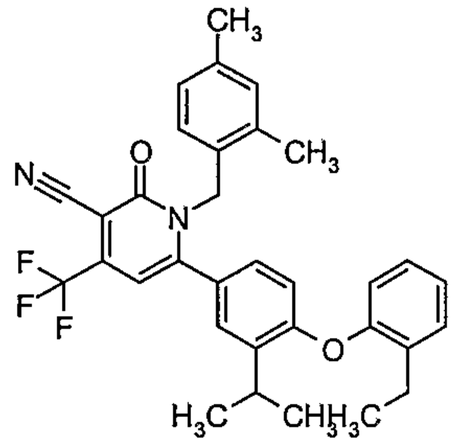
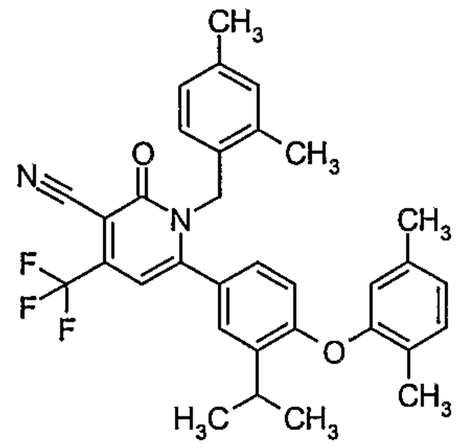
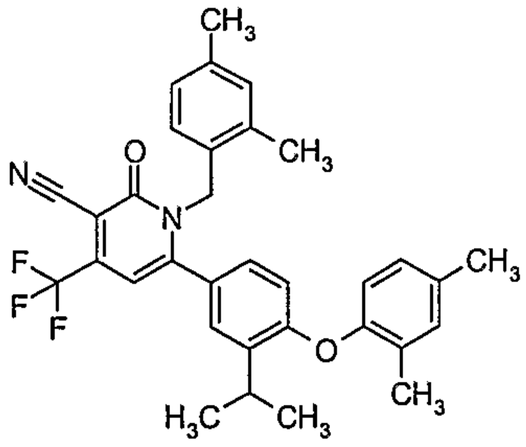
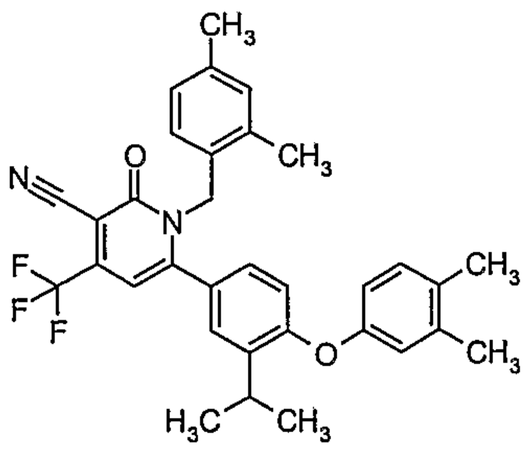
13		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-(4-{[4-(phenylamino)phenyl]oxy}phenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
14		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-[4-({4-[(phenylmethyl)amino]phenyl}oxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
15		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethylbenzamide
16		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-(4-{[3-(piperidin-1-ylcarbonyl)phenyl]oxy}phenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
17		1-[(2,4-dimethylphenyl)methyl]-6-[4-({3-[(3-hydroxypiperidin-1-yl)carbonyl]phenyl}oxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
18		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(phenylmethyl)benzamide

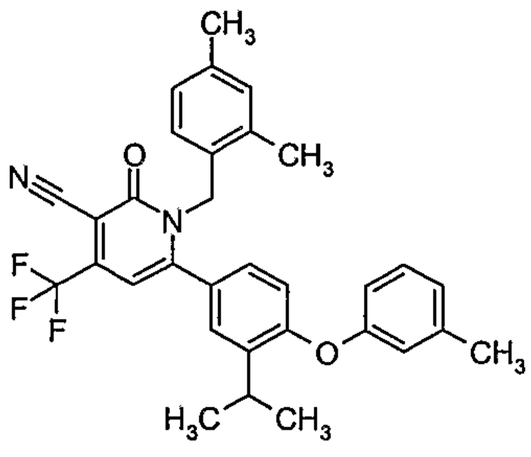
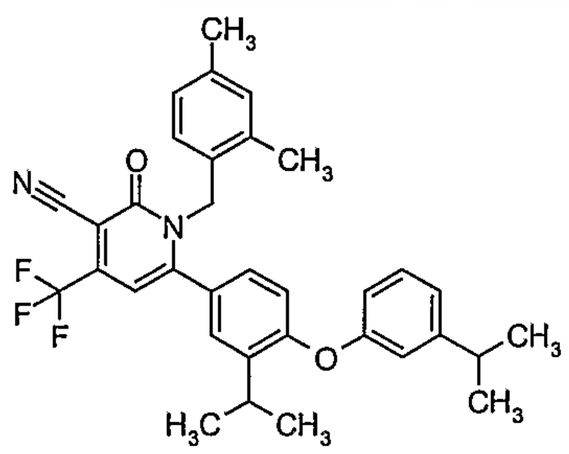
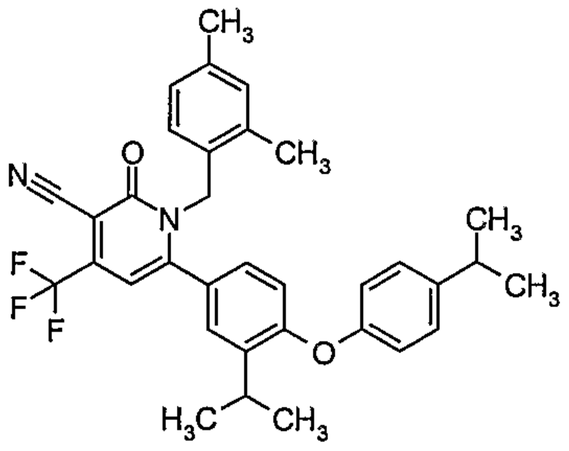
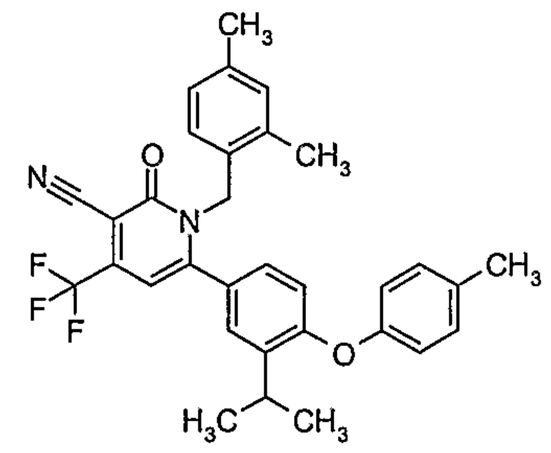
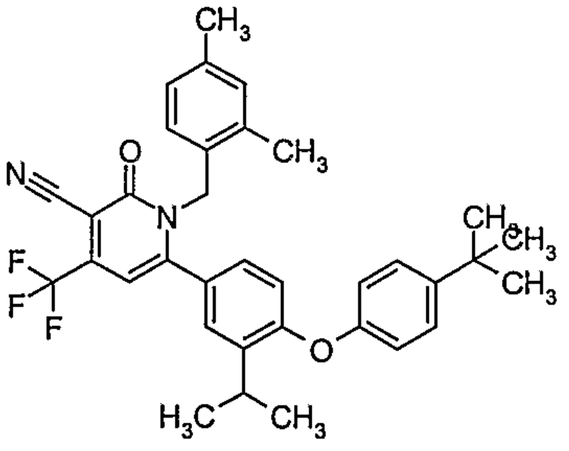
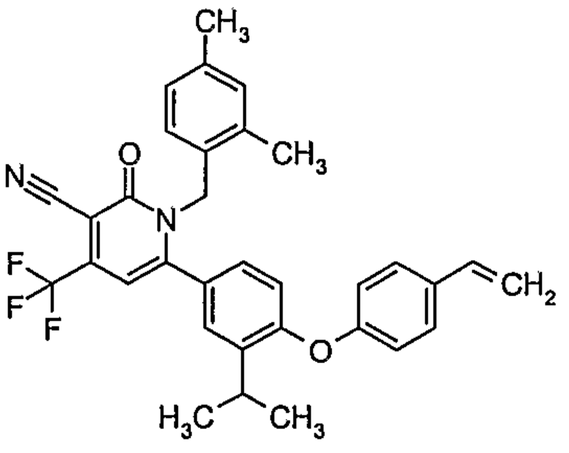
19		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N'-phenylbenzohydrazide
20		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-cyclopentylbenzamide
21		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-methyl-N-(methyloxy)benzamide
22	Chiral 	3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[(1S)-1-phenylethyl]benzamide
23	Chiral 	3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[(1R)-1-phenylethyl]benzamide
24		1-[(2,4-dichlorophenyl)methyl]-2-oxo-6-{4-[(phenylmethyl)oxy]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

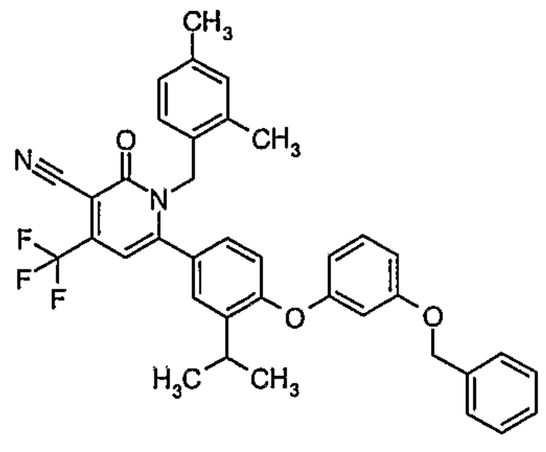
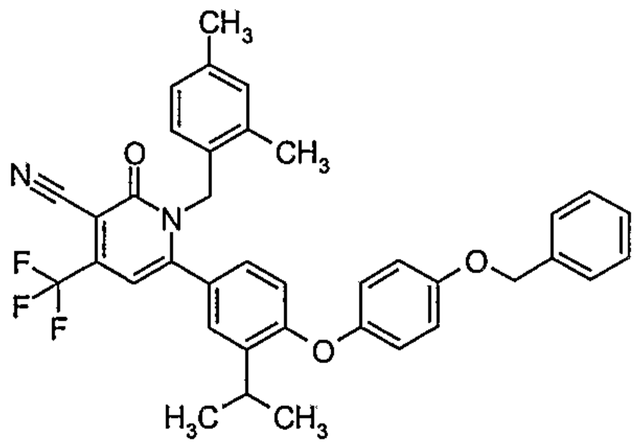
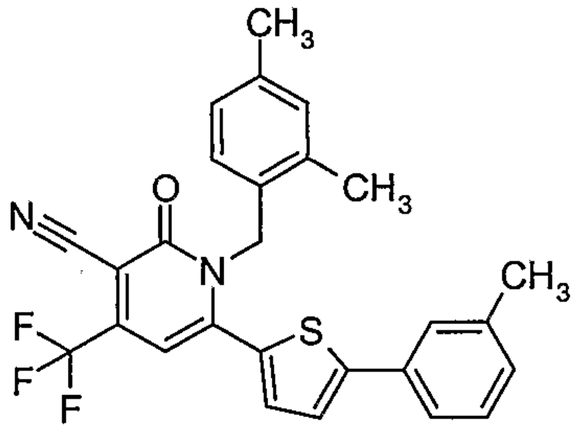
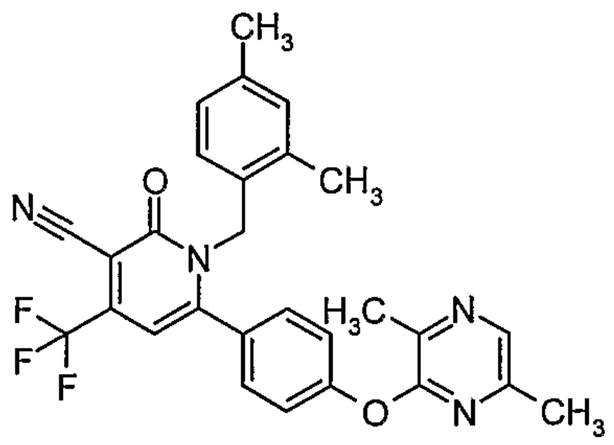
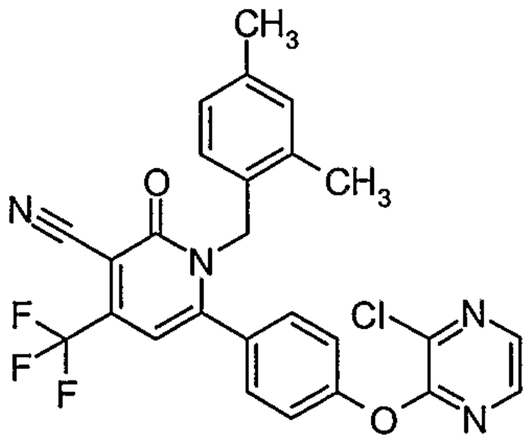
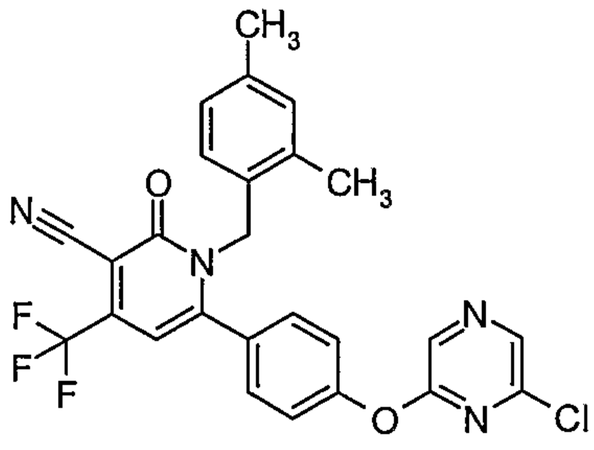
25		1-[(2,4-dichlorophenyl)methyl]-6-(4-hydroxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
26		1-[(2,4-dichlorophenyl)methyl]-2-oxo-6-[4-(pyrazin-2-yloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
27		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(pyrazin-2-yloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
28		1-[(2,4-difluorophenyl)methyl]-6-(4-hydroxyphenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
29		1-[(2,4-dichlorophenyl)methyl]-3-[(dimethylamino)methyl]-6-phenyl-4-(trifluoromethyl)pyridin-2(1H)-one
30		1-[(2,4-dichlorophenyl)methyl]-2-oxo-6-[4-(phenyloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

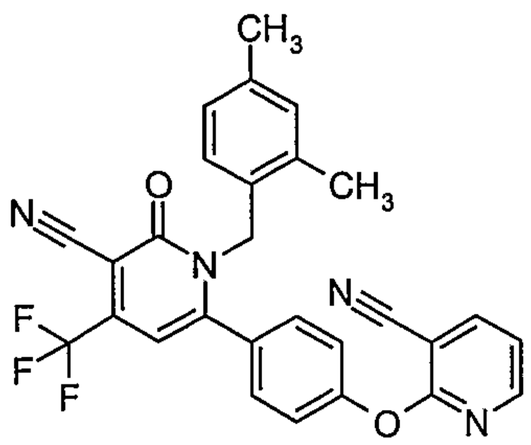
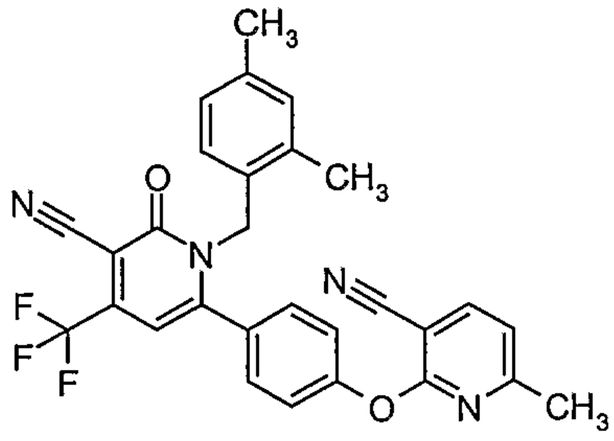
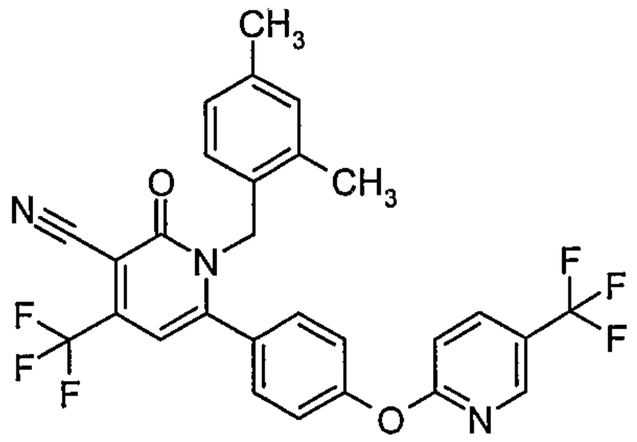
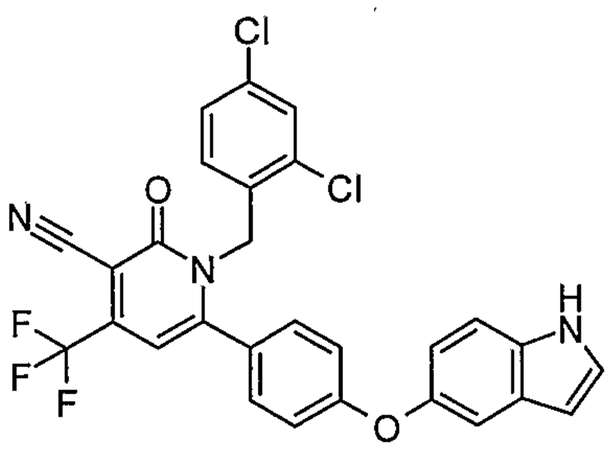
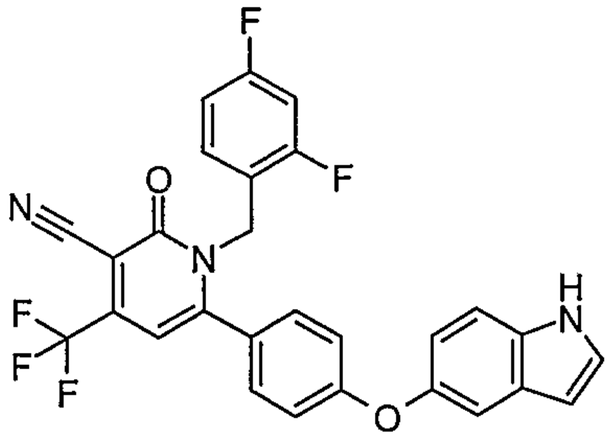
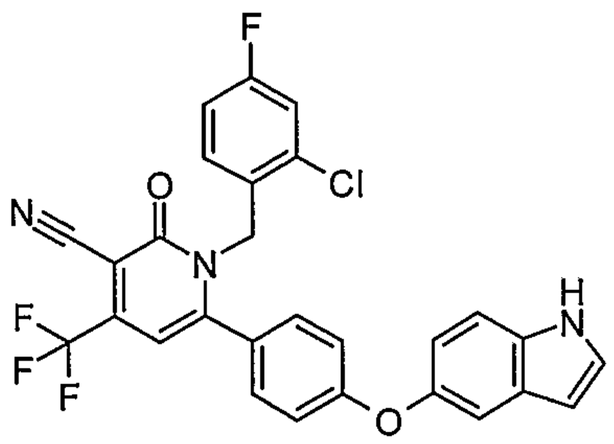
31		ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
32		1-[(2,4-dimethylphenyl)methyl]-6-(4-{[3-(hydroxymethyl)phenyl]oxy}phenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
33		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(phenyloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
34		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[(phenylmethyl)oxy]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
35		1-[(2-chloro-4-fluorophenyl)methyl]-2-oxo-6-phenyl-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
36		1-[(2-chloro-4-fluorophenyl)methyl]-2-oxo-6-[4-(phenyloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

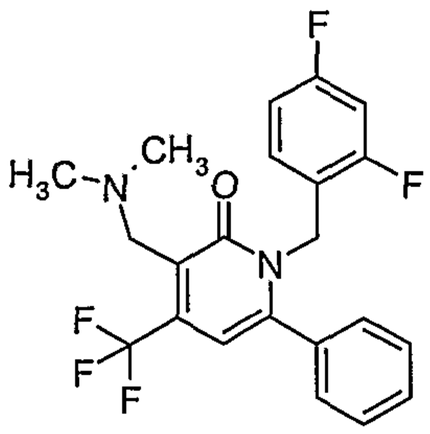
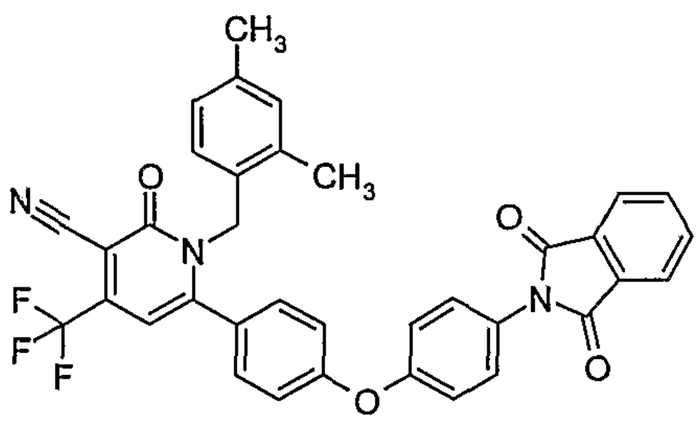
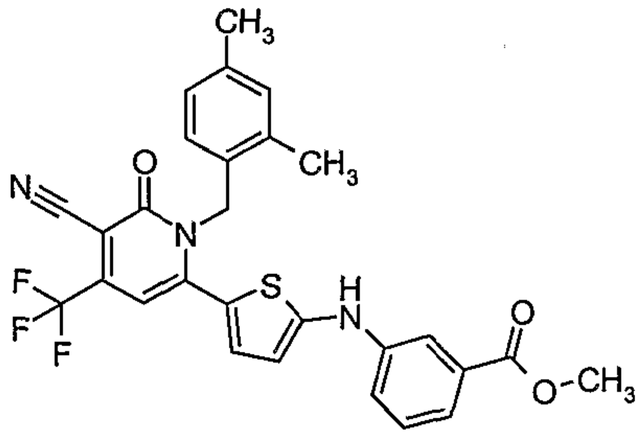
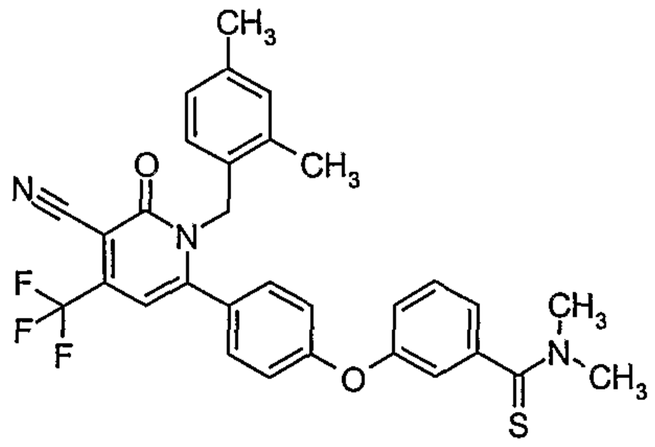
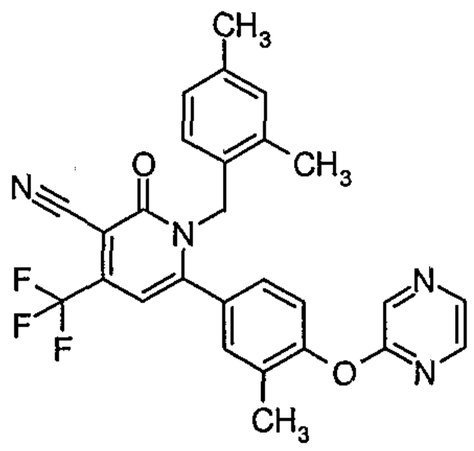
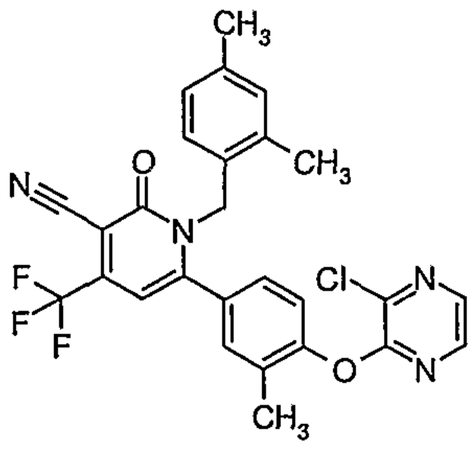
37		1-[(2-chloro-4-fluorophenyl)methyl]-2-oxo-6-{4-[(phenylmethyl)oxy]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
38		1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(pentafluoroethyl)-6-[4-(phenyloxy)phenyl]-1,2-dihydropyridine-3-carbonitrile
39		6-(5-bromo-2-thienyl)-1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
40		6-(5-bromo-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
41		1-[(2,4-difluorophenyl)methyl]-6-[5-(3-methylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
42		1-[(2,4-dichlorophenyl)methyl]-6-[5-(3-methylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

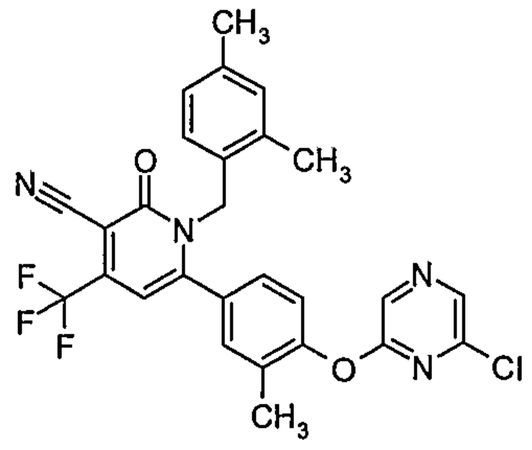
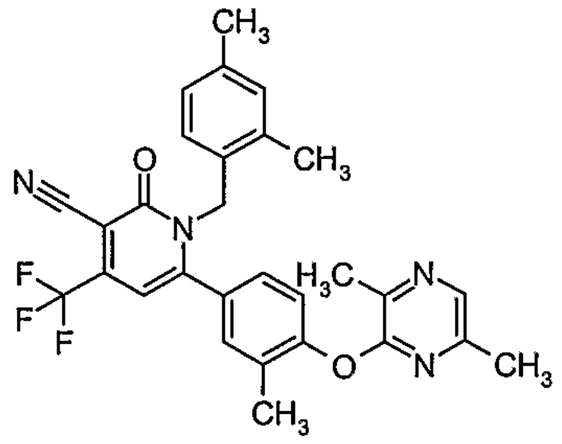
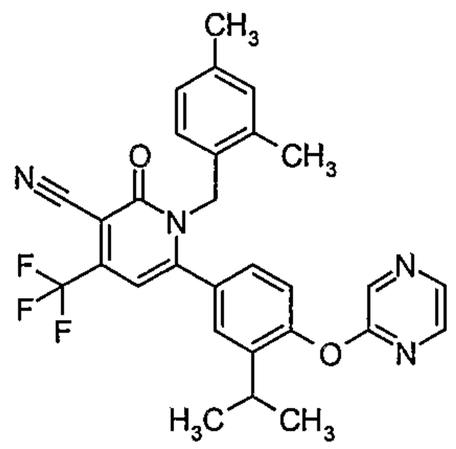
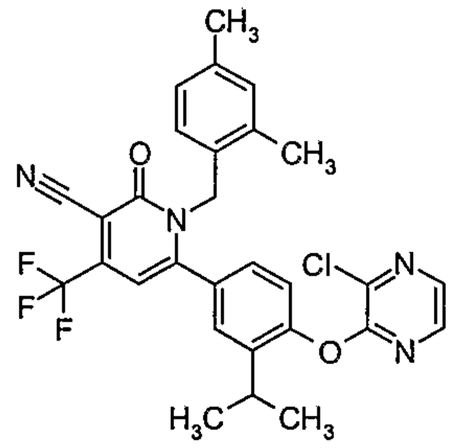
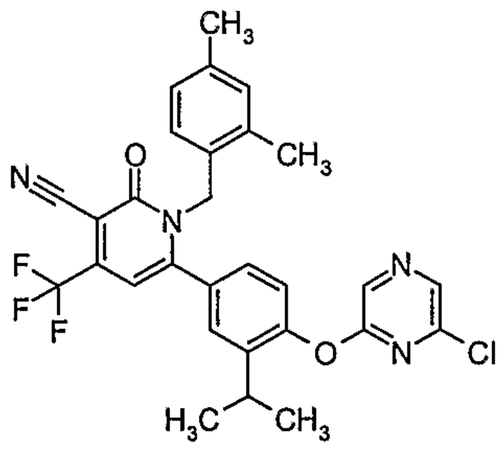
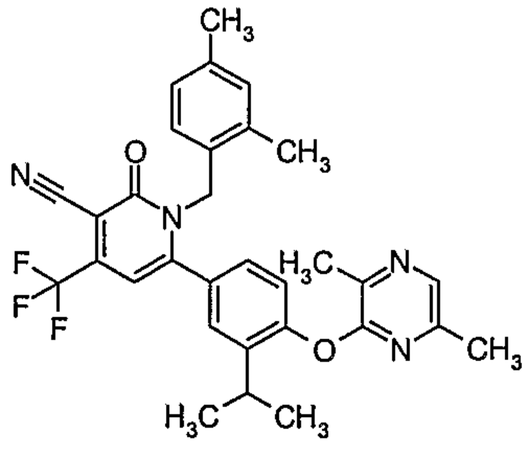
43		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-(phenyloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
44		1-[(2,4-dimethylphenyl)methyl]-6-{3-(1-methylethyl)-4-[(2-methylphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
45		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(2-ethylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
46		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(2,5-dimethylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
47		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(2,4-dimethylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
48		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(3,4-dimethylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

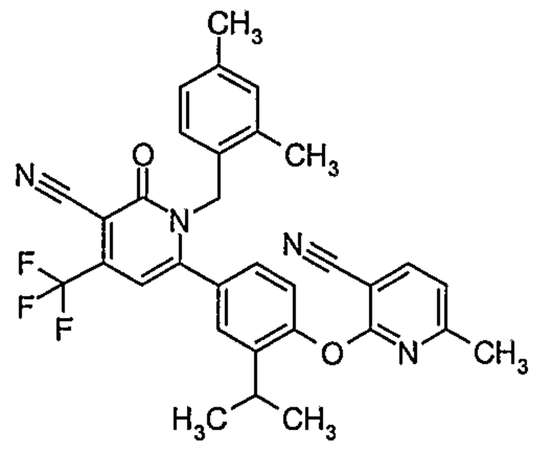
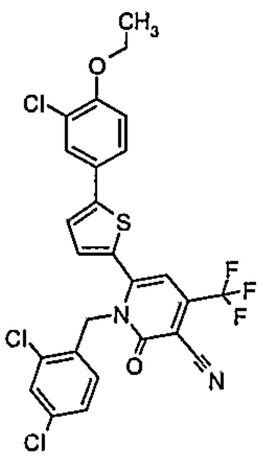
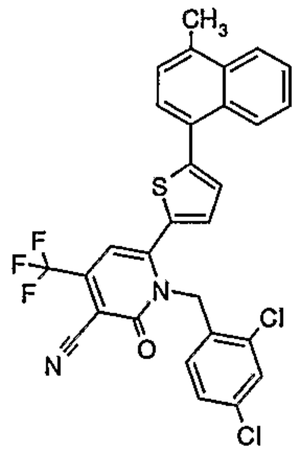
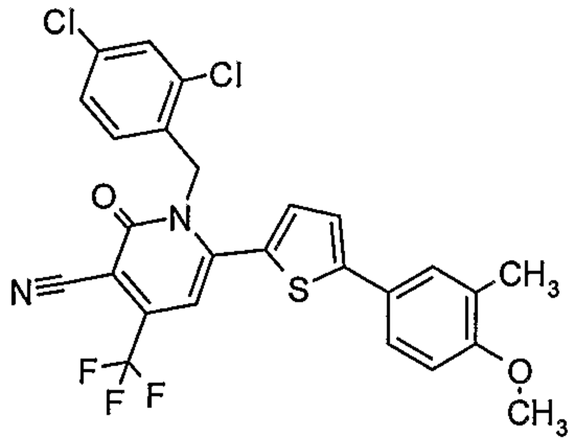
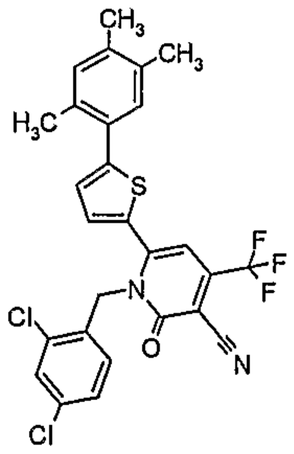
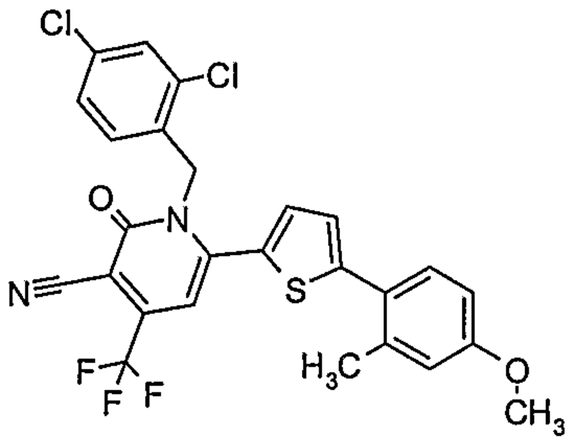
49		1-[(2,4-dimethylphenyl)methyl]-6-{3-(1-methylethyl)-4-[(3-methylphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
50		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-{[3-(1-methylethyl)phenyl]oxy}phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
51		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-{[4-(1-methylethyl)phenyl]oxy}phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
52		1-[(2,4-dimethylphenyl)methyl]-6-{3-(1-methylethyl)-4-[(4-methylphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
53		6-[4-{[4-(1,1-dimethylethyl)phenyl]oxy}-3-(1-methylethyl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
54		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(4-ethenylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

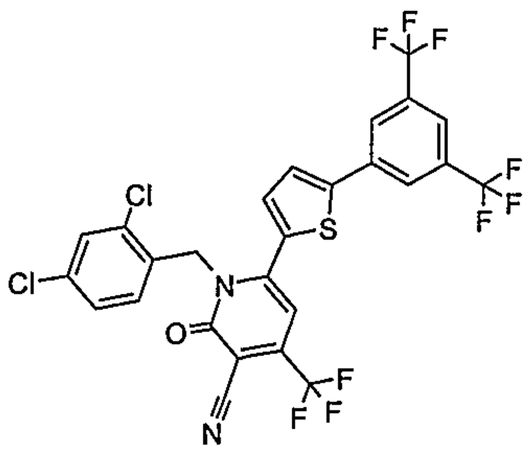
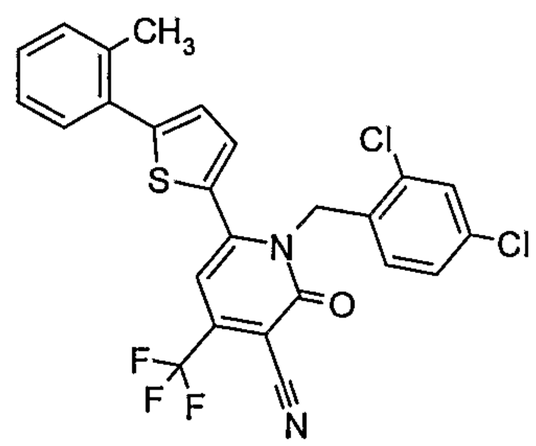
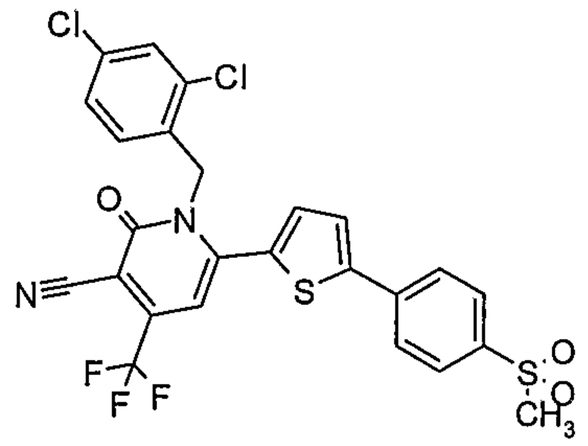
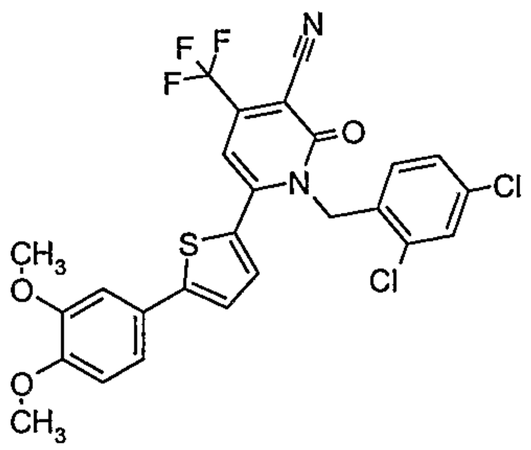
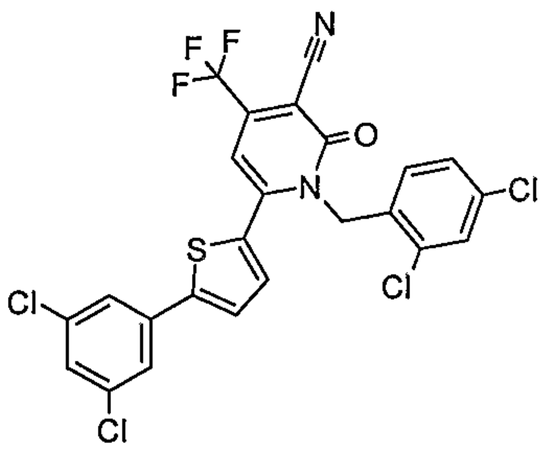
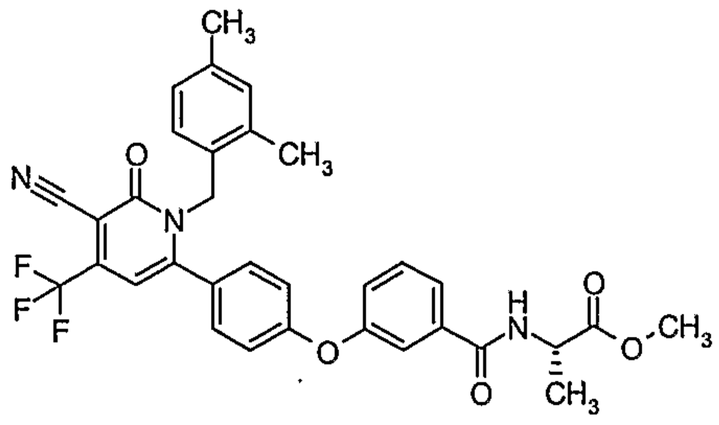
55		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-({3-[(phenylmethyl)oxy]phenyl}oxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
56		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-({4-[(phenylmethyl)oxy]phenyl}oxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
57		1-[(2,4-dimethylphenyl)methyl]-6-[5-(3-methylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
58		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(3,6-dimethylpyrazin-2-yl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
59		6-{4-[(3-chloropyrazin-2-yl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
60		6-{4-[(6-chloropyrazin-2-yl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

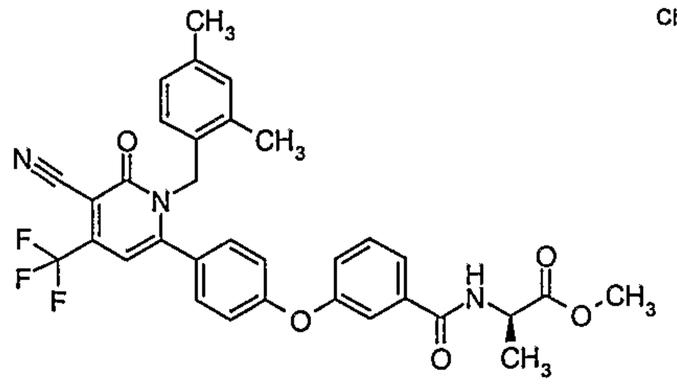
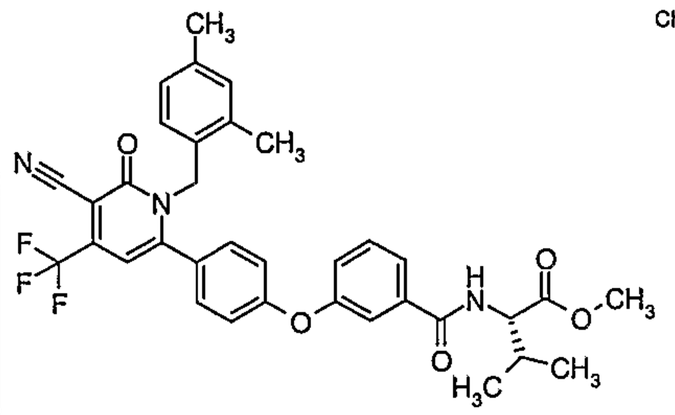
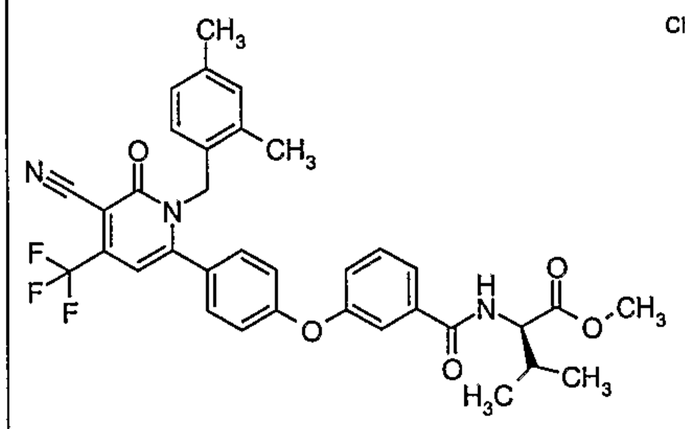
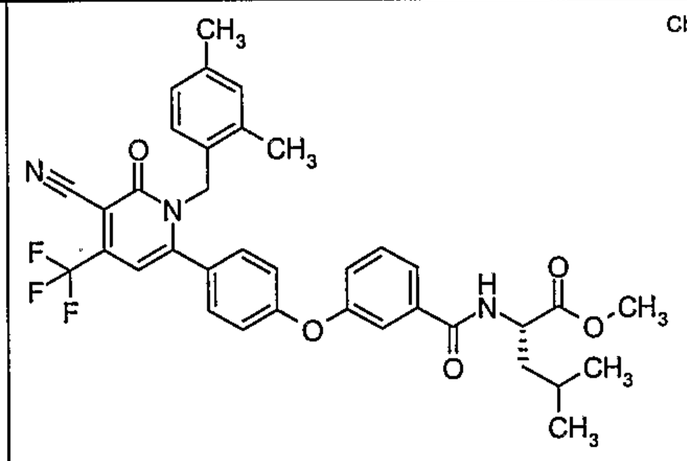
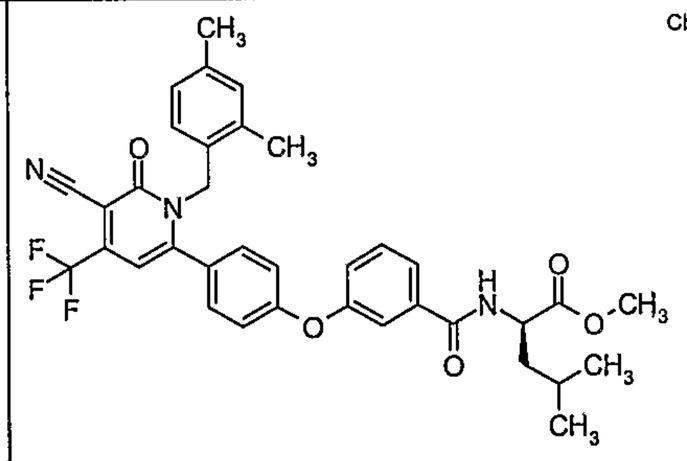
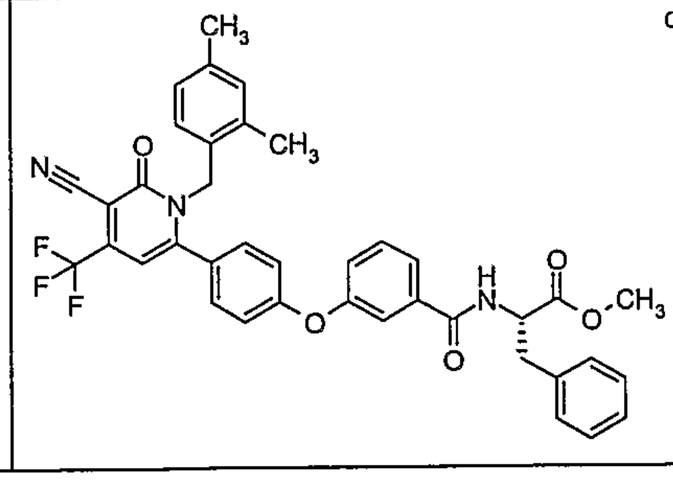
61		2-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]pyridine-3-carbonitrile
62		2-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-6-methylpyridine-3-carbonitrile
63		1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-1,2-dihydropyridine-3-carbonitrile
64		1-[(2,4-dichlorophenyl)methyl]-6-[4-(1H-indol-5-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
65		1-[(2,4-difluorophenyl)methyl]-6-[4-(1H-indol-5-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
66		1-[(2-chloro-4-fluorophenyl)methyl]-6-[4-(1H-indol-5-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

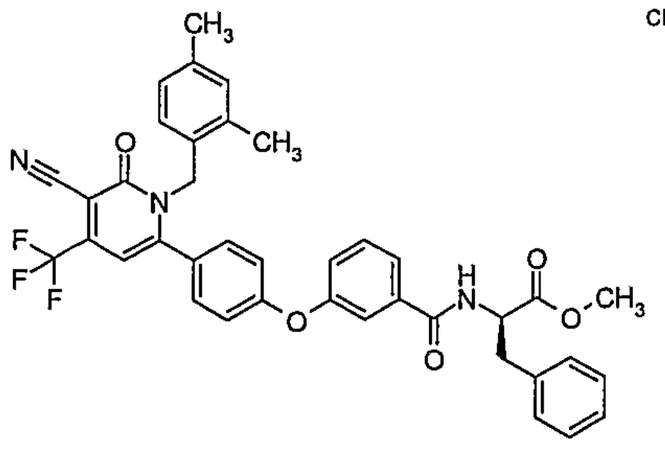
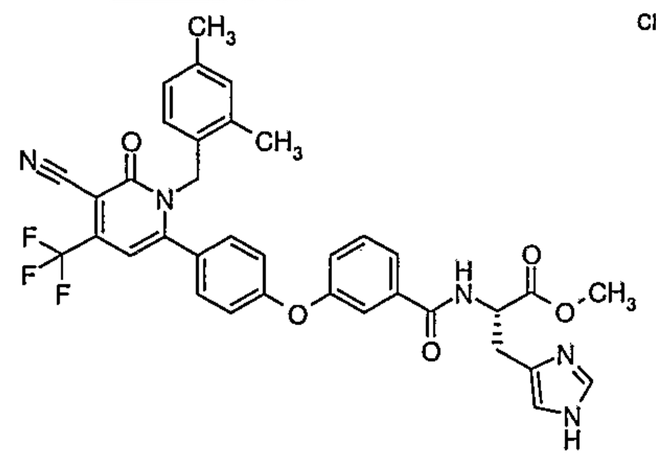
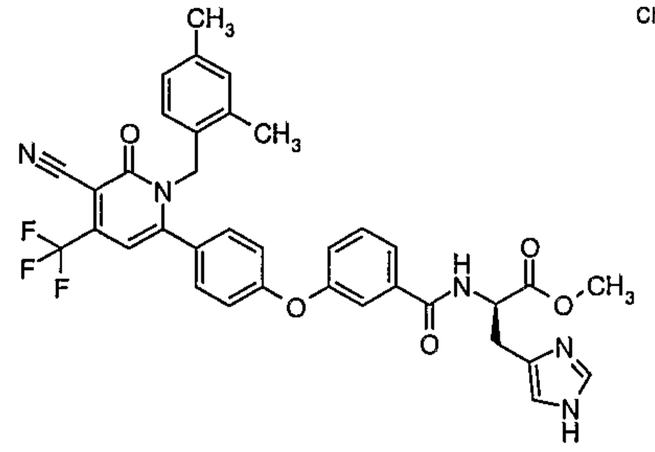
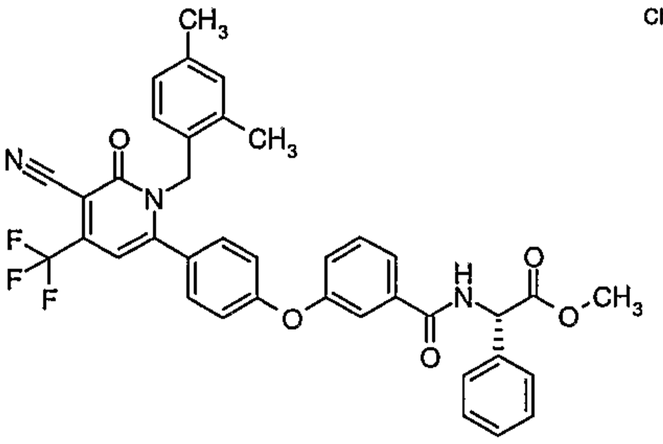
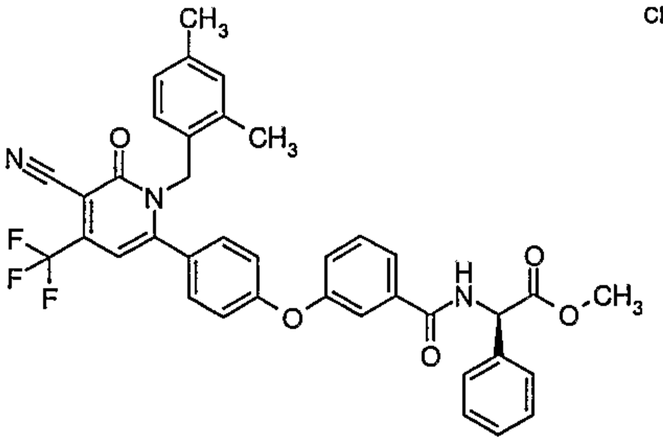
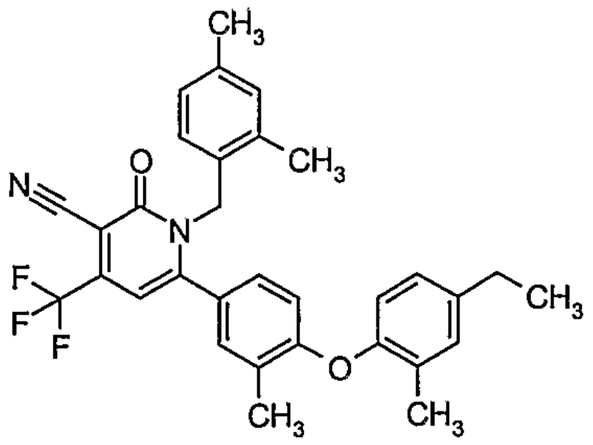
67		1-[(2,4-difluorophenyl)methyl]-3-[(dimethylamino)methyl]-6-phenyl-4-(trifluoromethyl)pyridin-2(1H)-one
68		1-[(2,4-dimethylphenyl)methyl]-6-(4-{[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]oxy}phenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
69		methyl 3-[(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)amino]benzoate
70		3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethylbenzenecarbothioamide
71		1-[(2,4-dimethylphenyl)methyl]-6-[3-methyl-4-(pyrazin-2-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
72		6-{4-[(3-chloropyrazin-2-yl)oxy]-3-methylphenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

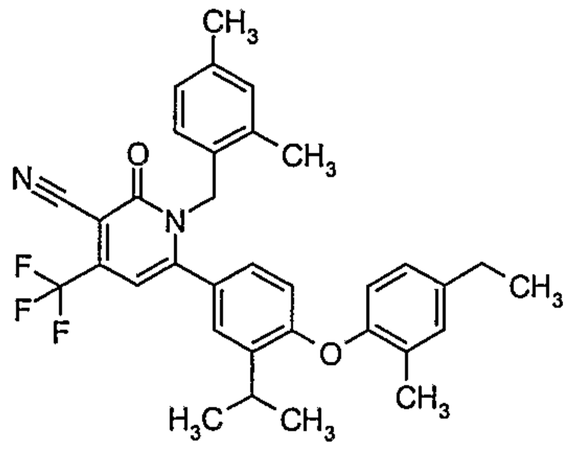
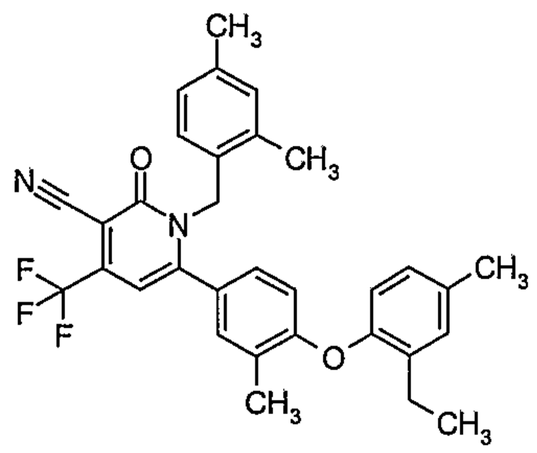
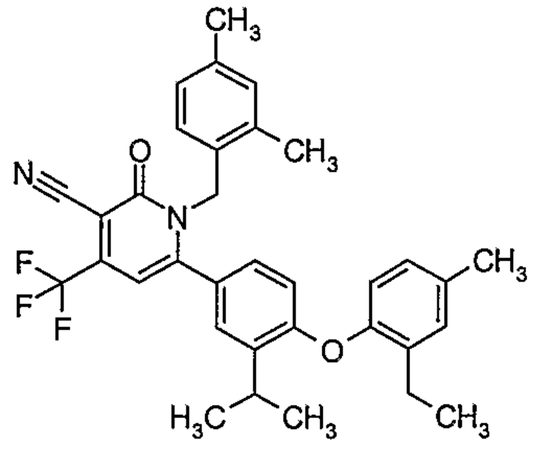
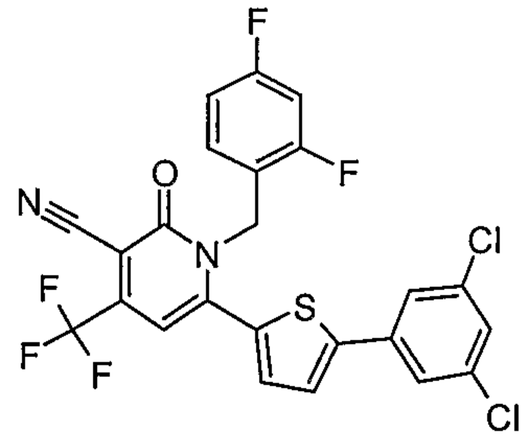
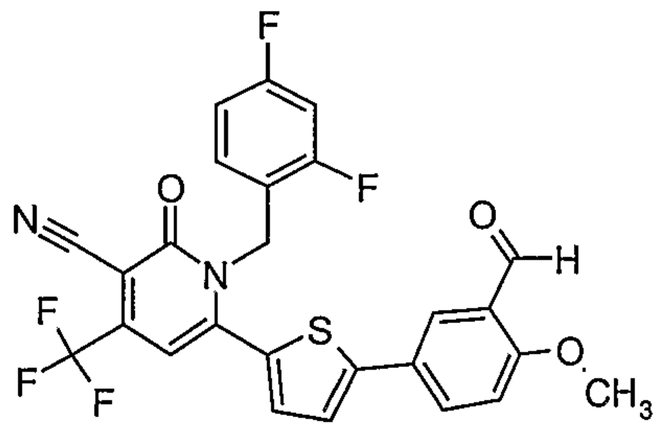
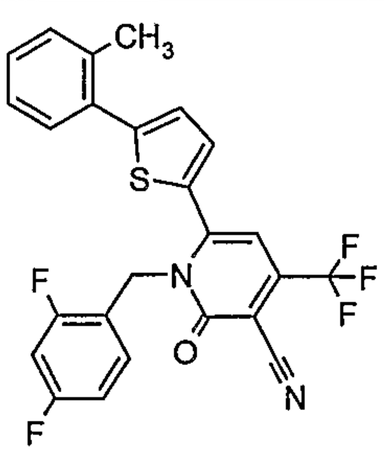
73		6-{4-[(6-chloropyrazin-2-yl)oxy]-3-methylphenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
74		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(3,6-dimethylpyrazin-2-yl)oxy]-3-methylphenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
75		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methylethyl)-4-(pyrazin-2-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
76		6-{4-[(3-chloropyrazin-2-yl)oxy]-3-(1-methylethyl)phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
77		6-{4-[(6-chloropyrazin-2-yl)oxy]-3-(1-methylethyl)phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
78		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(3,6-dimethylpyrazin-2-yl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

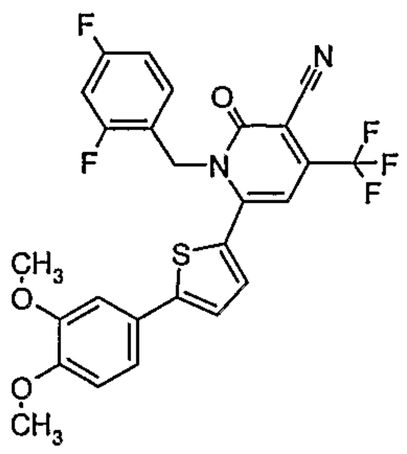
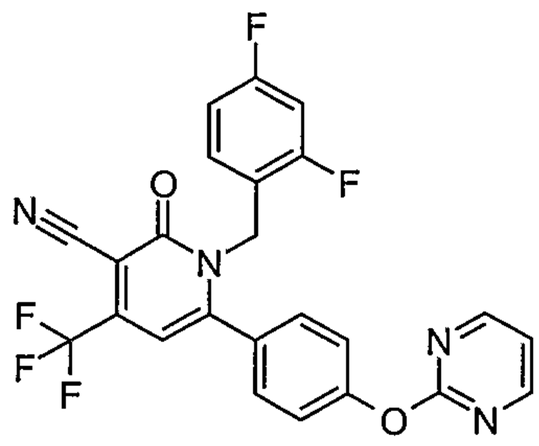
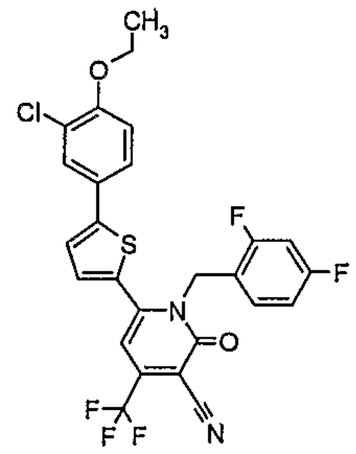
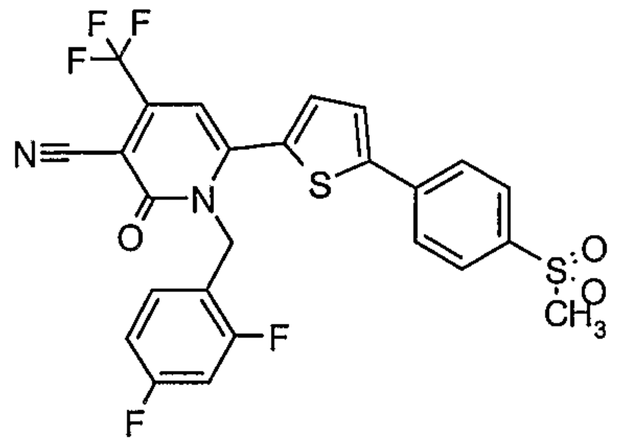
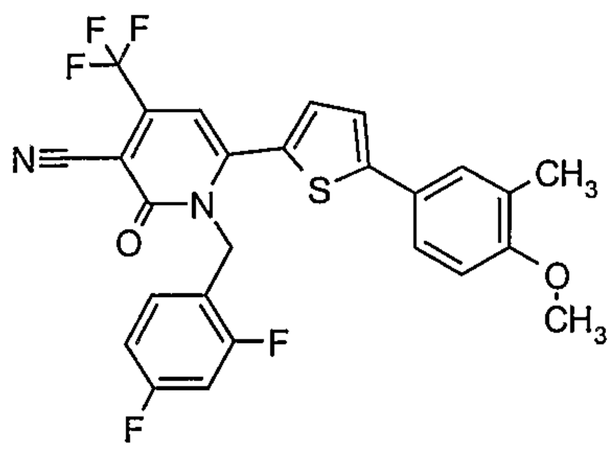
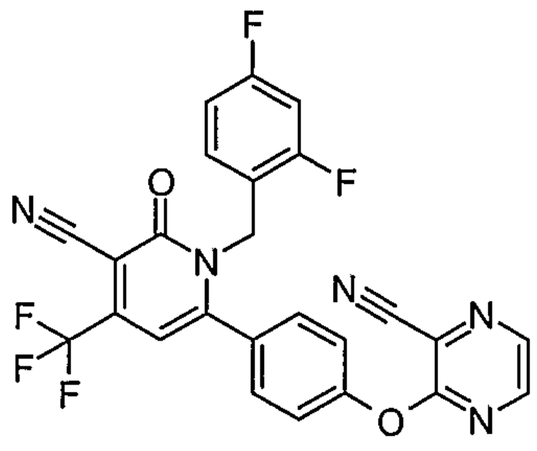
79		2-{[4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-(1-methylethyl)phenyl]oxy}-6-methylpyridine-3-carbonitrile
80		6-{5-[3-chloro-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
81		1-[(2,4-dichlorophenyl)methyl]-6-[5-(4-methylnaphthalen-1-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
82		1-[(2,4-dichlorophenyl)methyl]-6-{5-[3-methyl-4-(methyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
83		1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-[5-(2,4,5-trimethylphenyl)-2-thienyl]-1,2-dihydropyridine-3-carbonitrile
84		1-[(2,4-dichlorophenyl)methyl]-6-{5-[2-methyl-4-(methyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

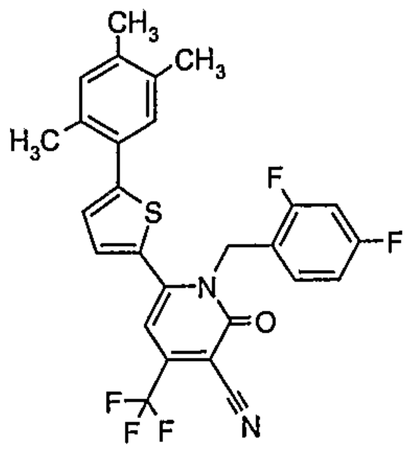
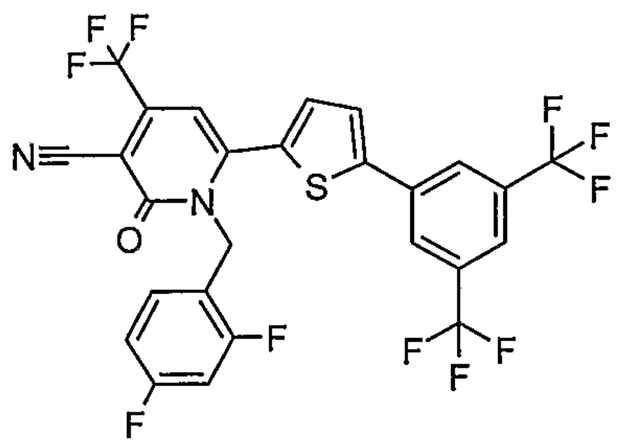
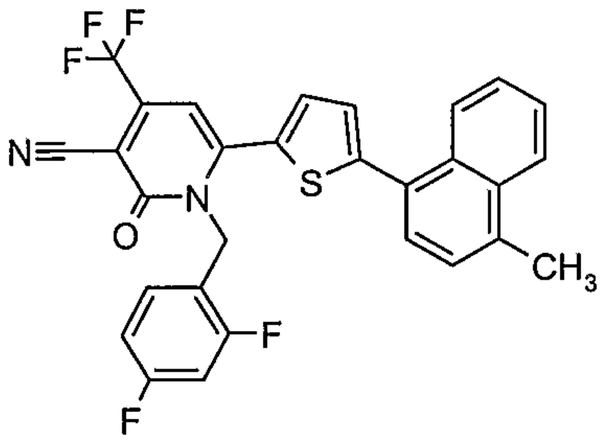
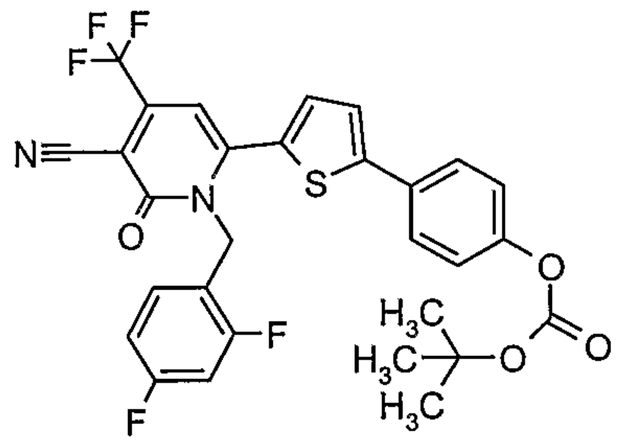
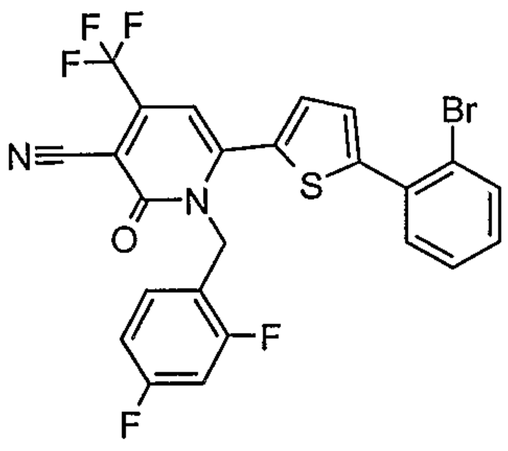
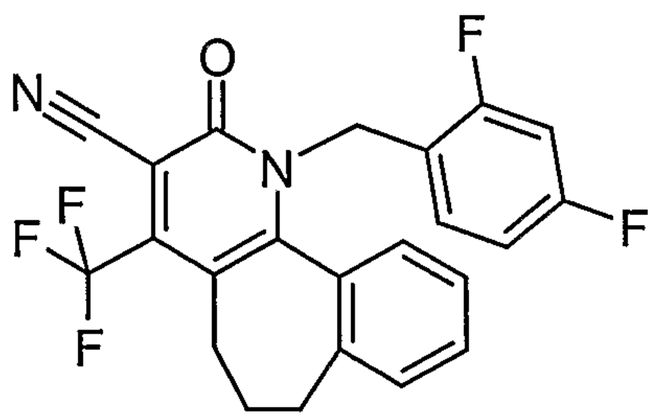
85		6-{5-[3,5-bis(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
86		1-[(2,4-dichlorophenyl)methyl]-6-[5-(2-methylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
87		1-[(2,4-dichlorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
88		6-{5-[3,4-bis(methyloxy)phenyl]-2-thienyl}-1-[(2,4-dichlorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
89		1-[(2,4-dichlorophenyl)methyl]-6-[5-(3,5-dichlorophenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
90		methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-L-alaninate

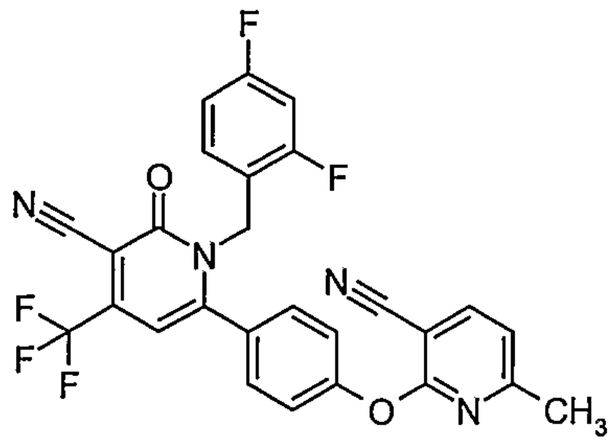
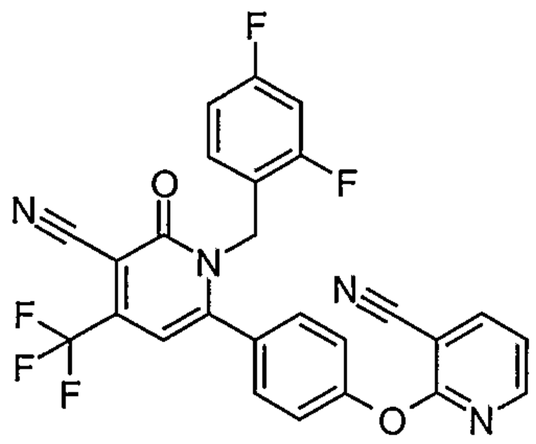
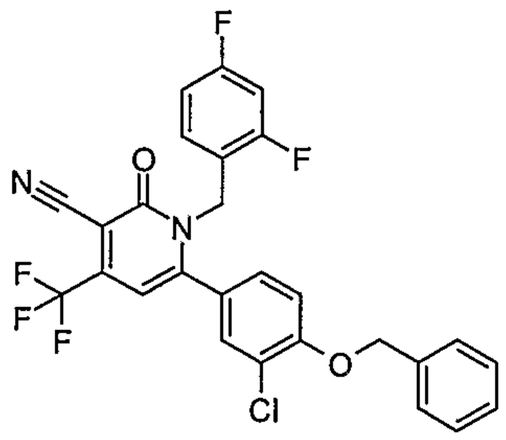
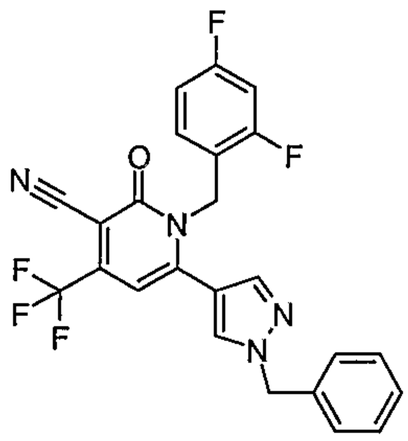
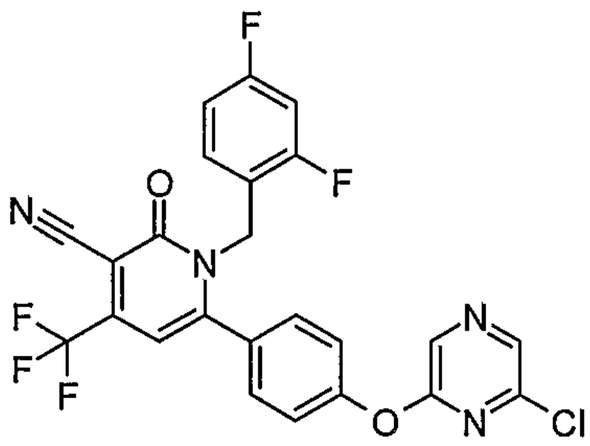
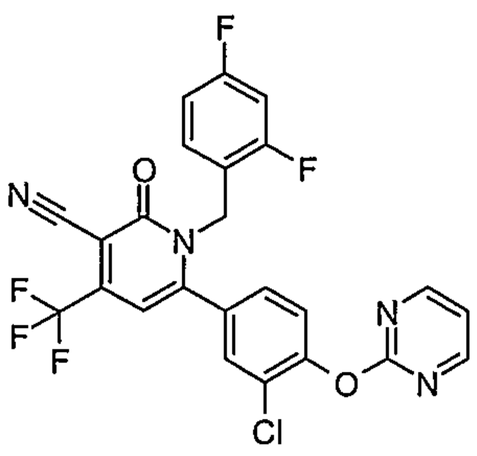
91	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-D-alaninate
92	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-L-valinate
93	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-D-valinate
94	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-L-leucinate
95	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-D-leucinate
96	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-L-phenylalaninate

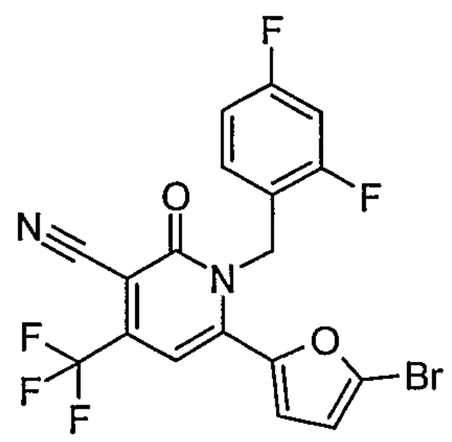
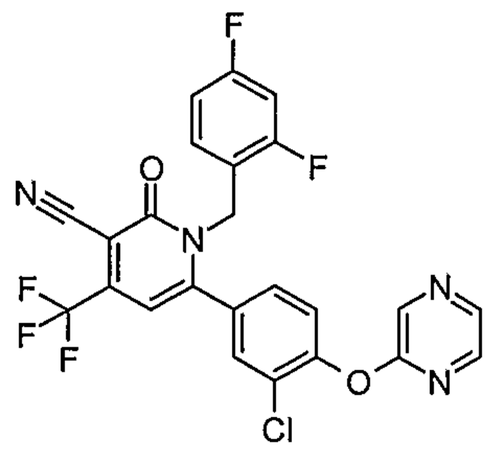
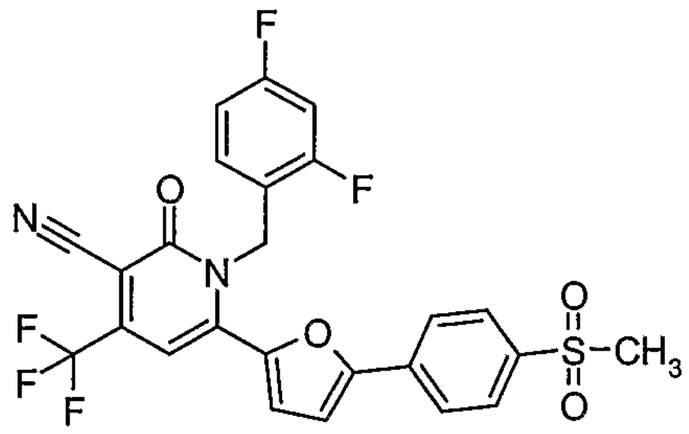
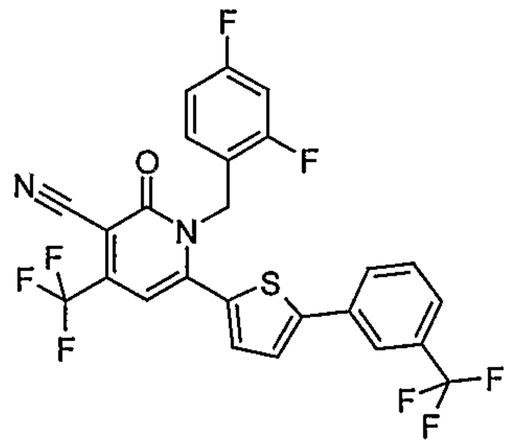
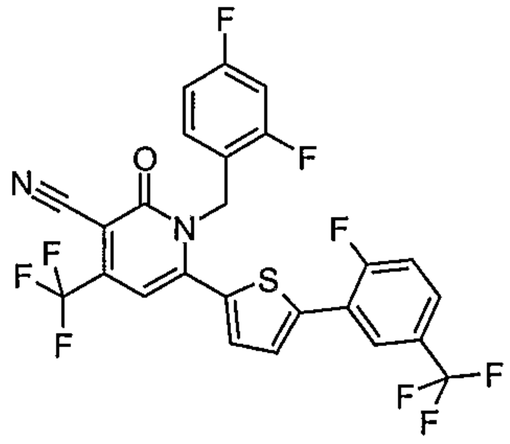
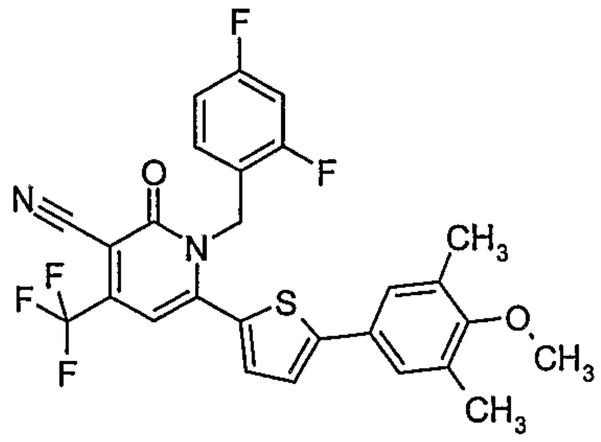
97	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-D-phenylalaninate
98	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-L-histidinate
99	 Chiral	methyl N-({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)-D-histidinate
100	 Chiral	methyl (2S)-[({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)amino](phenyl)ethanoate
101	 Chiral	methyl (2R)-[({3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbonyl)amino](phenyl)ethanoate
102		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(4-ethyl-2-methylphenyl)oxy]-3-methylphenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

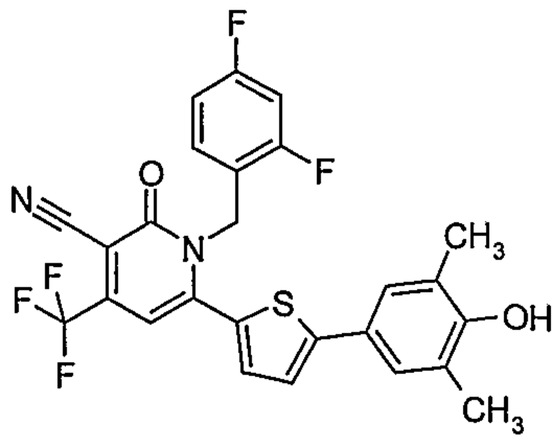
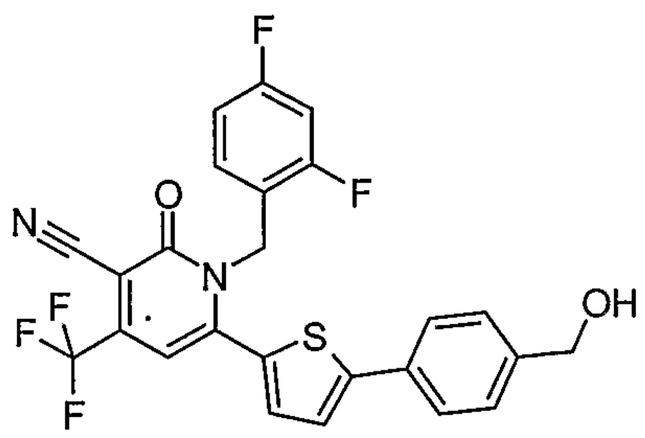
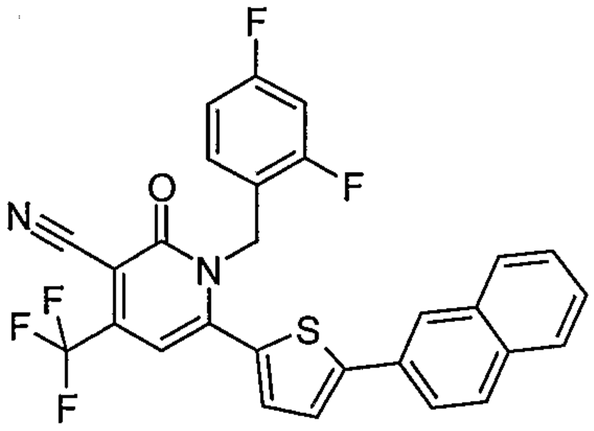
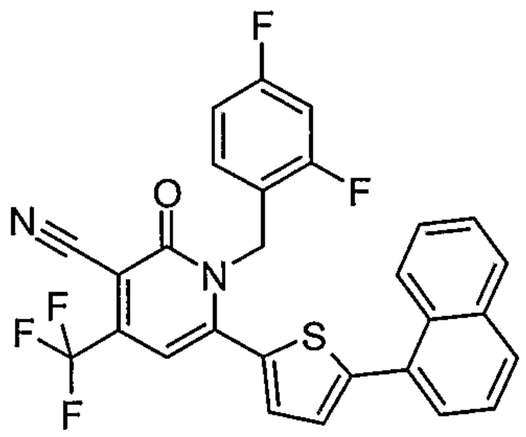
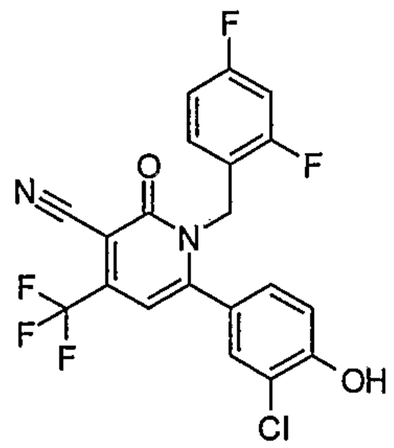
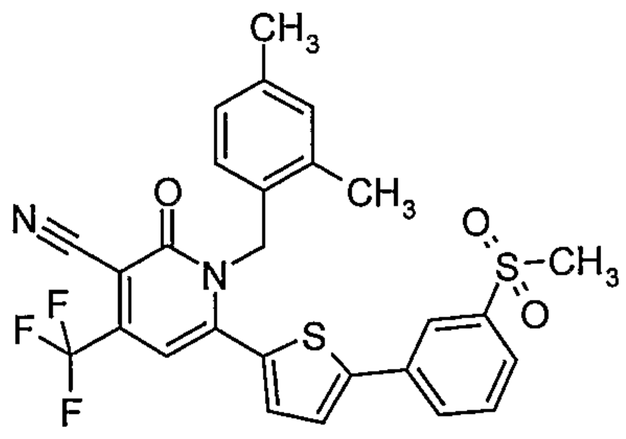
103		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(4-ethyl-2-methylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
104		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(2-ethyl-4-methylphenyl)oxy]-3-methylphenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
105		1-[(2,4-dimethylphenyl)methyl]-6-{4-[(2-ethyl-4-methylphenyl)oxy]-3-(1-methylethyl)phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
106		6-[5-(3,5-dichlorophenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
107		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-formyl-4-(methyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
108		1-[(2,4-difluorophenyl)methyl]-6-[5-(2-methylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

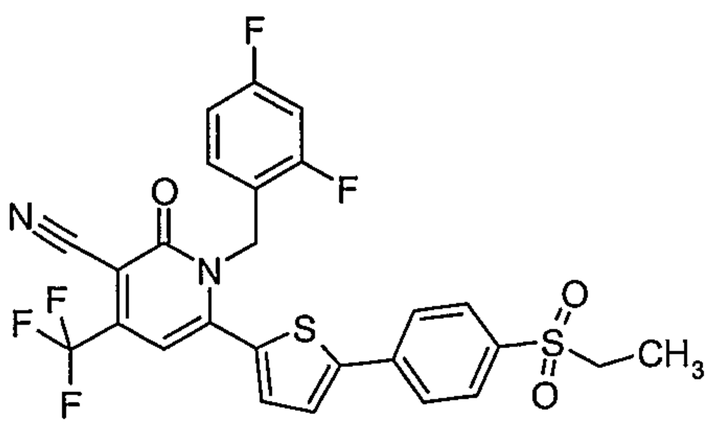
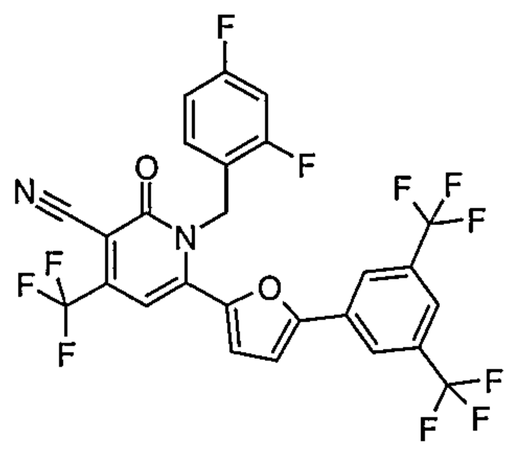
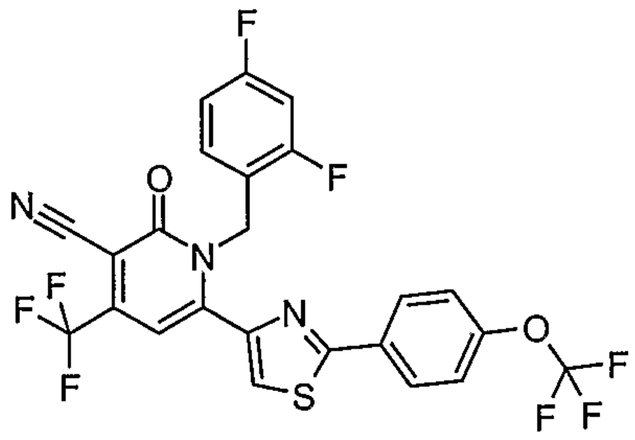
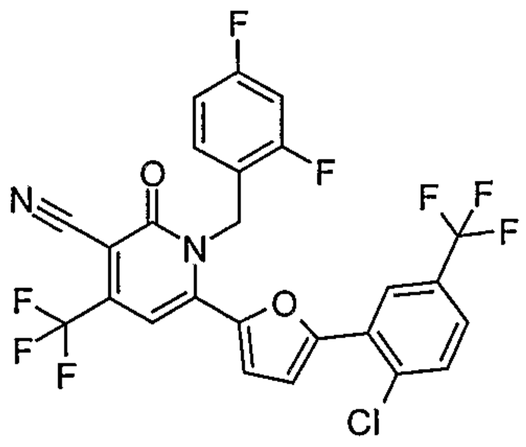
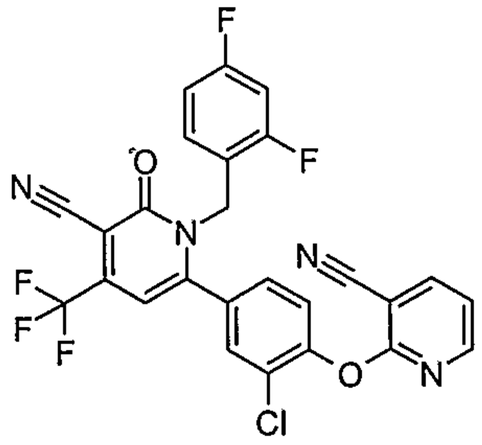
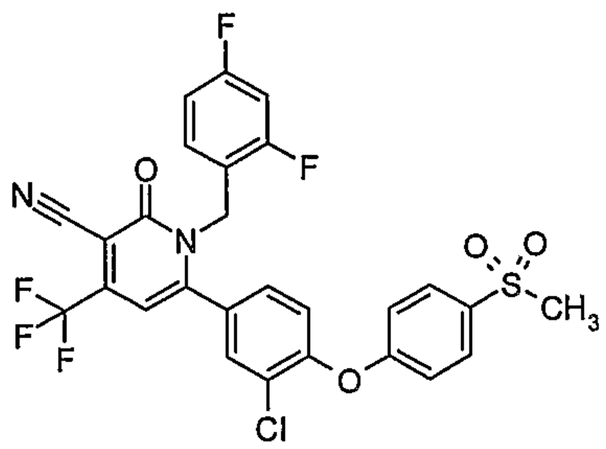
109		6-{5-[3,4-bis(methyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
110		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(pyrimidin-2-yloxy)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
111		6-{5-[3-chloro-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
112		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
113		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-methyl-4-(methyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
114		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]pyrazine-2-carbonitrile

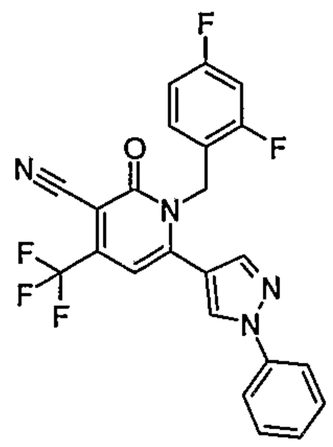
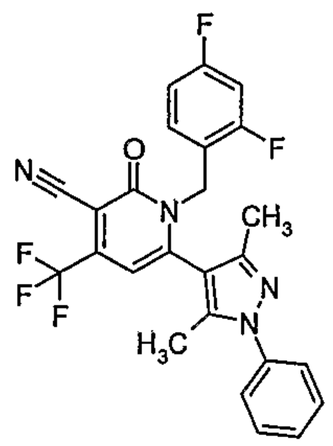
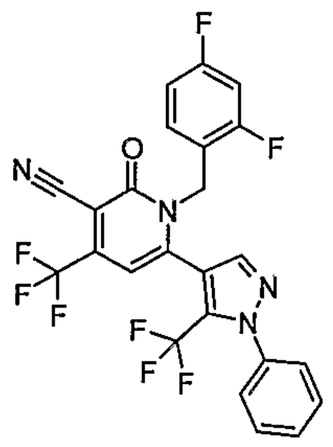
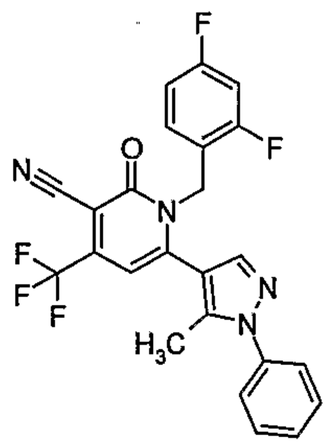
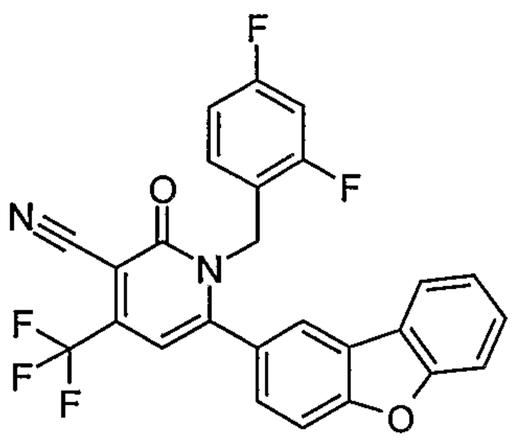
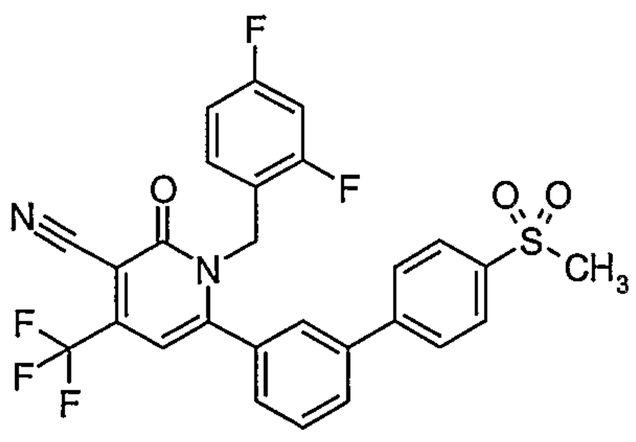
115		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-[5-(2,4,5-trimethylphenyl)-2-thienyl]-1,2-dihydropyridine-3-carbonitrile
116		6-{5-[3,5-bis(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
117		1-[(2,4-difluorophenyl)methyl]-6-[5-(4-methylnaphthalen-1-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
118		4-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)phenyl 1,1-dimethylethyl carbonate
119		6-[5-(2-bromophenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
120		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-2,5,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile

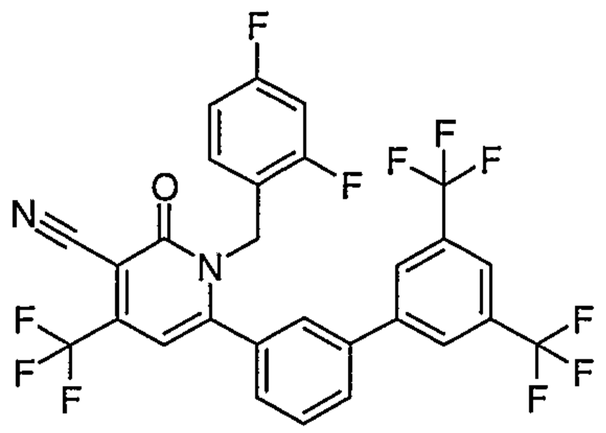
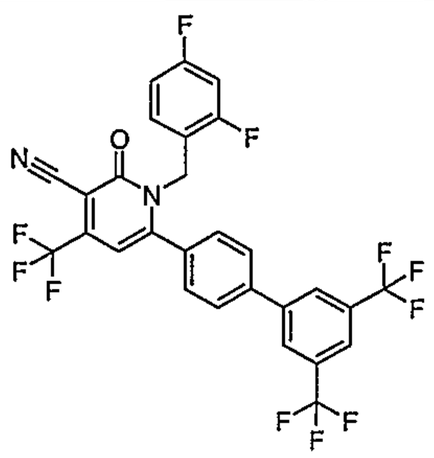
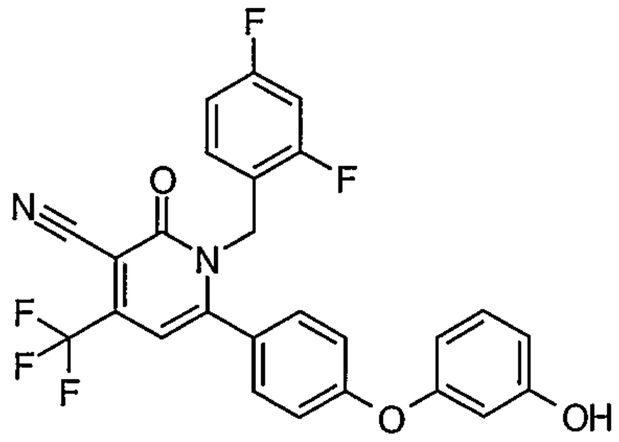
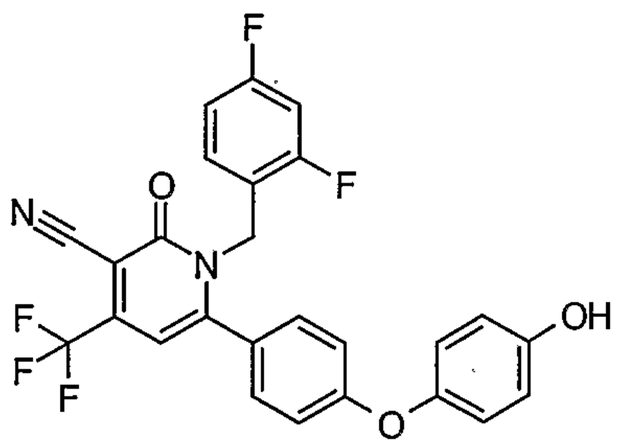
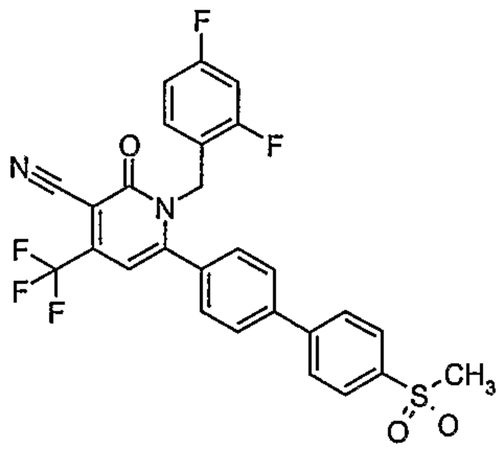
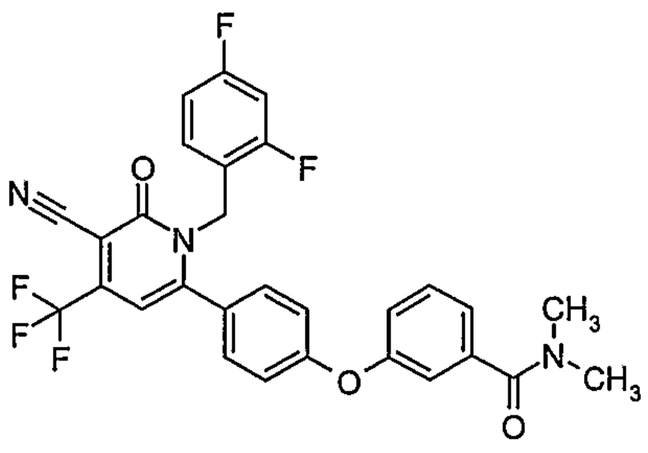
121		2-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-6-methylpyridine-3-carbonitrile
122		2-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]pyridine-3-carbonitrile
123		6-{3-chloro-4-[(phenylmethyl)oxy]phenyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
124		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[1-(phenylmethyl)-1H-pyrazol-4-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
125		6-{4-[(6-chloropyrazin-2-yl)oxy]phenyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
126		6-[3-chloro-4-(pyrimidin-2-yloxy)phenyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

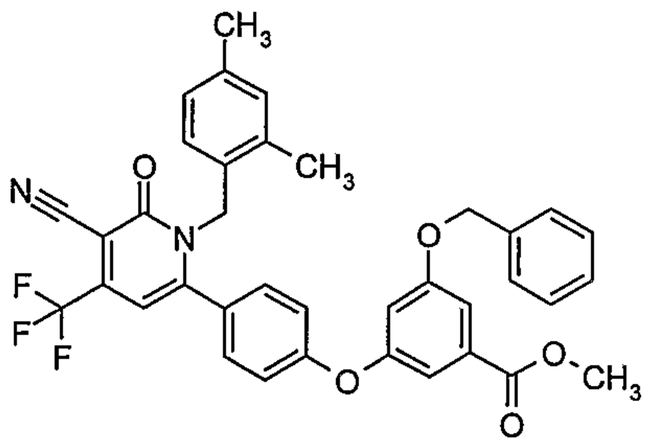
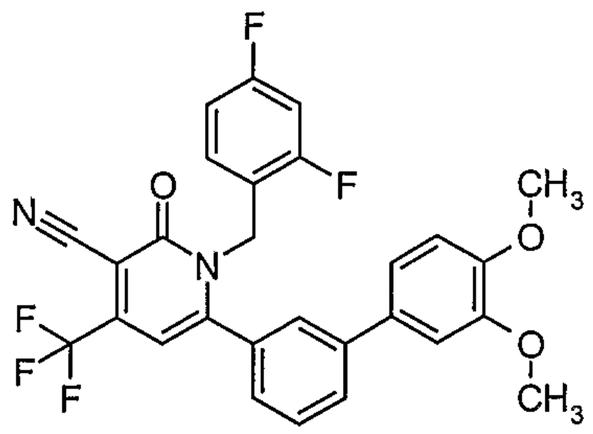
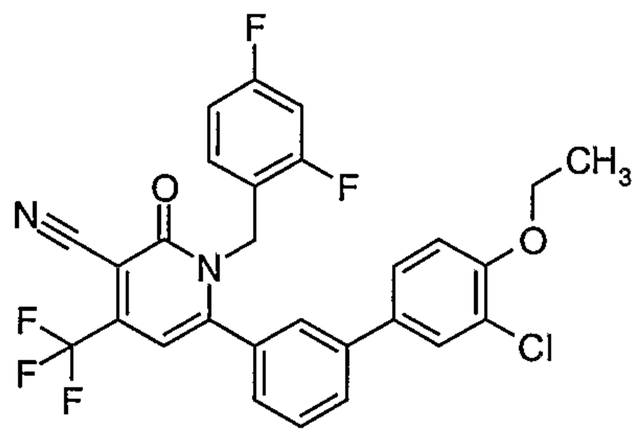
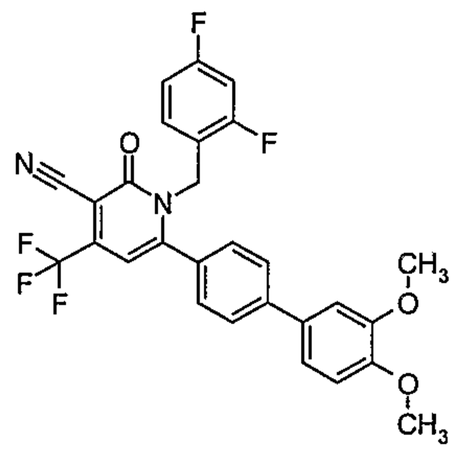
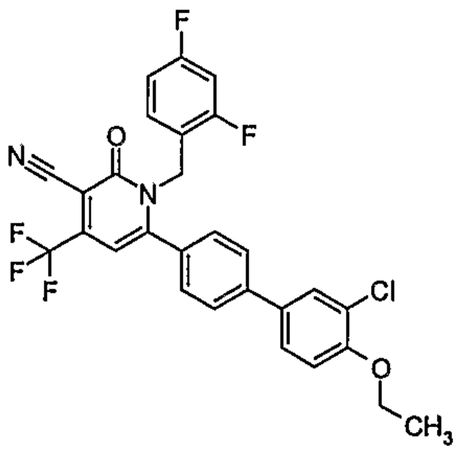
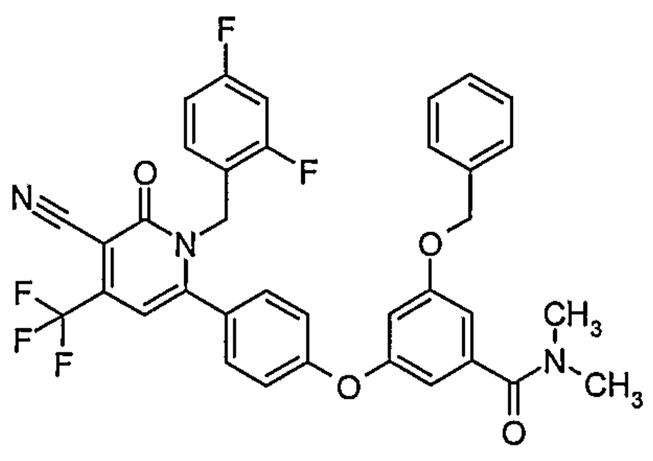
127		6-(5-bromofuran-2-yl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
128		6-[3-chloro-4-(pyrazin-2-yloxy)phenyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
129		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
130		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-{5-[3-(trifluoromethyl)phenyl]-2-thienyl}-1,2-dihydropyridine-3-carbonitrile
131		1-[(2,4-difluorophenyl)methyl]-6-{5-[2-fluoro-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
132		1-[(2,4-difluorophenyl)methyl]-6-{5-[3,5-dimethyl-4-(methyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

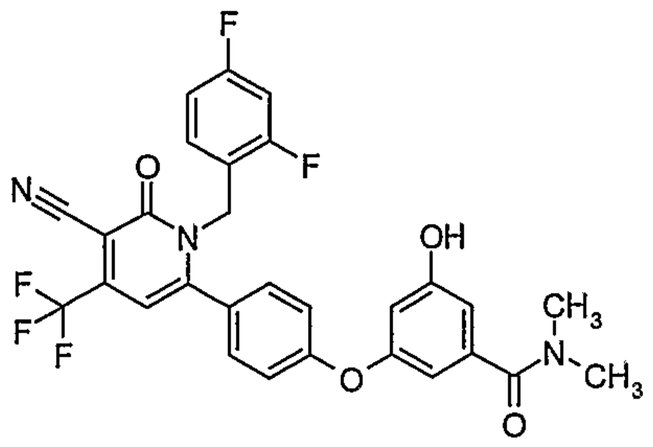
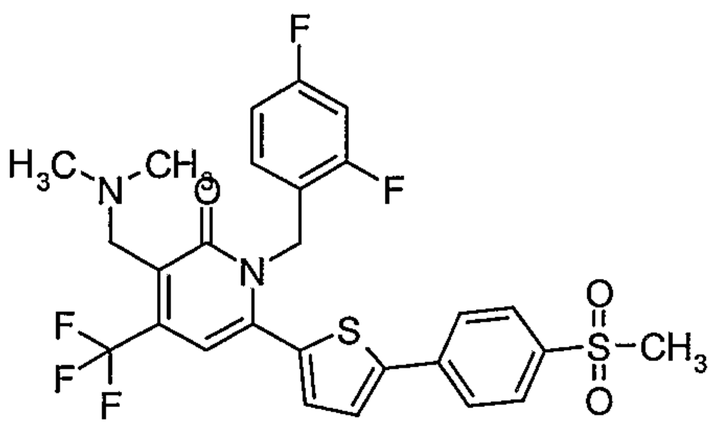
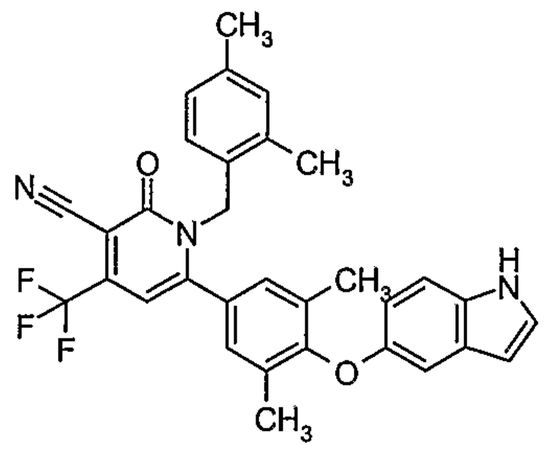
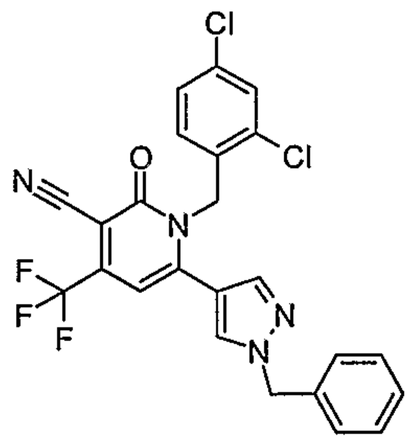
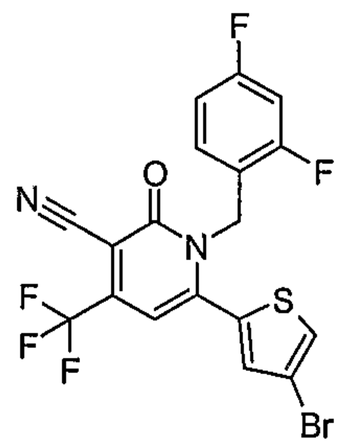
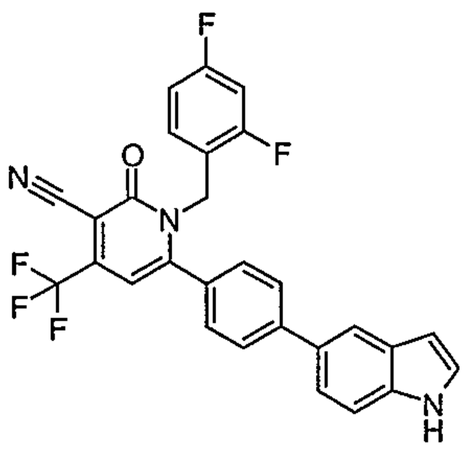
133		1-[(2,4-difluorophenyl)methyl]-6-[5-(4-hydroxy-3,5-dimethylphenyl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
134		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(hydroxymethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
135		1-[(2,4-difluorophenyl)methyl]-6-(5-naphthalen-2-yl-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
136		1-[(2,4-difluorophenyl)methyl]-6-(5-naphthalen-1-yl-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
137		6-(3-chloro-4-hydroxyphenyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
138		1-[(2,4-dimethylphenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

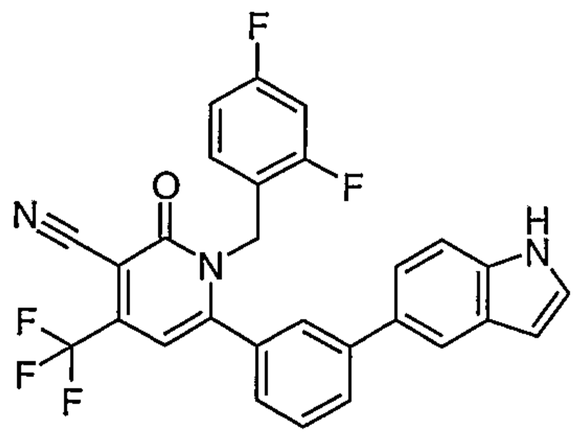
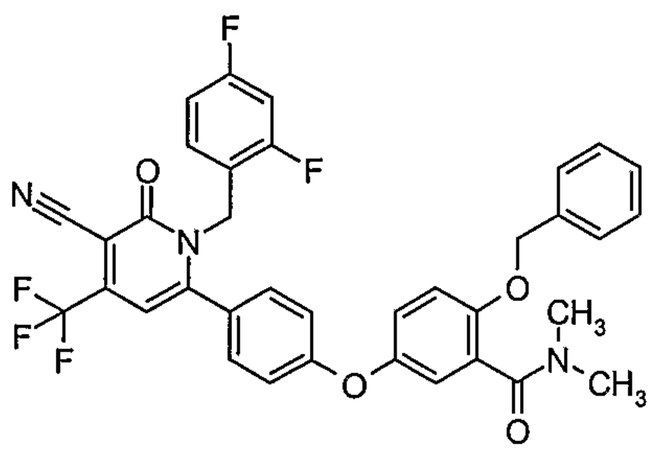
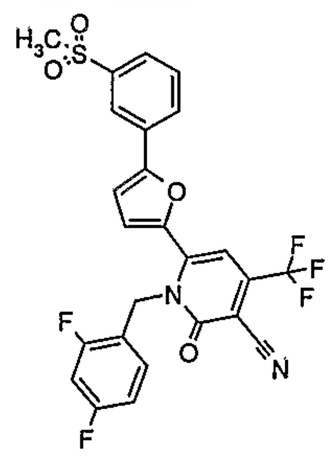
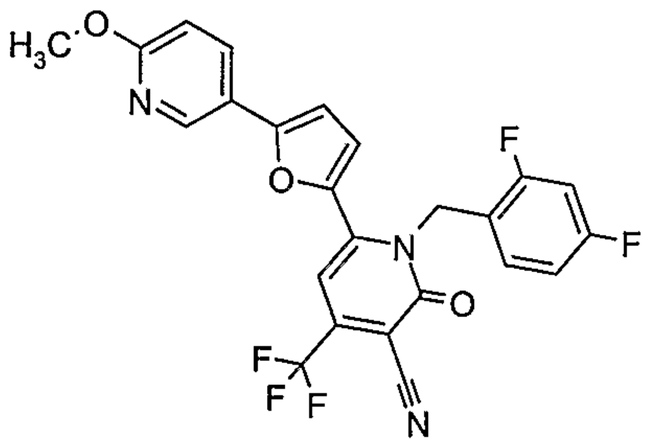
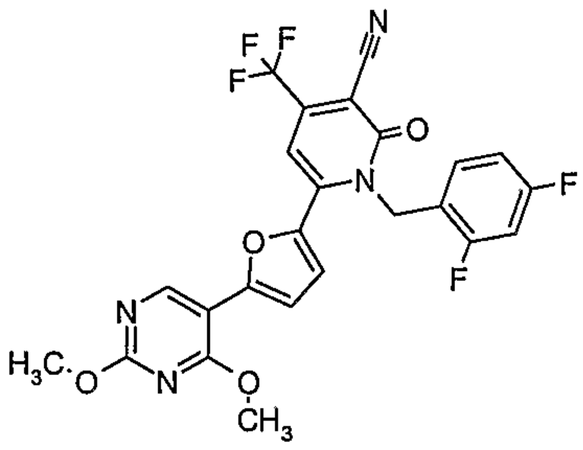
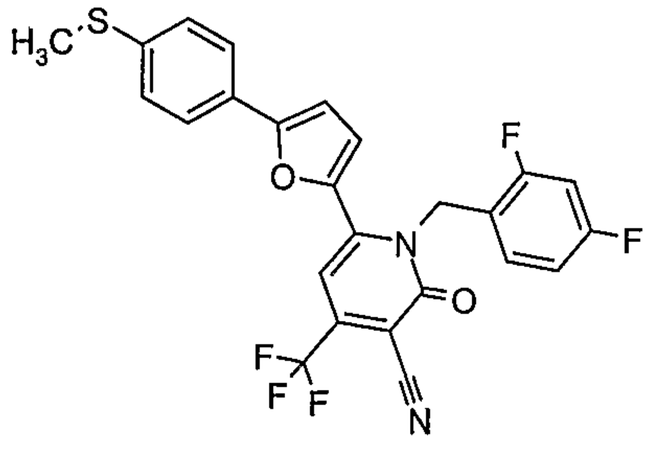
139		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
140		6-{5-[3,5-bis(trifluoromethyl)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
141		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-(2-{4-[(trifluoromethyl)oxy]phenyl}-1,3-thiazol-4-yl)-1,2-dihydropyridine-3-carbonitrile
142		6-{5-[2-chloro-5-(trifluoromethyl)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
143		2-[(2-chloro-4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]pyridine-3-carbonitrile
144		6-(3-chloro-4-{[4-(methylsulfonyl)phenyl]oxy}phenyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

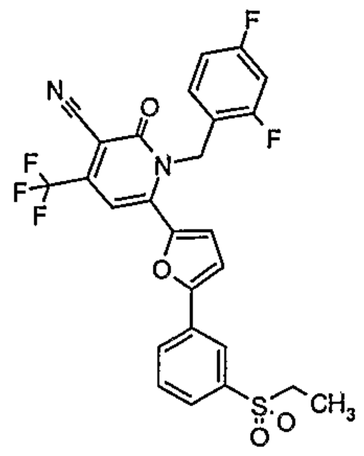
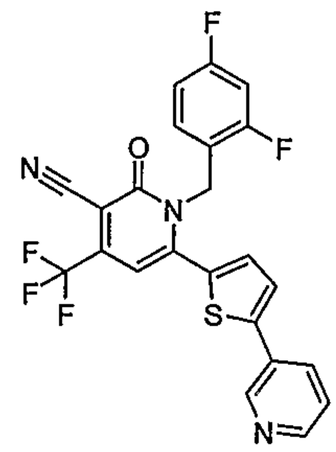
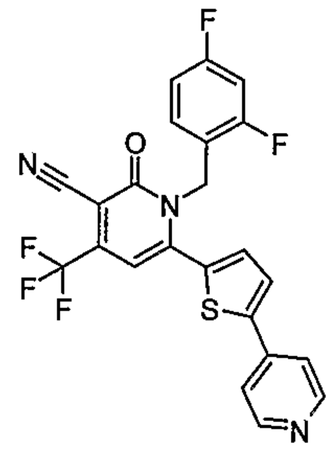
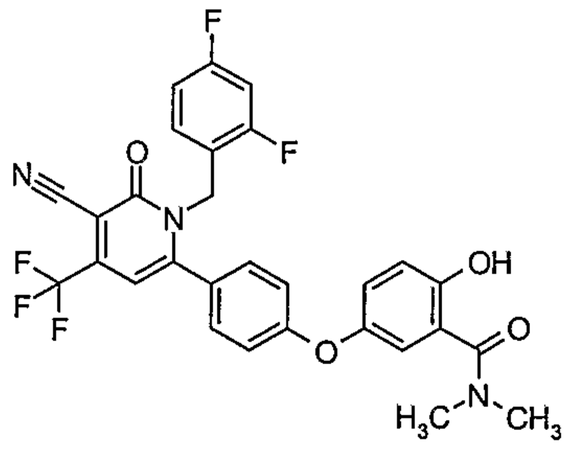
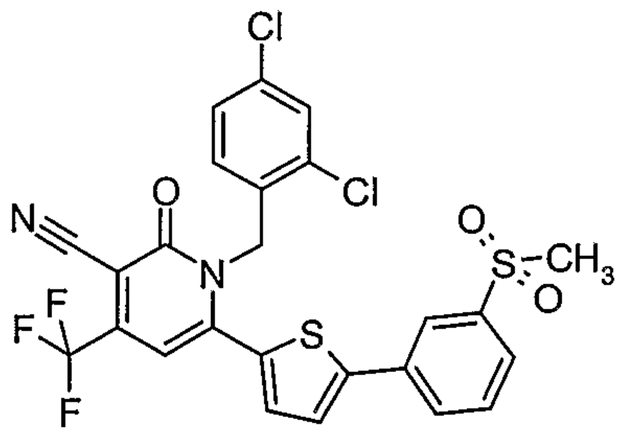
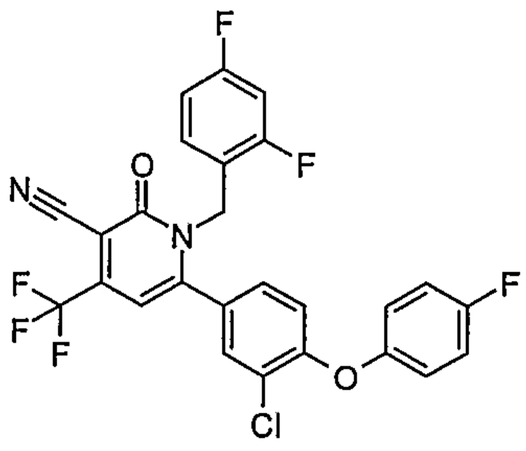
145		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(1-phenyl-1H-pyrazol-4-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
146		1-[(2,4-difluorophenyl)methyl]-6-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
147		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
148		1-[(2,4-difluorophenyl)methyl]-6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
149		6-dibenzo[b,d]furan-2-yl-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
150		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

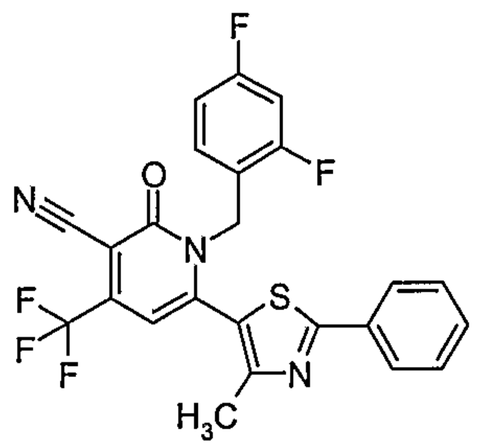
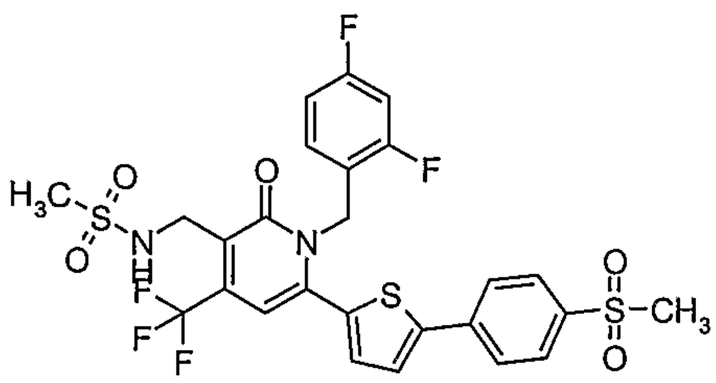
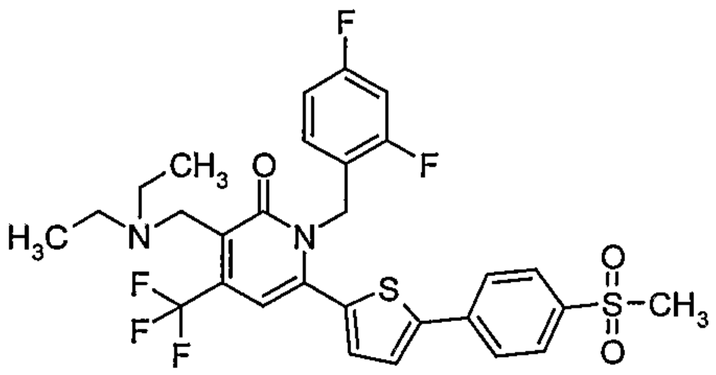
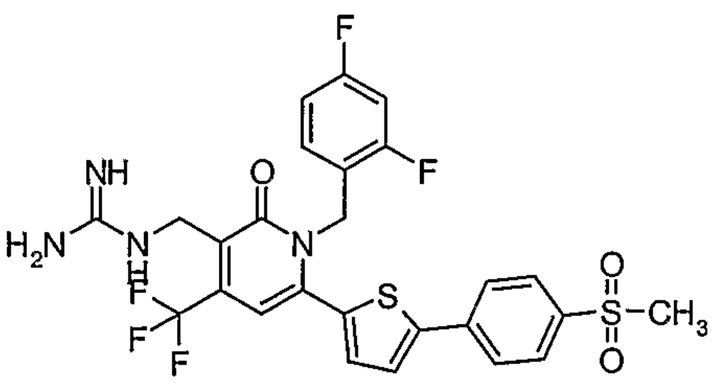
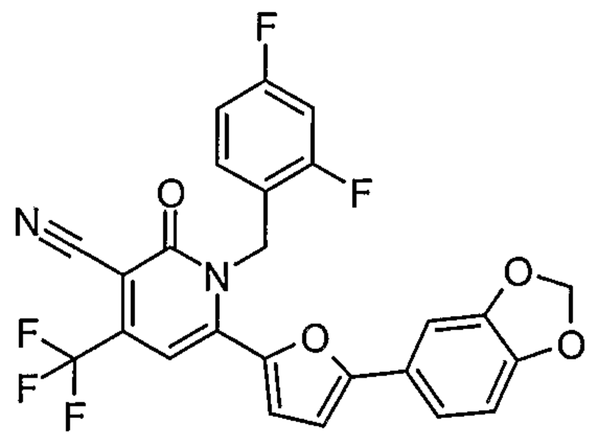
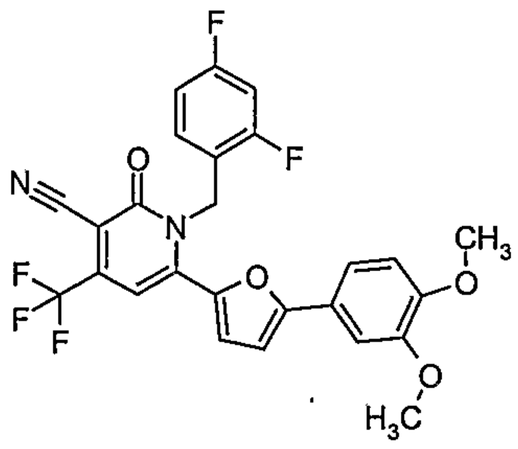
151		6-[3',5'-bis(trifluoromethyl)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
152		6-[3',5'-bis(trifluoromethyl)biphenyl-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
153		1-[(2,4-difluorophenyl)methyl]-6-{4-[(3-hydroxyphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
154		1-[(2,4-difluorophenyl)methyl]-6-{4-[(4-hydroxyphenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
155		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylsulfonyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
156		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethylbenzamide

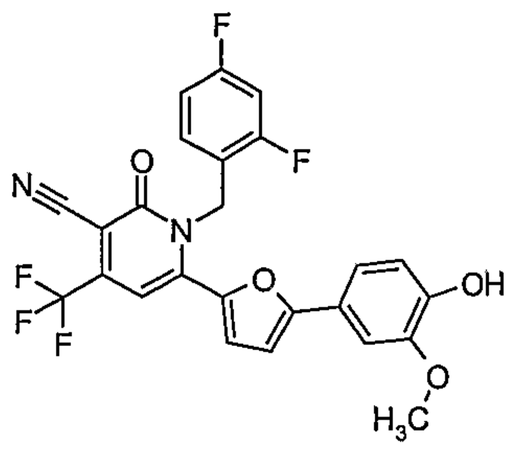
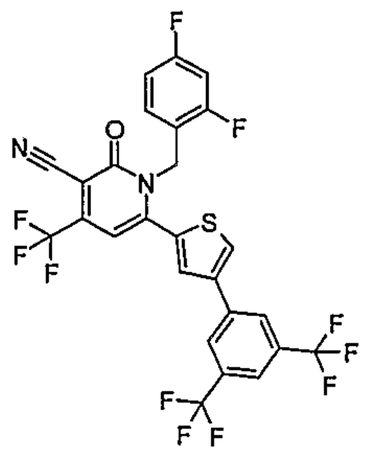
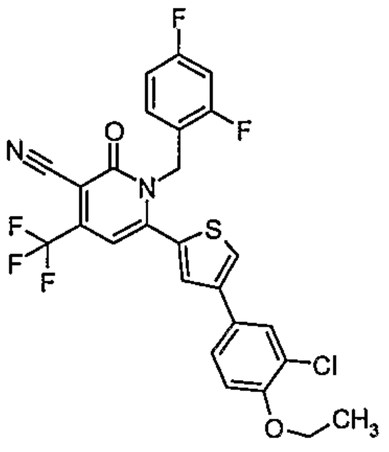
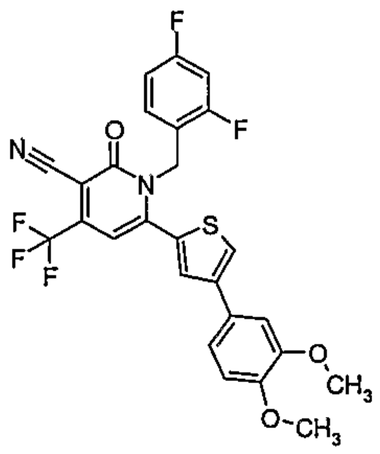
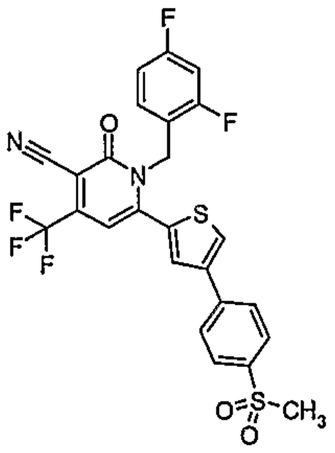
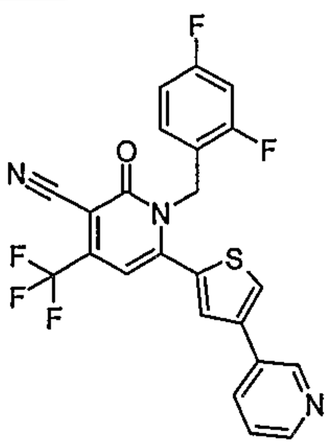
157		methyl 3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-5-[(phenylmethyl)oxy]benzoate
158		6-[3',4'-bis(methyloxy)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
159		6-[3'-chloro-4'-(ethyloxy)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
160		6-[3',4'-bis(methyloxy)biphenyl-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
161		6-[3'-chloro-4'-(ethyloxy)biphenyl-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
162		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethyl-5-[(phenylmethyl)oxy]benzamide

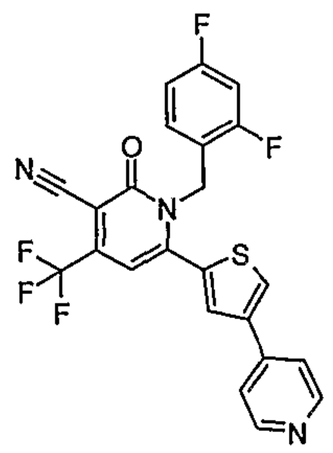
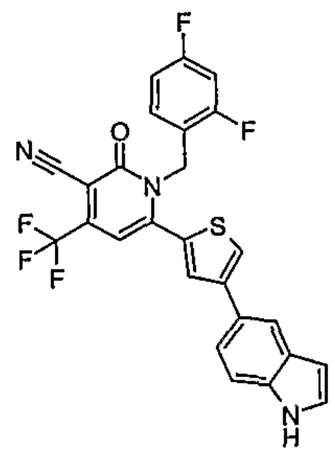
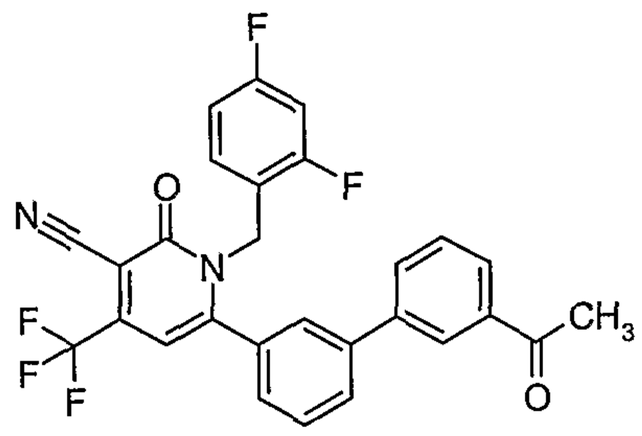
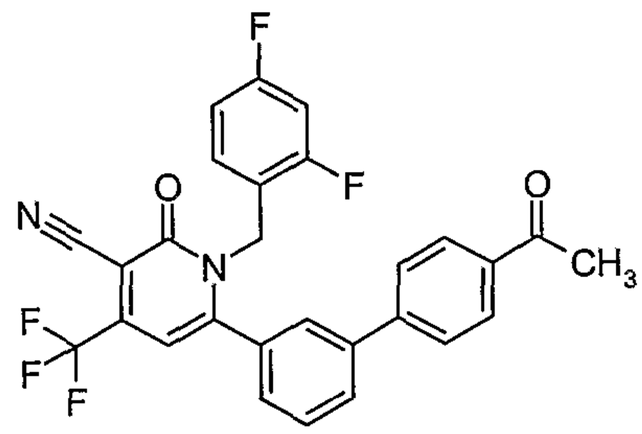
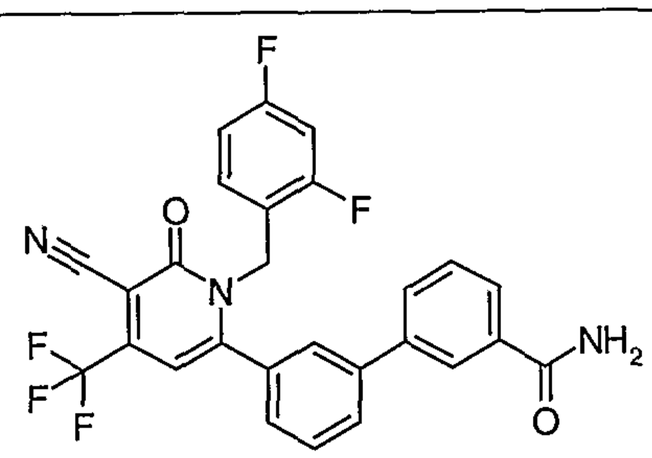
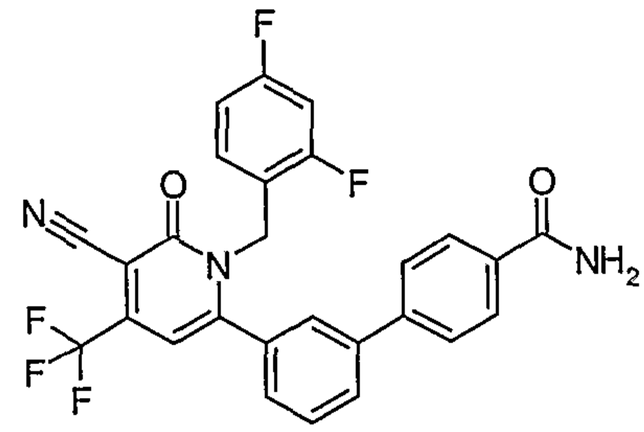
163		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-5-hydroxy-N,N-dimethylbenzamide
164		1-[(2,4-difluorophenyl)methyl]-3-[(dimethylamino)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)pyridin-2(1H)-one
165		1-[(2,4-dimethylphenyl)methyl]-6-[4-(1H-indol-5-yloxy)-3,5-dimethylphenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
166		1-[(2,4-dichlorophenyl)methyl]-2-oxo-6-[1-(phenylmethyl)-1H-pyrazol-4-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
167		6-(4-bromo-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
168		1-[(2,4-difluorophenyl)methyl]-6-[4-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

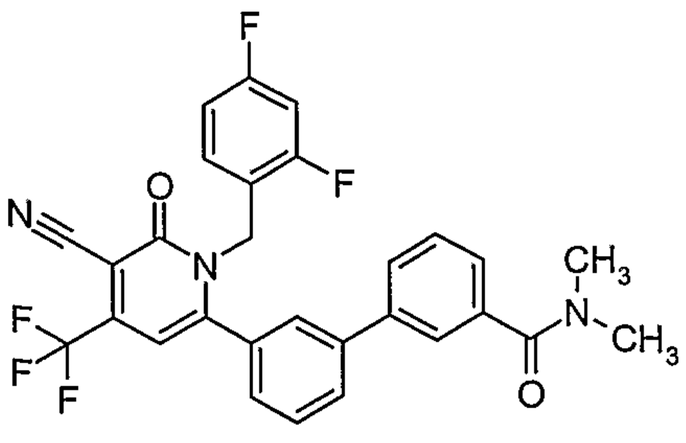
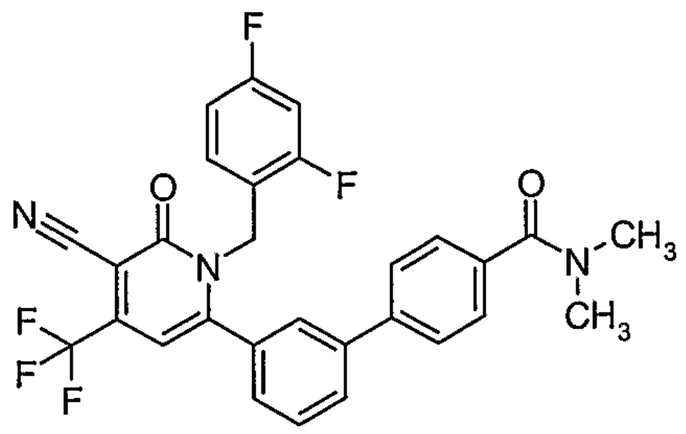
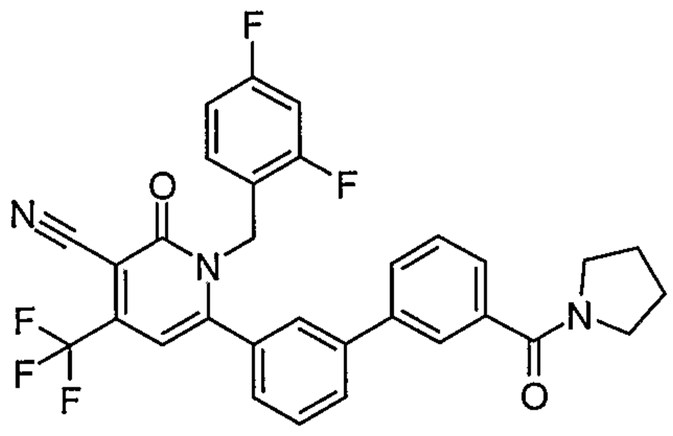
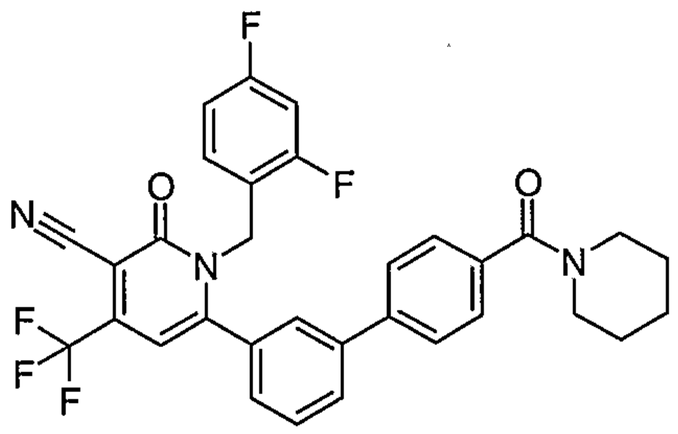
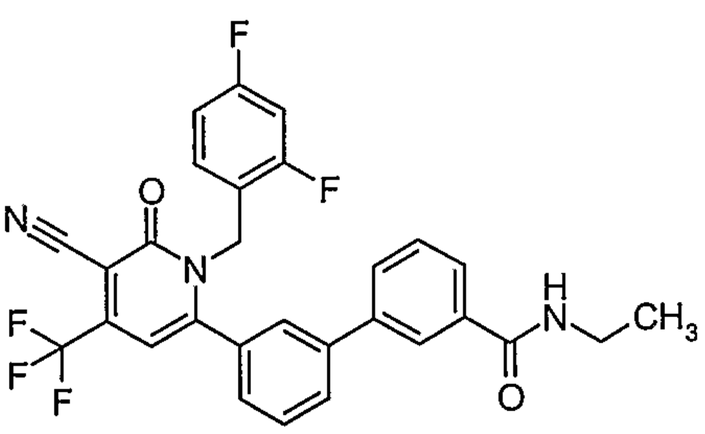
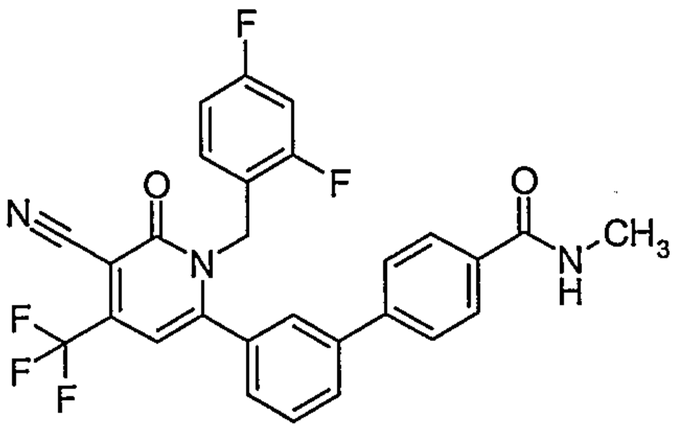
169		1-[(2,4-difluorophenyl)methyl]-6-[3-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
170		5-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethyl-2-[(phenylmethyl)oxy]benzamide
171		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
172		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(methyloxy)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
173		6-{5-[2,4-bis(methyloxy)pyrimidin-5-yl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
174		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylthio)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

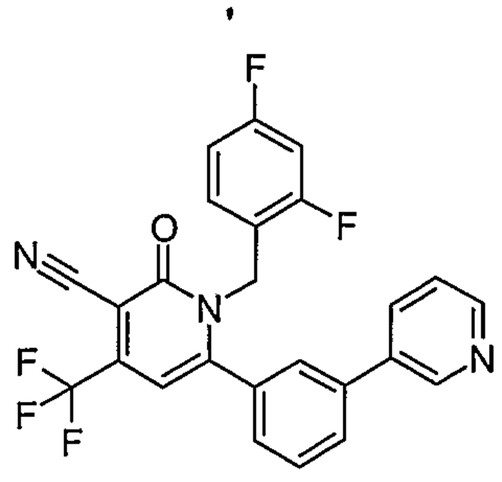
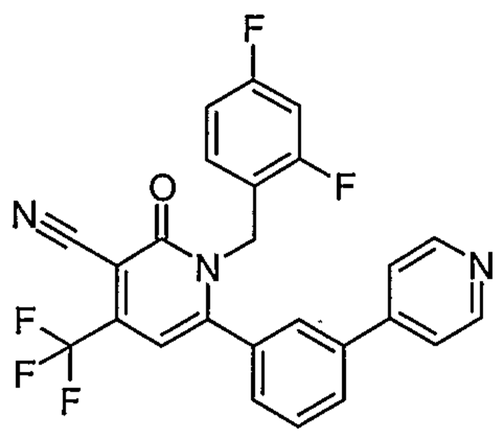
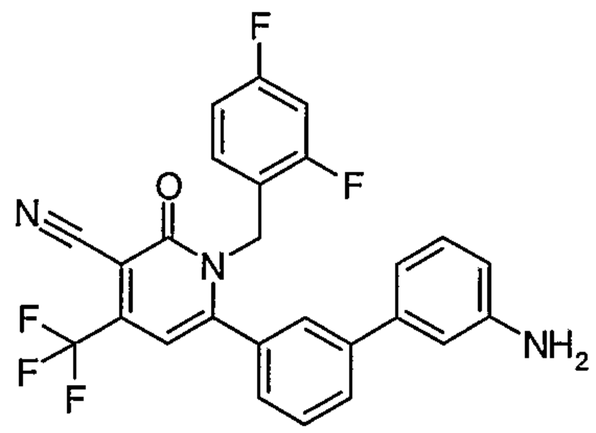
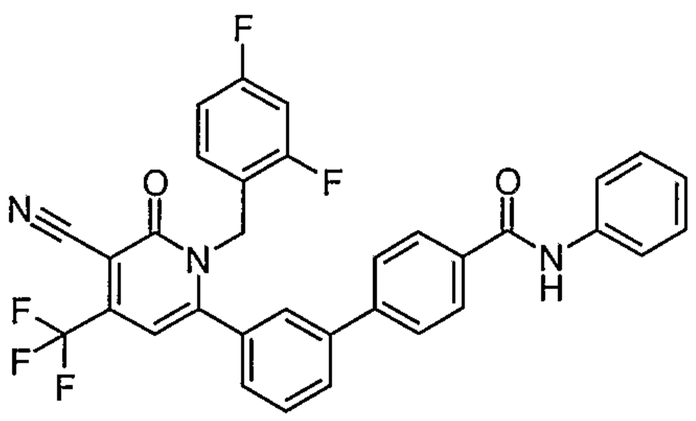
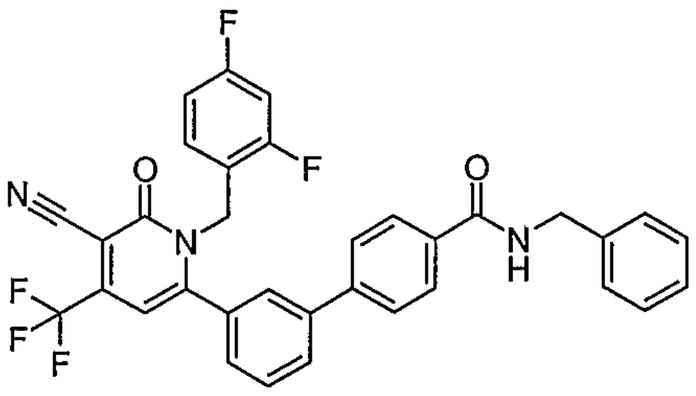
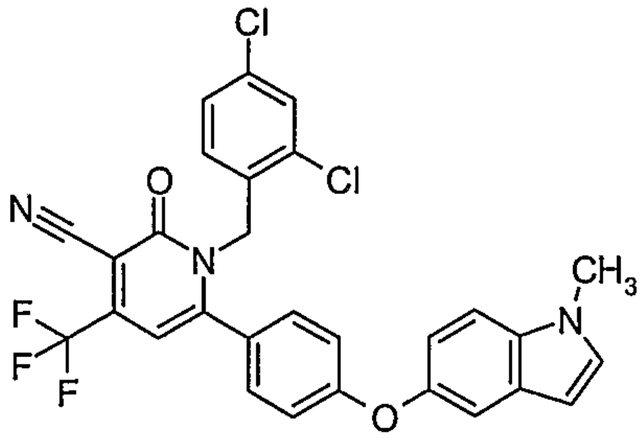
175		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
176		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-pyridin-3-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
177		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-pyridin-4-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
178		5-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-2-hydroxy-N,N-dimethylbenzamide
179		1-[(2,4-dichlorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
180		6-{3-chloro-4-[(4-fluorophenyl)oxy]phenyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

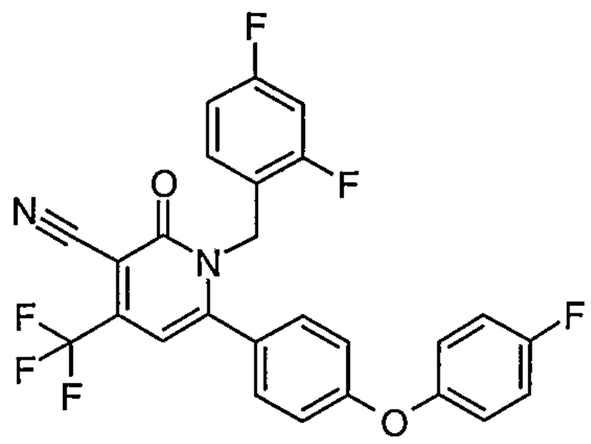
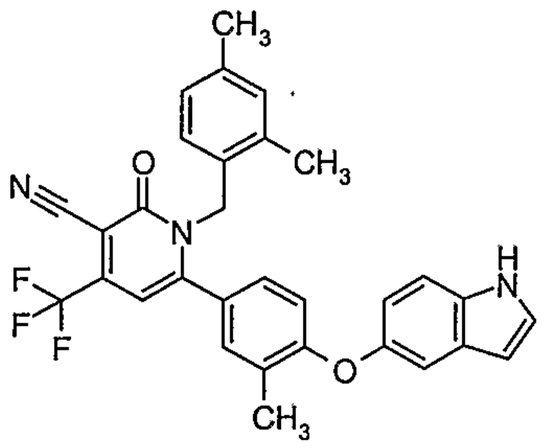
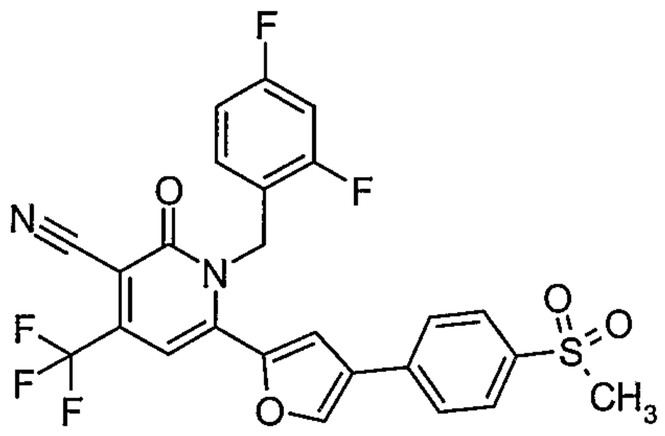
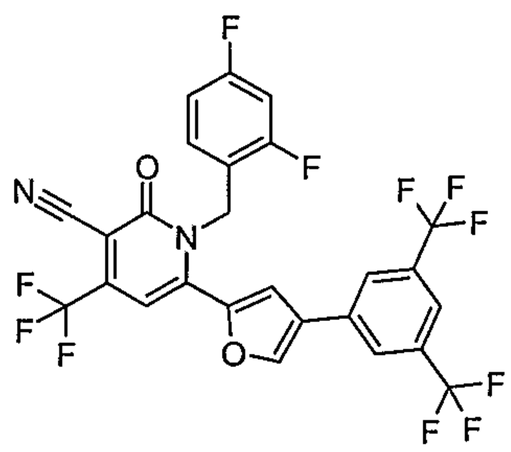
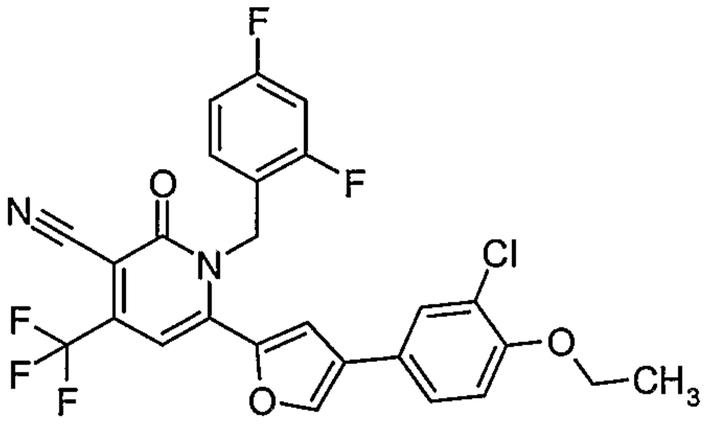
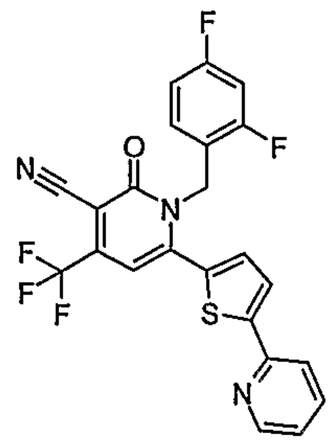
181		1-[(2,4-difluorophenyl)methyl]-6-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
182		N-({1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}methyl)methanesulfonamide
183		3-[(diethylamino)methyl]-1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)pyridin-2(1H)-one
184		1-({1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}methyl)guanidine
185		6-[5-(1,3-benzodioxol-5-yl)furan-2-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
186		6-{5-[3,4-bis(methyloxy)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

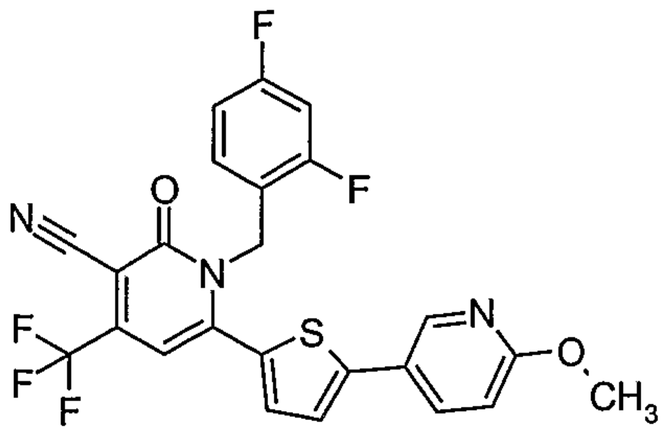
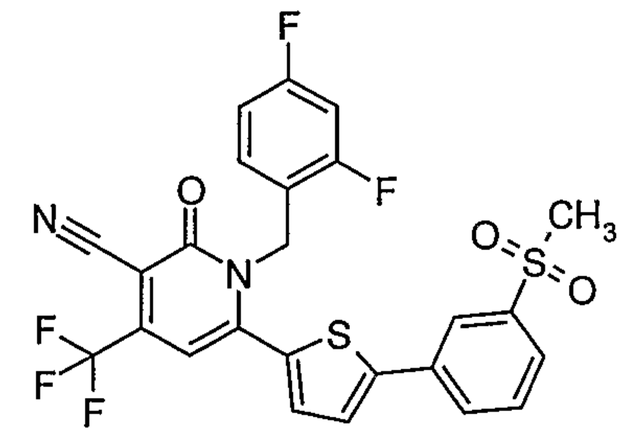
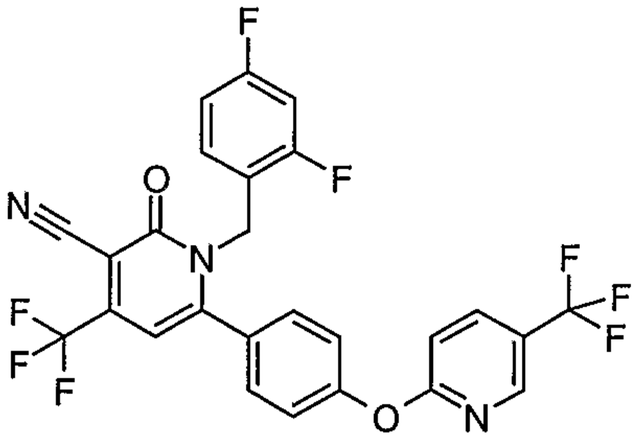
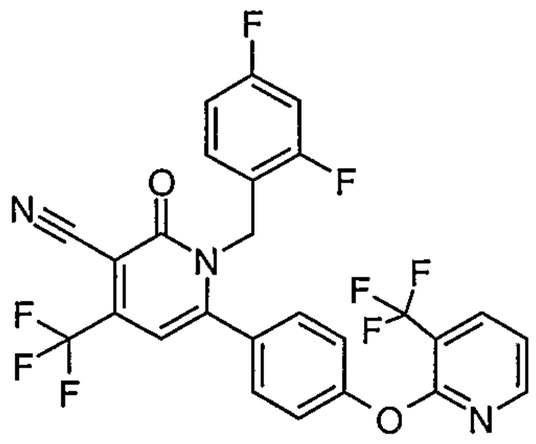
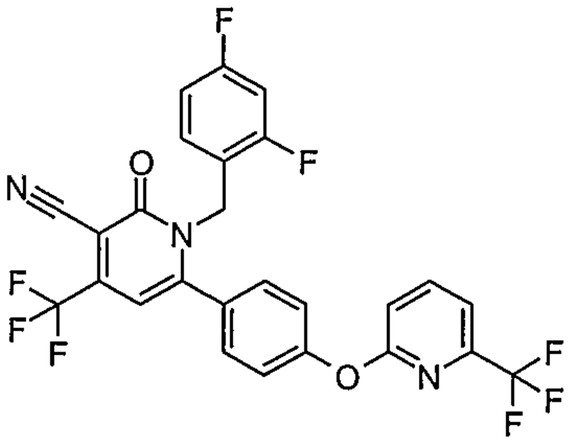
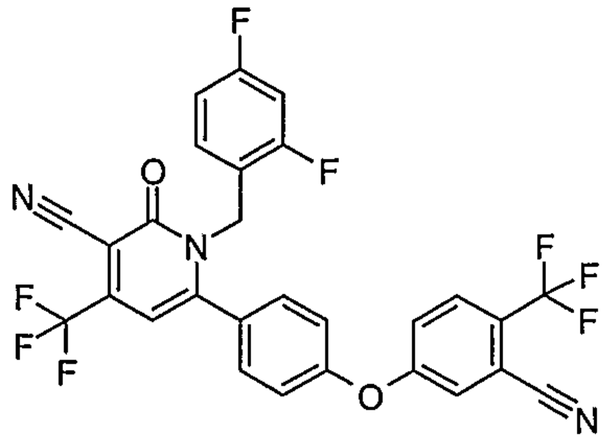
187		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-hydroxy-3-(methyloxy)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
188		6-{4-[3,5-bis(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
189		6-{4-[3-chloro-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
190		6-{4-[3,4-bis(methyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
191		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
192		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-pyridin-3-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

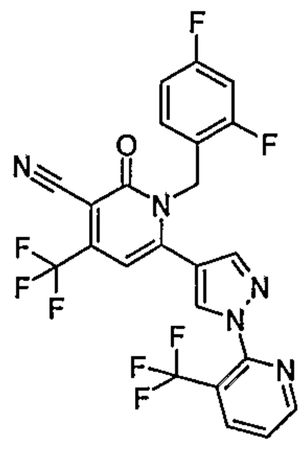
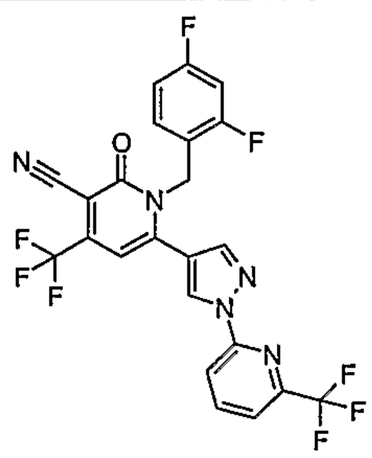
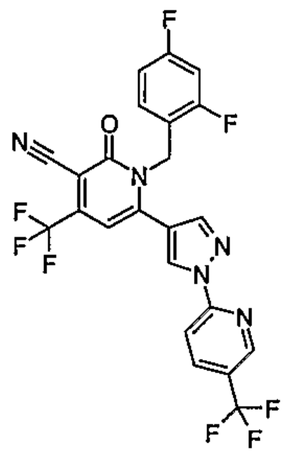
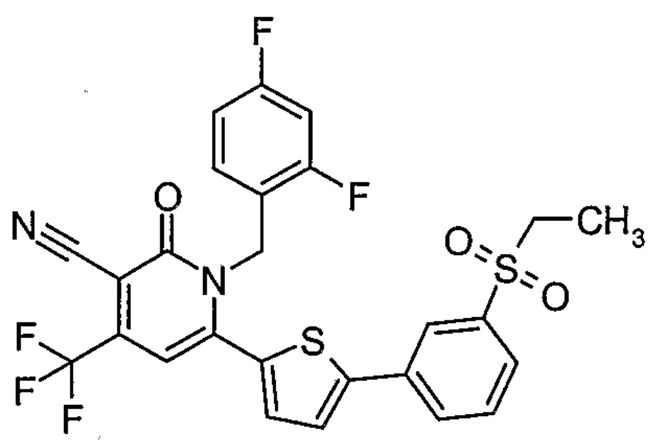
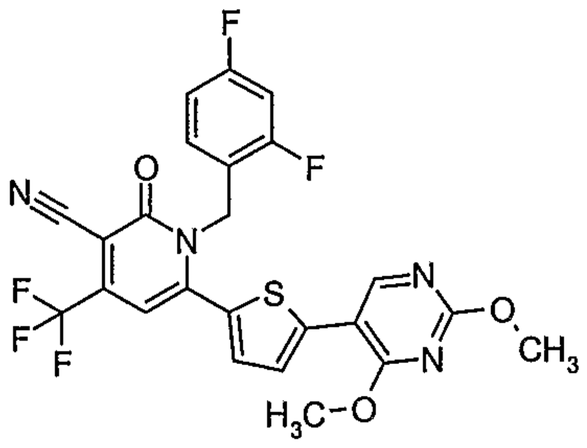
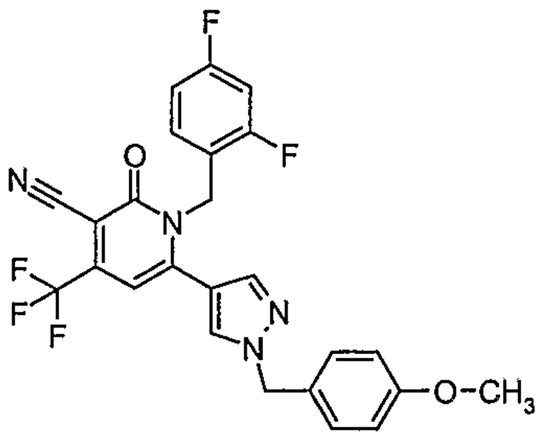
193		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-pyridin-4-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
194		1-[(2,4-difluorophenyl)methyl]-6-[4-(1H-indol-5-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
195		6-(3'-acetylbiphenyl-3-yl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
196		6-(4'-acetylbiphenyl-3-yl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
197		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxamide
198		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-carboxamide

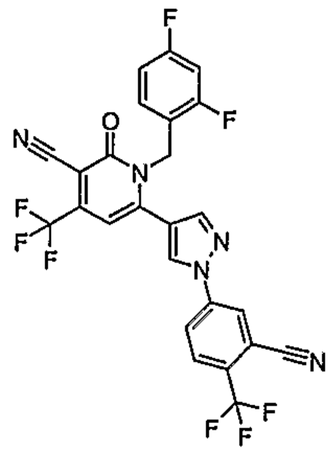
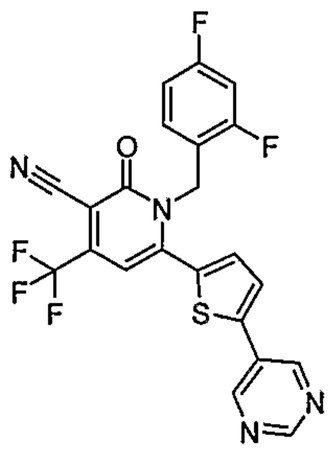
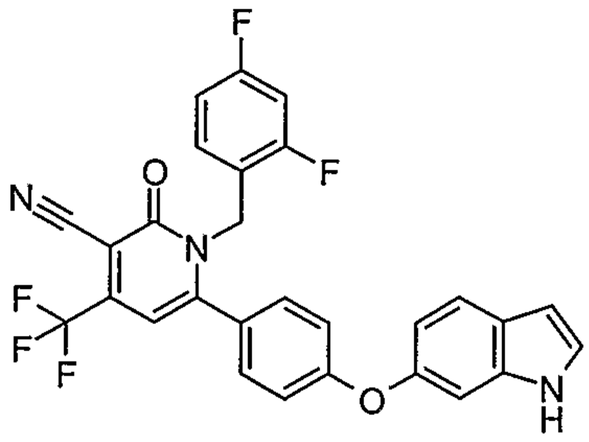
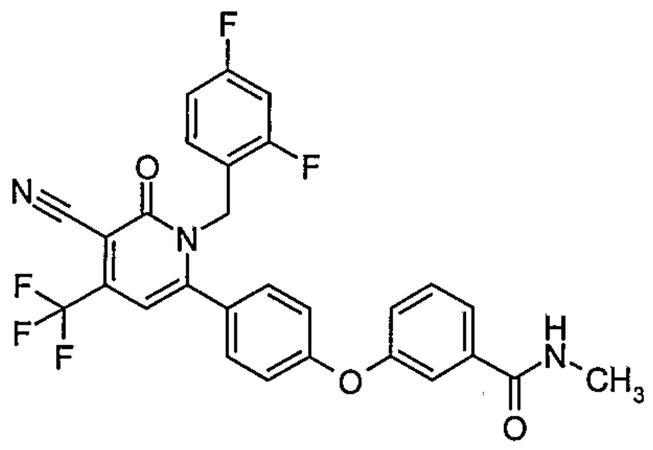
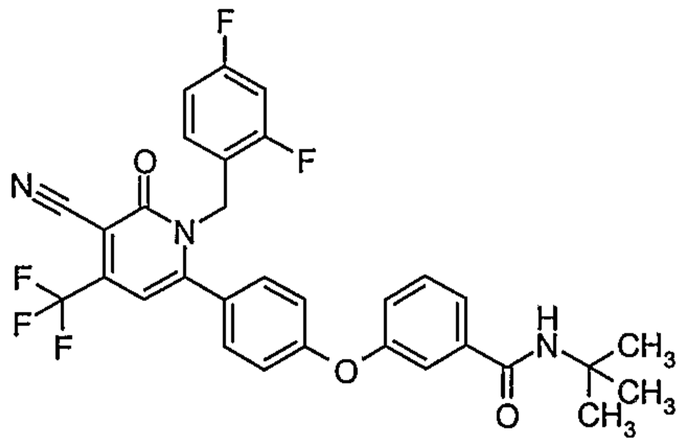
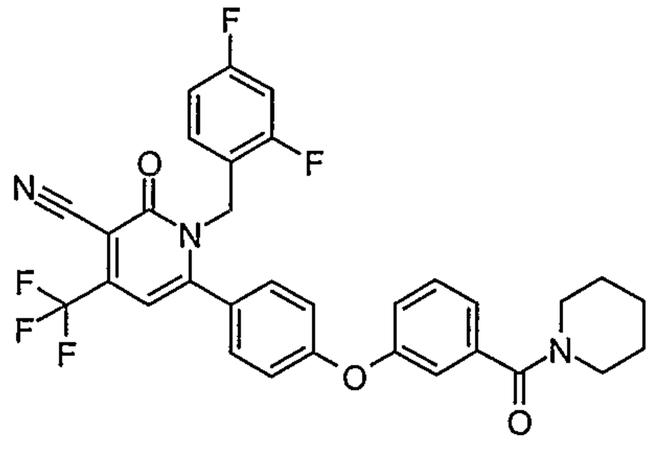
199		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N,N-dimethylbiphenyl-3-carboxamide
200		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N,N-dimethylbiphenyl-4-carboxamide
201		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3'-(pyrrolidin-1-ylcarbonyl)biphenyl-3-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
202		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4'-(piperidin-1-ylcarbonyl)biphenyl-3-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
203		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-3-carboxamide
204		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-methylbiphenyl-4-carboxamide

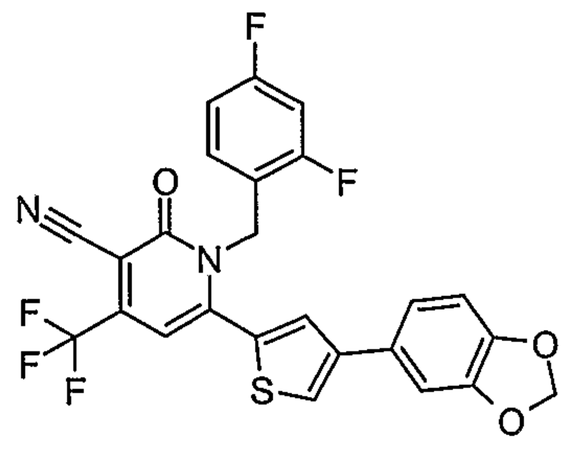
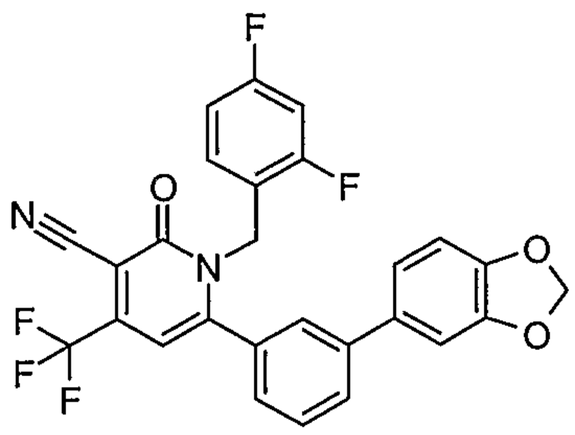
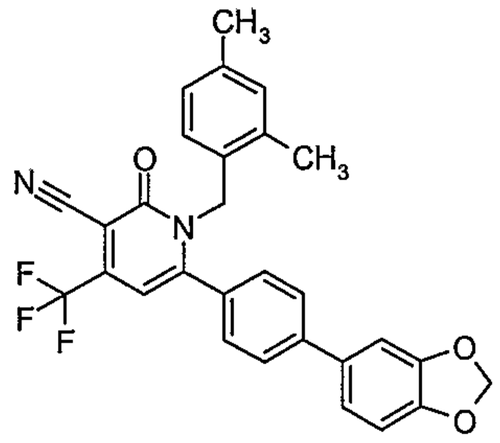
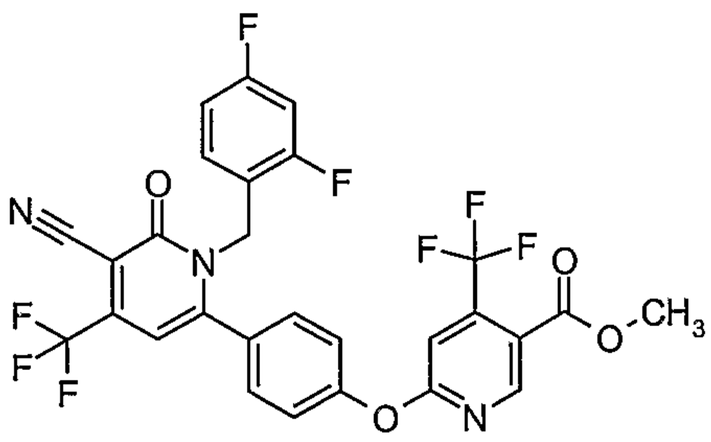
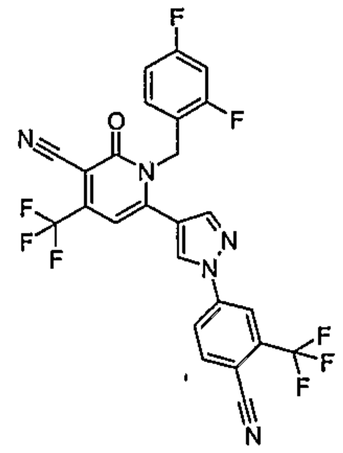
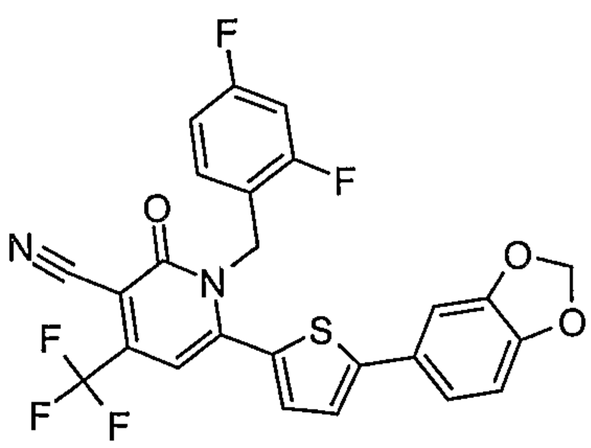
205		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(3-pyridin-3-ylphenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
206		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(3-pyridin-4-ylphenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
207		6-(3'-aminobiphenyl-3-yl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
208		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-phenylbiphenyl-4-carboxamide
209		3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-(phenylmethyl)biphenyl-4-carboxamide
210		1-[(2,4-dichlorophenyl)methyl]-6-{4-[(1-methyl-1H-indol-5-yl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

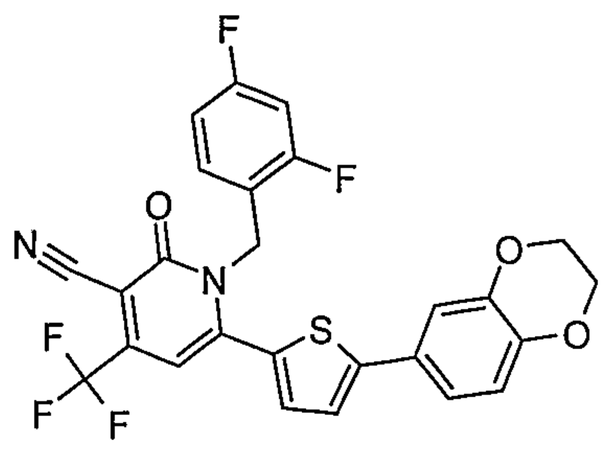
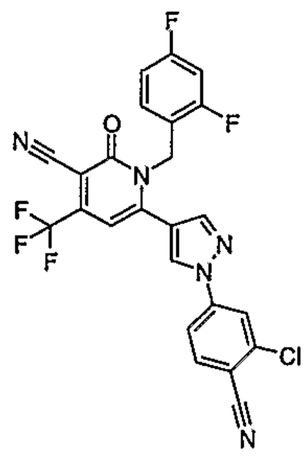
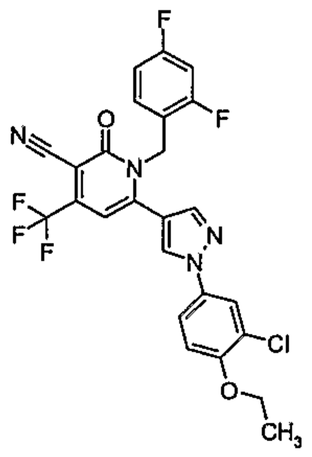
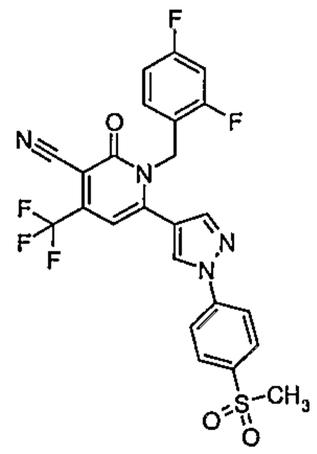
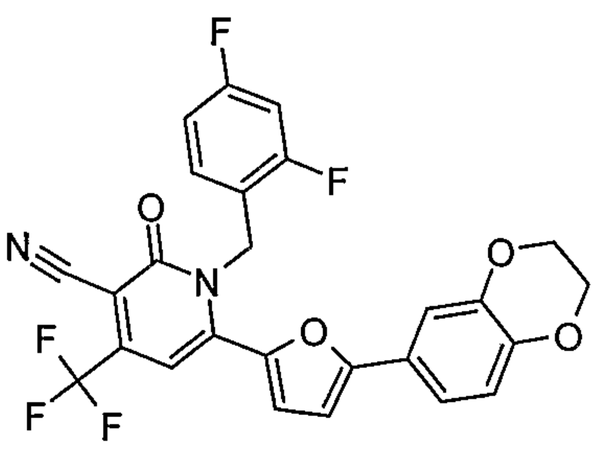
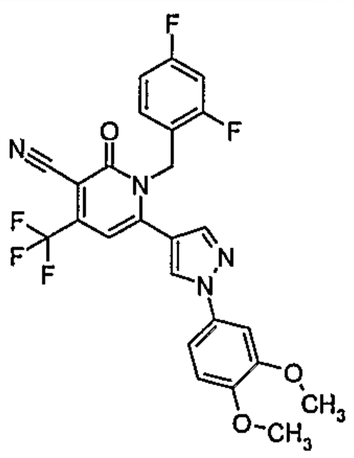
211		1-[(2,4-difluorophenyl)methyl]-6-{4-[(4-fluorophenyl)oxy]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
212		1-[(2,4-dimethylphenyl)methyl]-6-[4-(1H-indol-5-yloxy)-3-methylphenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
213		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
214		6-{4-[3,5-bis(trifluoromethyl)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
215		6-{4-[3-chloro-4-(ethyloxy)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
216		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-pyridin-2-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

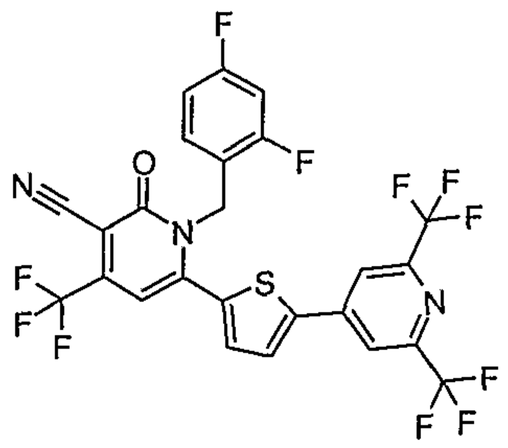
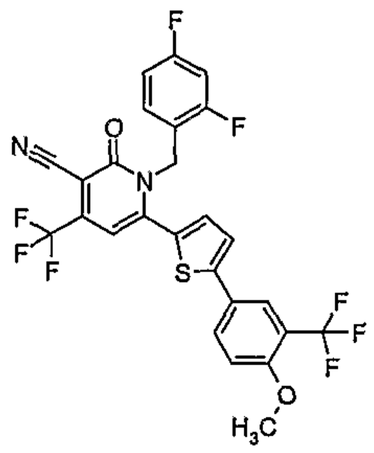
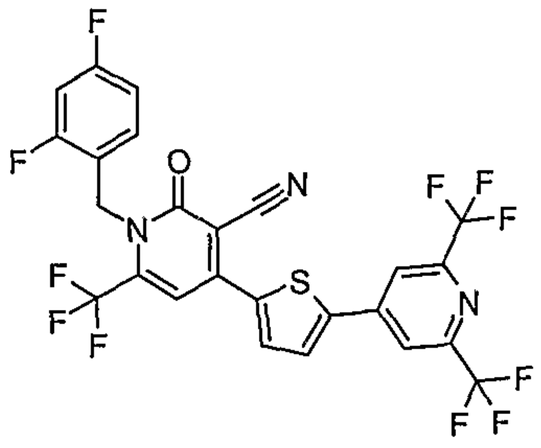
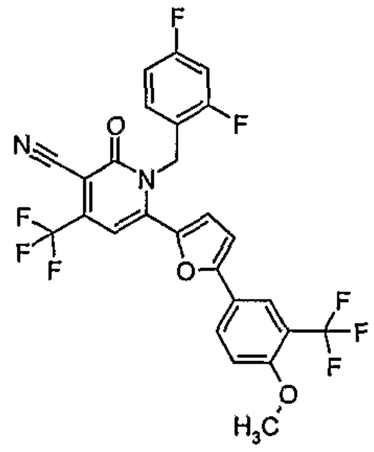
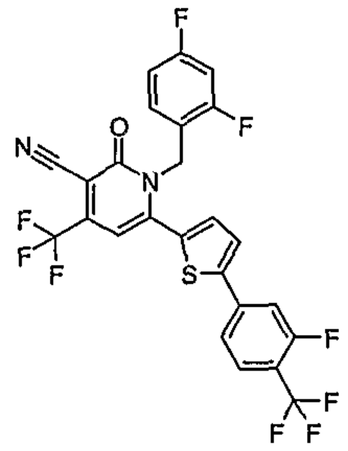
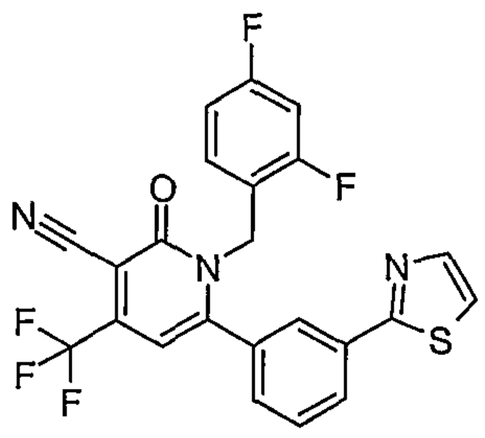
217		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(methyloxy)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
218		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
219		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-1,2-dihydropyridine-3-carbonitrile
220		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-(4-{[3-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-1,2-dihydropyridine-3-carbonitrile
221		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-1,2-dihydropyridine-3-carbonitrile
222		6-(4-{[3-cyano-4-(trifluoromethyl)phenyl]oxy}phenyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

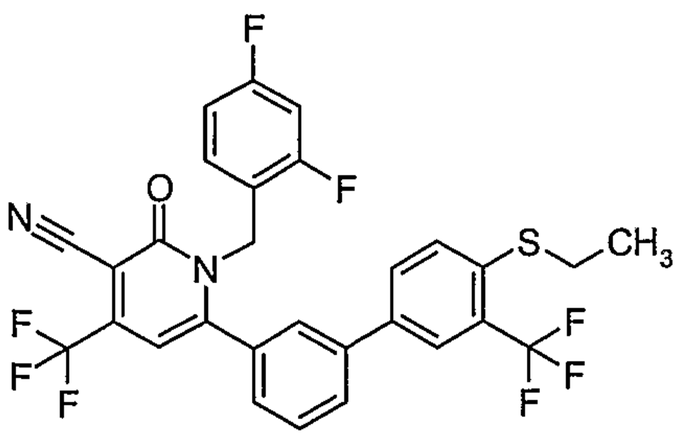
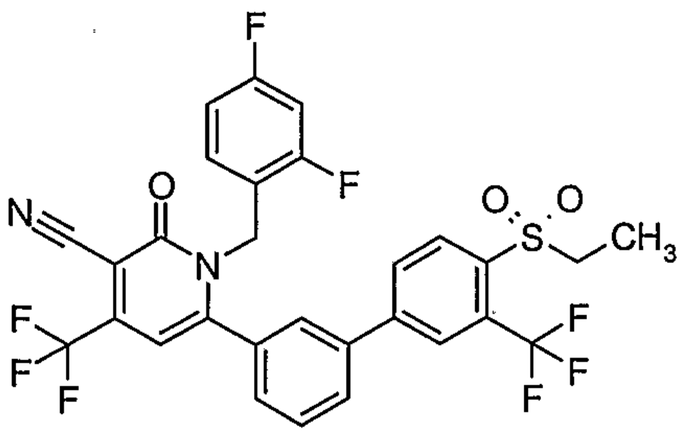
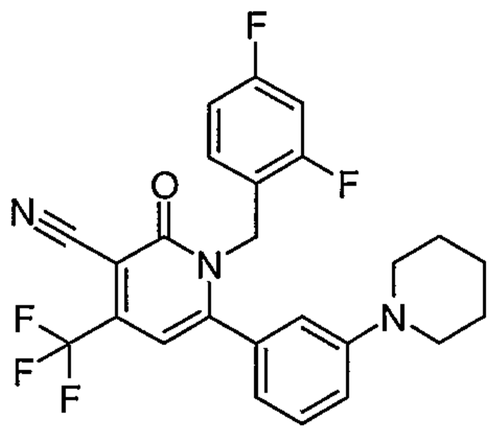
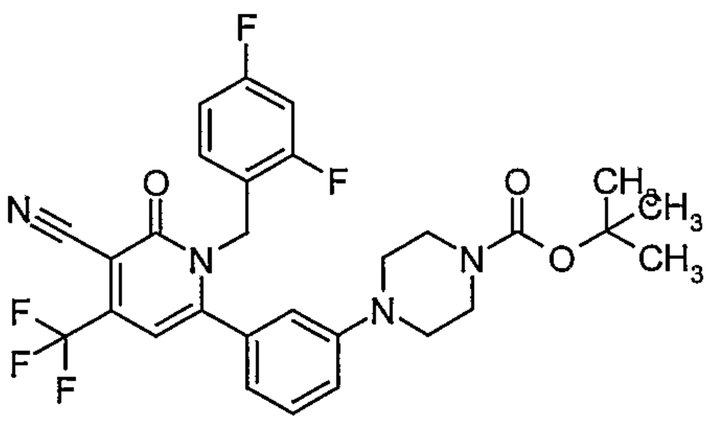
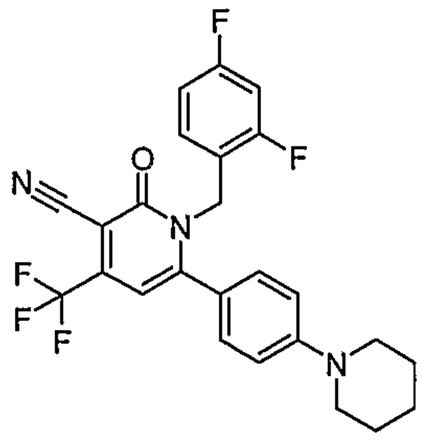
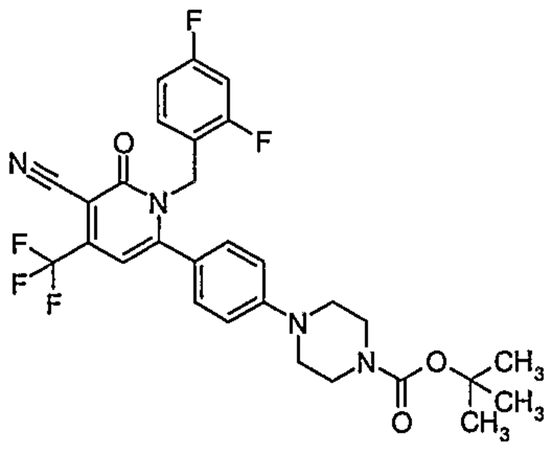
223		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-{1-[3-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}-1,2-dihydropyridine-3-carbonitrile
224		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-{1-[6-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}-1,2-dihydropyridine-3-carbonitrile
225		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-{1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrazol-4-yl}-1,2-dihydropyridine-3-carbonitrile
226		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
227		6-{5-[2,4-bis(methyloxy)pyrimidin-5-yl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
228		1-[(2,4-difluorophenyl)methyl]-6-(1-{[4-(methyloxy)phenyl]methyl}-1H-pyrazol-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

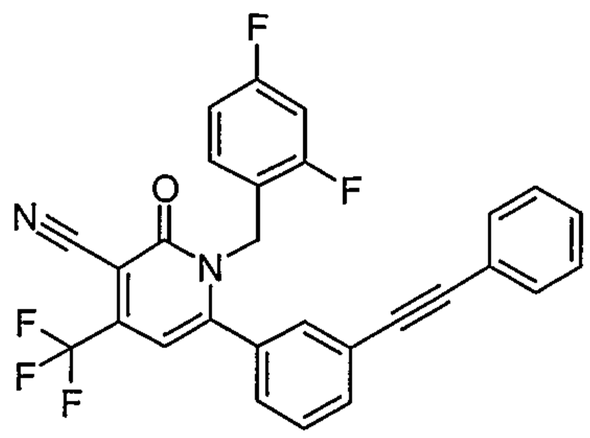
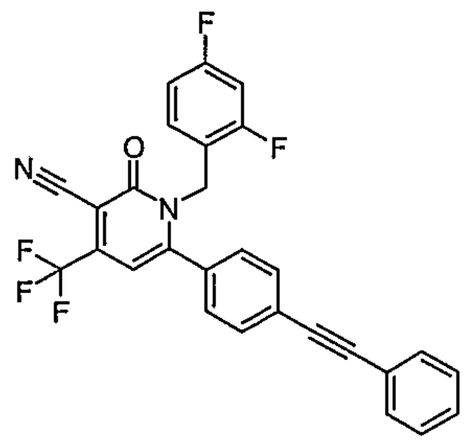
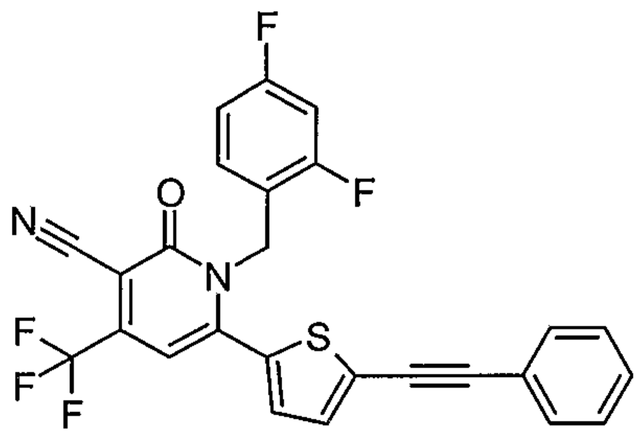
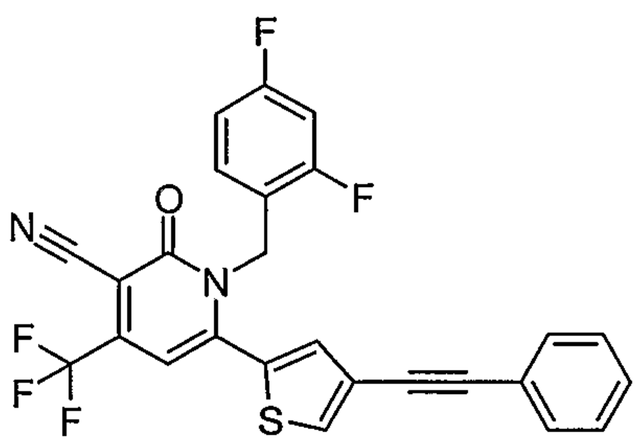
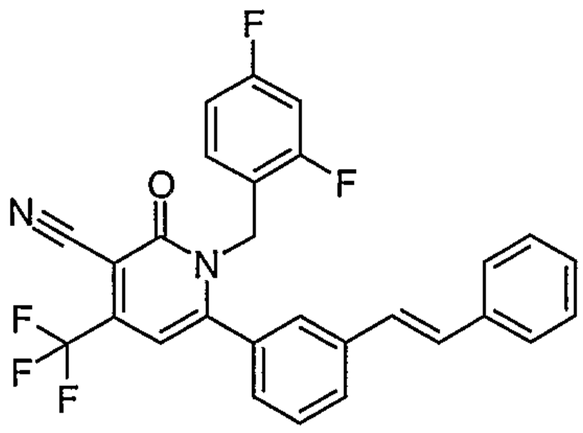
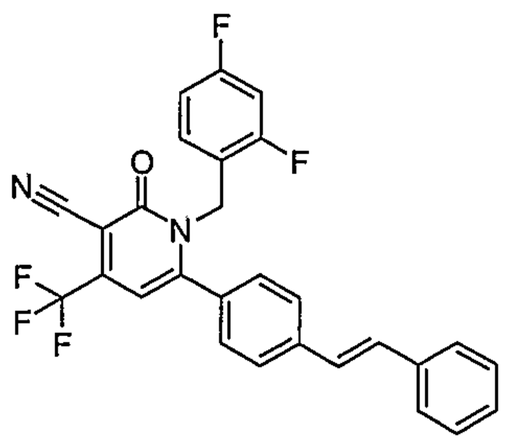
229		6-{1-[3-cyano-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
230		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-pyrimidin-5-yl-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
231		1-[(2,4-difluorophenyl)methyl]-6-[4-(1H-indol-6-yloxy)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
232		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-methylbenzamide
233		3-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(1,1-dimethylethyl)benzamide
234		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-{[3-(piperidin-1-ylcarbonyl)phenyl]oxy}phenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

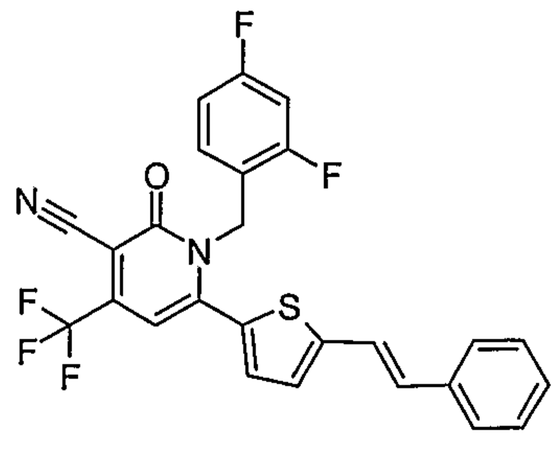
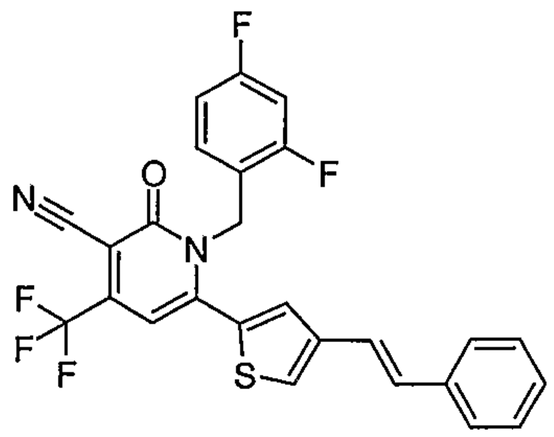
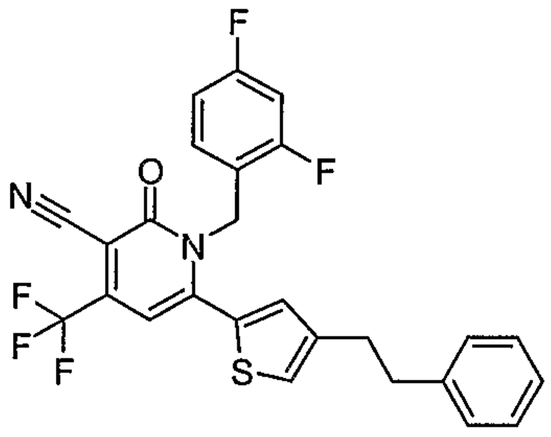
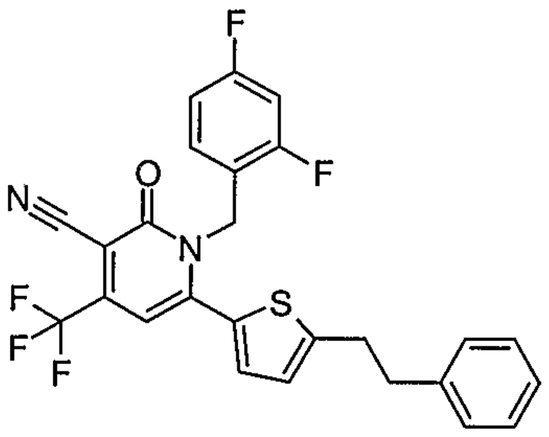
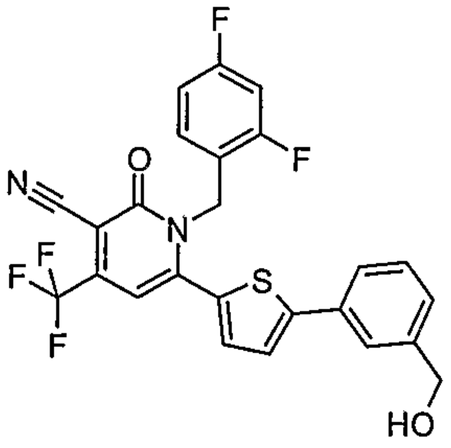
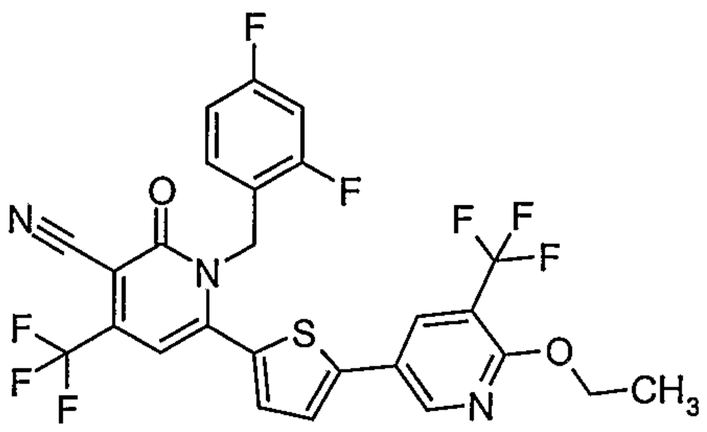
235		6-[4-(1,3-benzodioxol-5-yl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
236		6-[3-(1,3-benzodioxol-5-yl)phenyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
237		6-[4-(1,3-benzodioxol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
238		methyl 6-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-4-(trifluoromethyl)pyridine-3-carboxylate
239		6-{1-[4-cyano-3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
240		6-[5-(1,3-benzodioxol-5-yl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

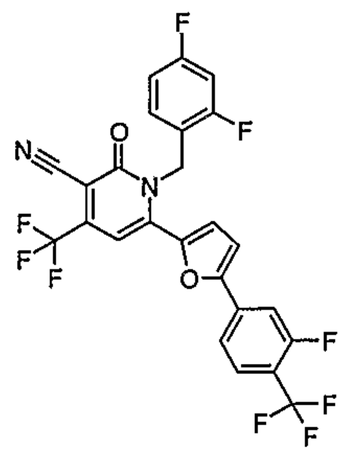
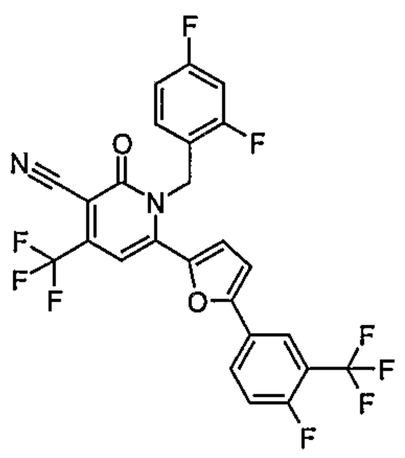
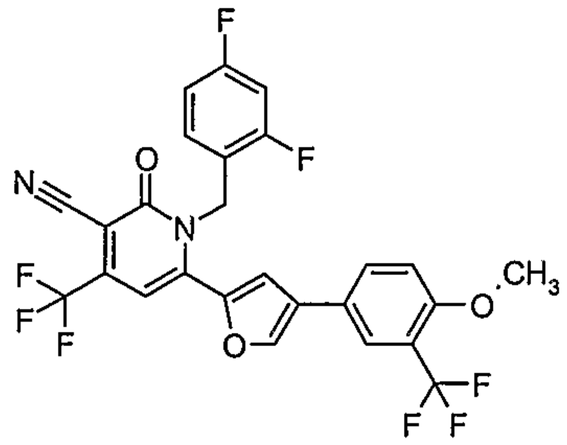
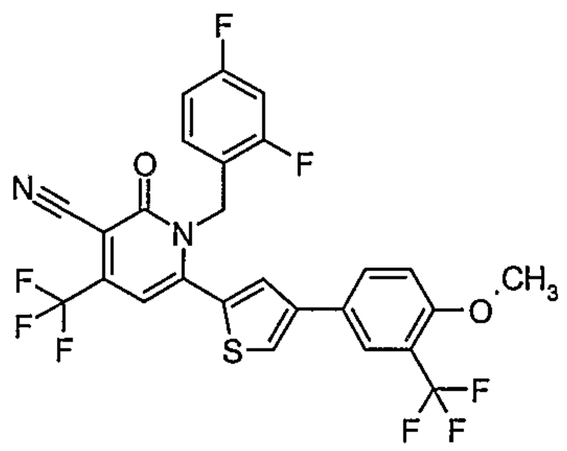
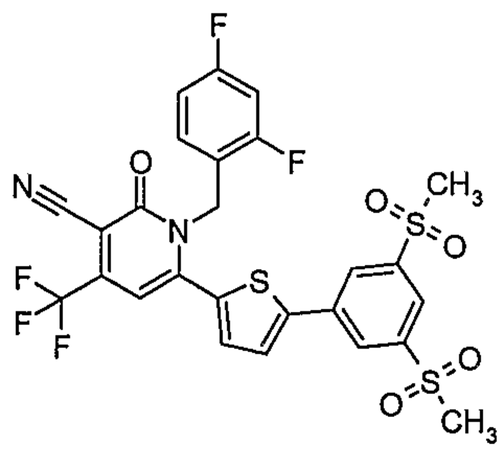
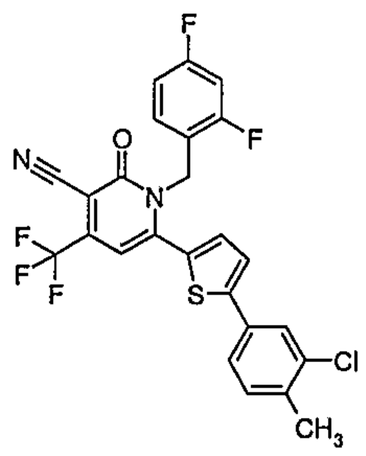
241		1-[(2,4-difluorophenyl)methyl]-6-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
242		6-[1-(3-chloro-4-cyanophenyl)-1H-pyrazol-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
243		6-{1-[3-chloro-4-(ethyloxy)phenyl]-1H-pyrazol-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
244		1-[(2,4-difluorophenyl)methyl]-6-{1-[4-(methylsulfonyl)phenyl]-1H-pyrazol-4-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
245		1-[(2,4-difluorophenyl)methyl]-6-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)furan-2-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
246		6-{1-[3,4-bis(methyloxy)phenyl]-1H-pyrazol-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

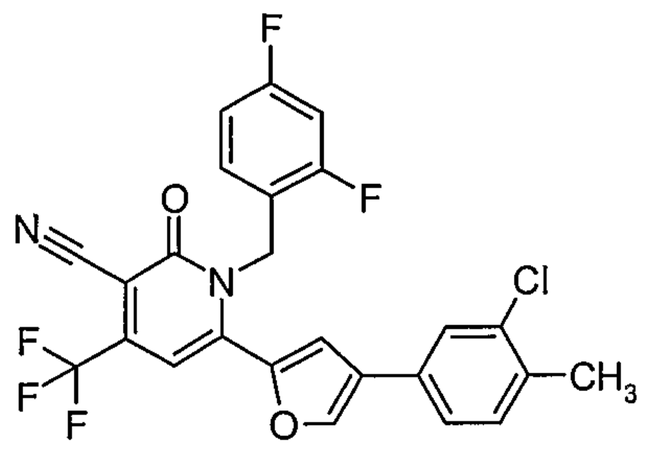
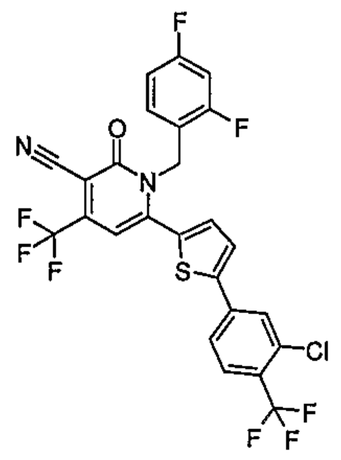
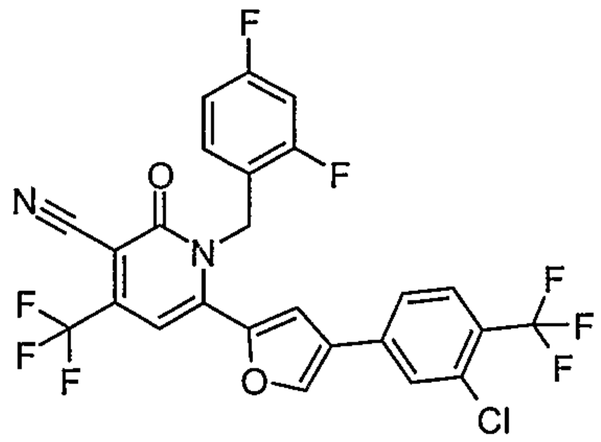
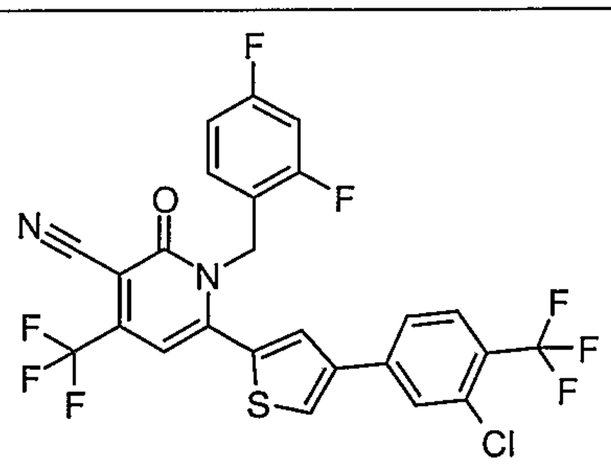
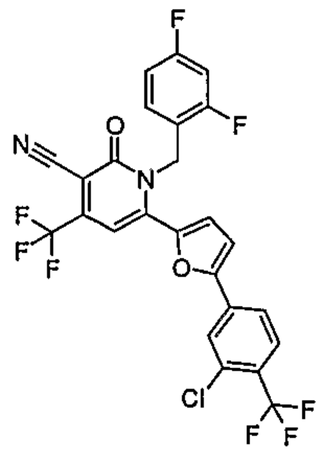
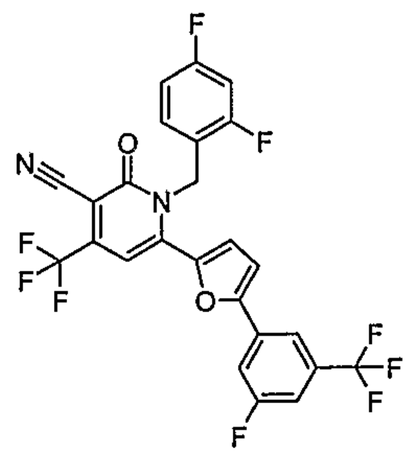
247		6-{5-[2,6-bis(trifluoromethyl)pyridin-4-yl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
248		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
249		4-{5-[2,6-bis(trifluoromethyl)pyridin-4-yl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
250		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
251		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-fluoro-4-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
252		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3-(1,3-thiazol-2-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

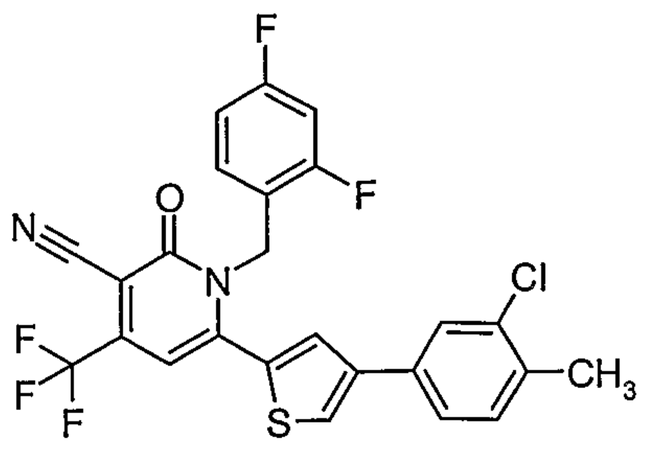
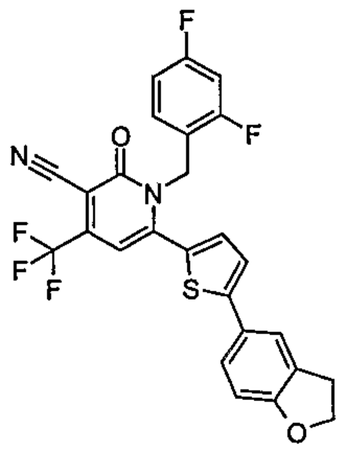
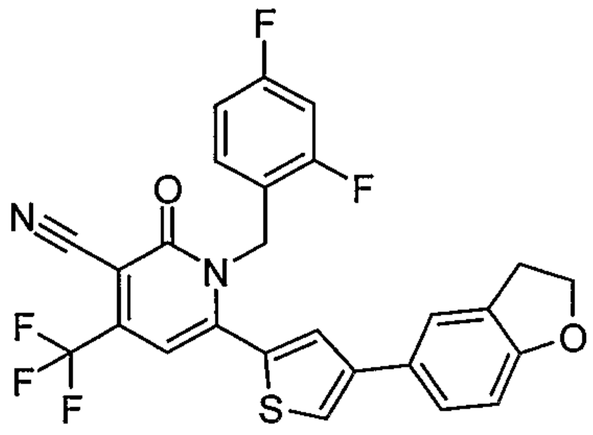
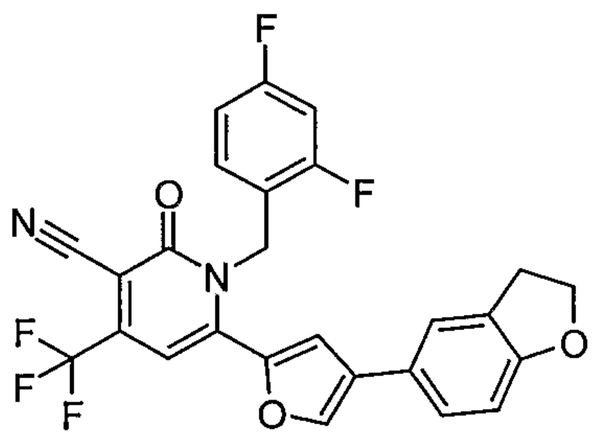
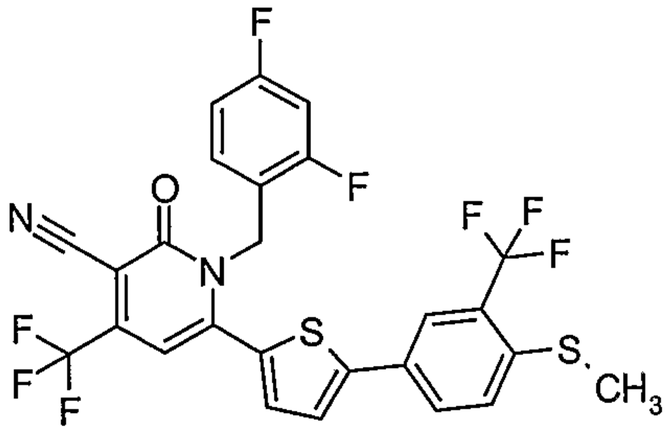
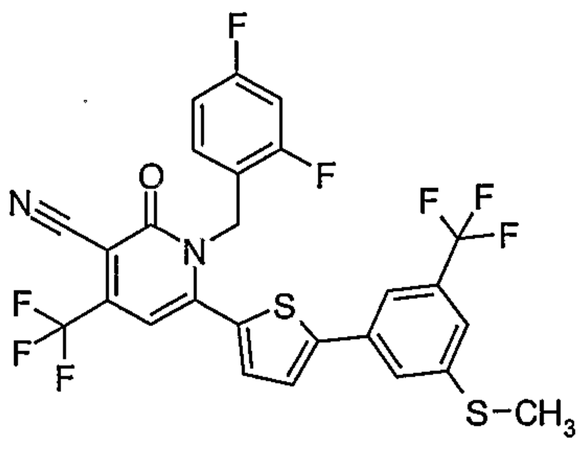
253		1-[(2,4-difluorophenyl)methyl]-6-[4'-(ethylthio)-3'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
254		1-[(2,4-difluorophenyl)methyl]-6-[4'-(ethylsulfonyl)-3'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
255		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(3-piperidin-1-ylphenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
256		1,1-dimethylethyl 4-(3-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)piperazine-1-carboxylate
257		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-piperidin-1-ylphenyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
258		1,1-dimethylethyl 4-(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)piperazine-1-carboxylate

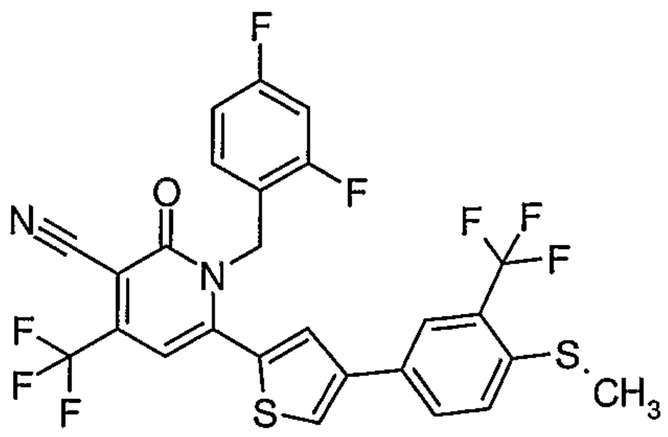
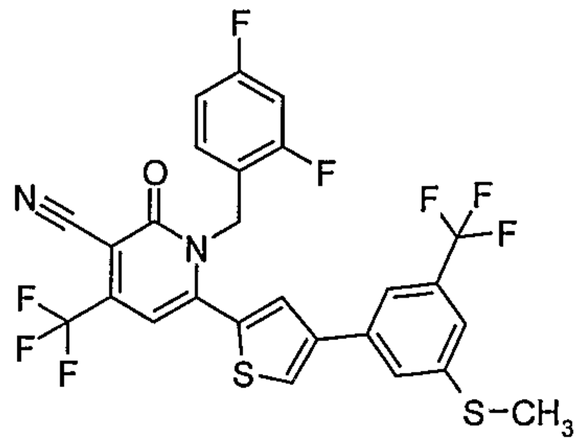
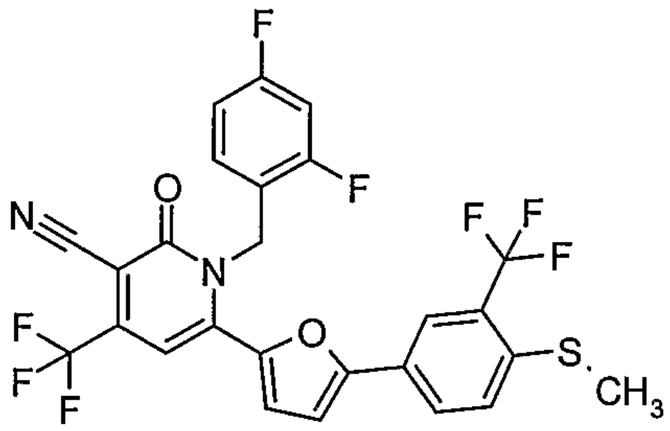
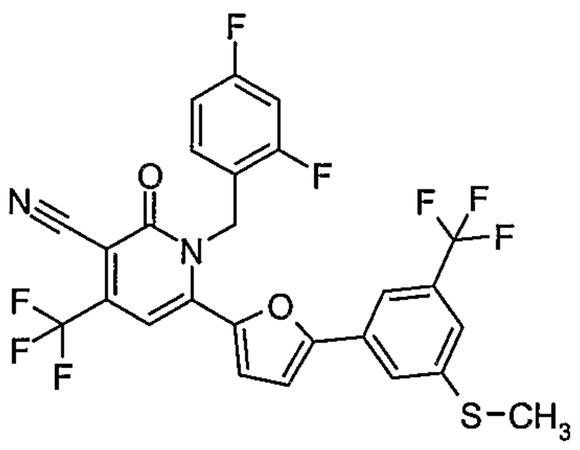
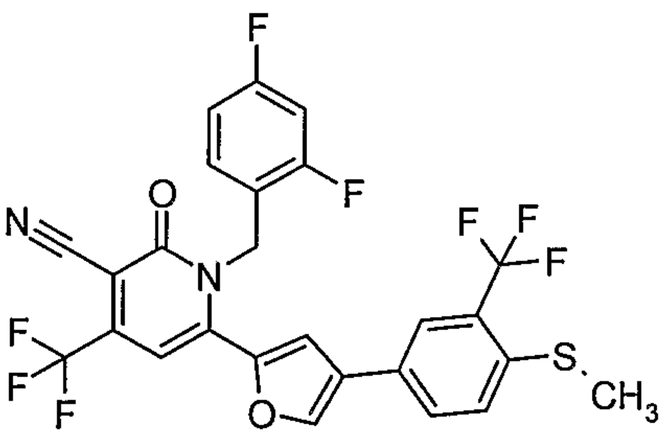
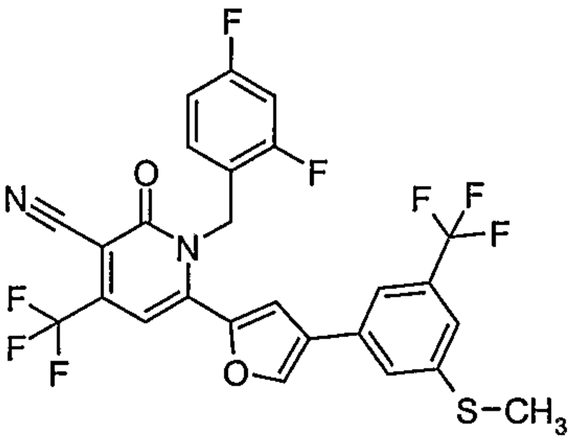
259		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3-(phenylethynyl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
260		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(phenylethynyl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
261		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[5-(phenylethynyl)-2-thienyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
262		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(phenylethynyl)-2-thienyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
263		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{3-[(E)-2-phenylethenyl]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
264		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[(E)-2-phenylethenyl]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

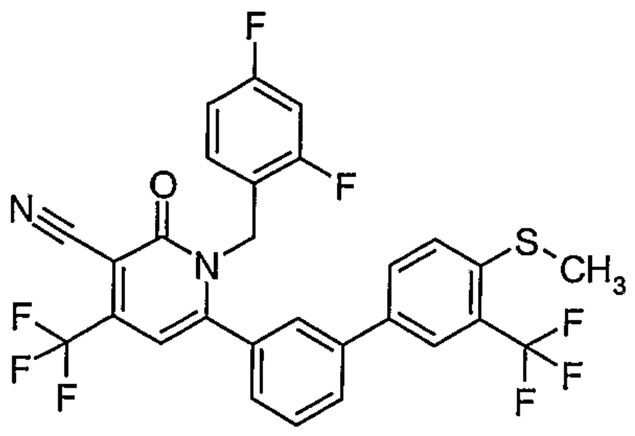
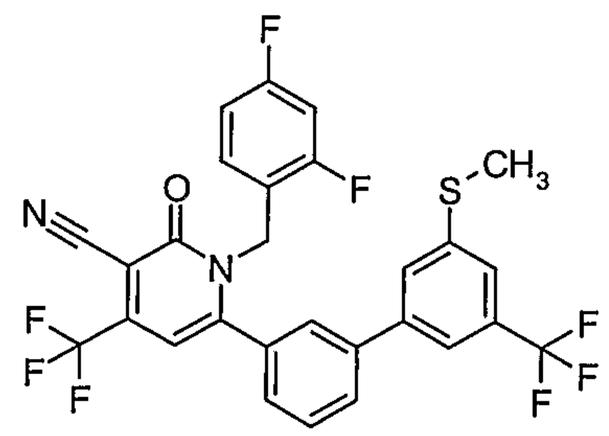
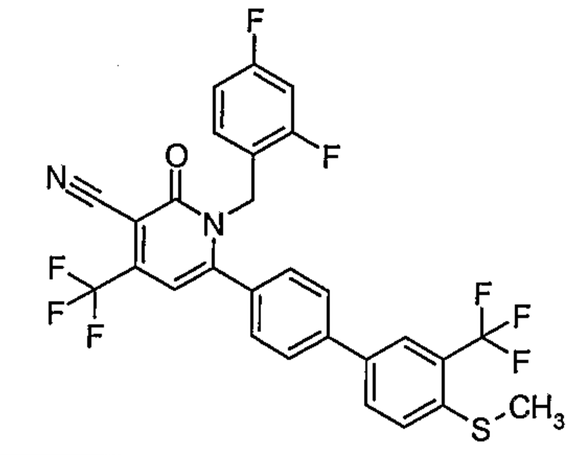
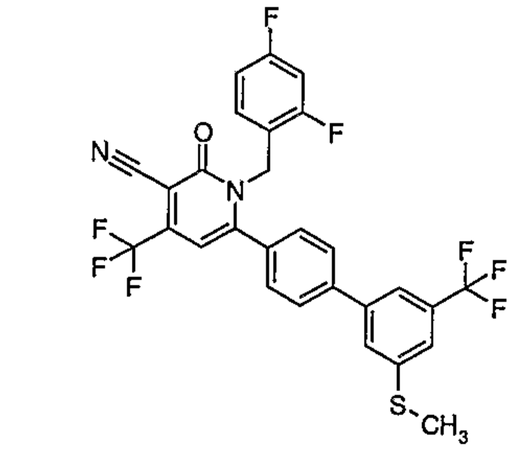
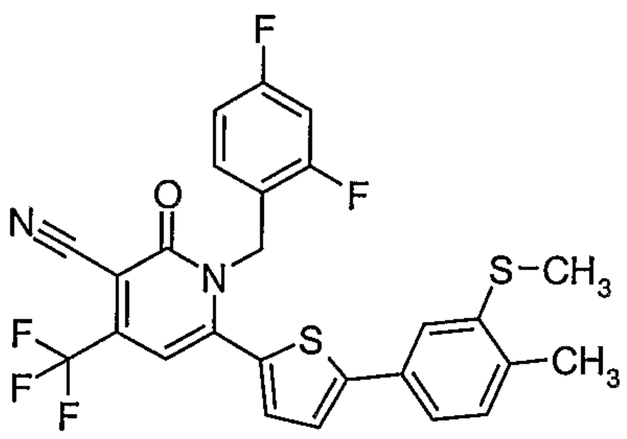
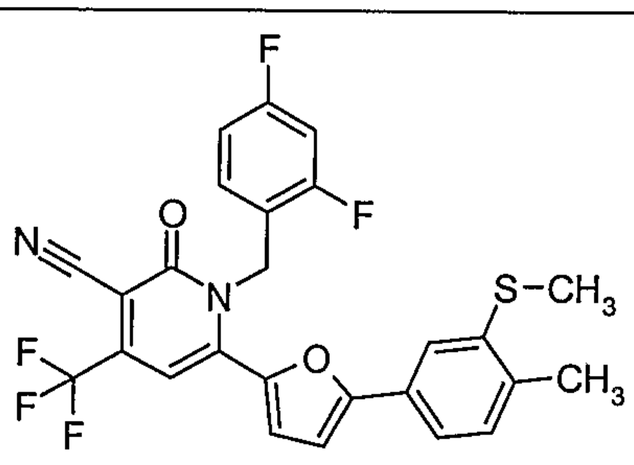
265		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{5-[(E)-2-phenylethenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
266		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[(E)-2-phenylethenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
267		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[4-(2-phenylethyl)-2-thienyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
268		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[5-(2-phenylethyl)-2-thienyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
269		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(hydroxymethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
270		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethyloxy)-5-(trifluoromethyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

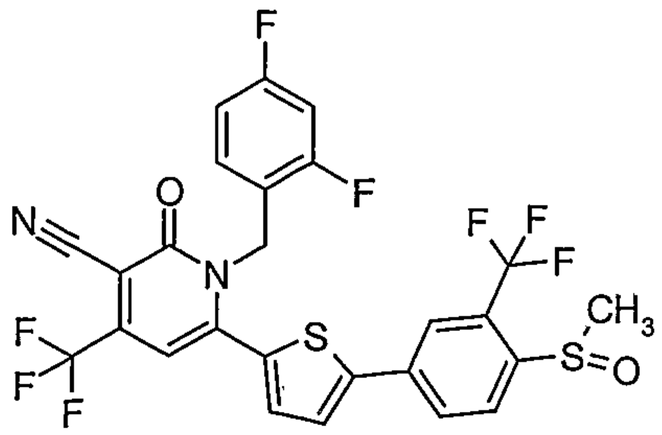
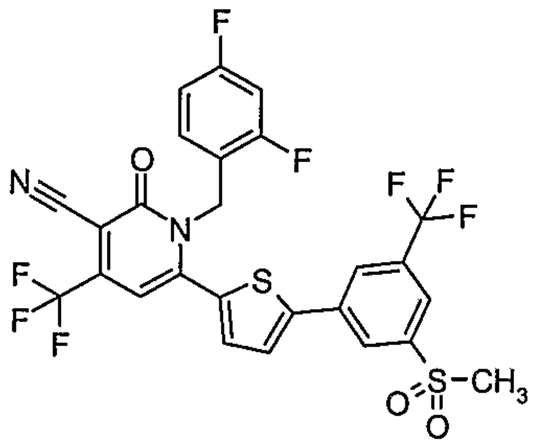
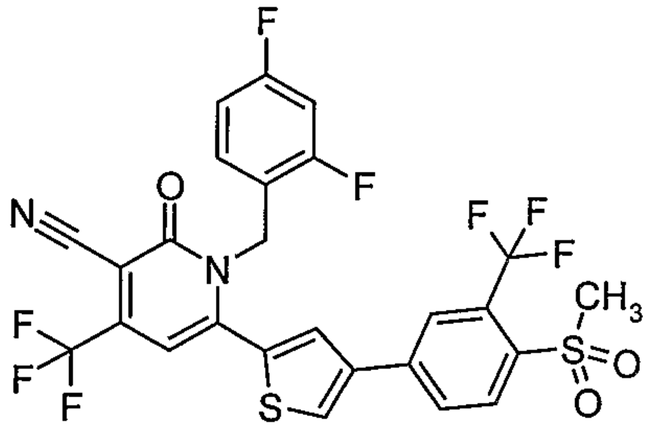
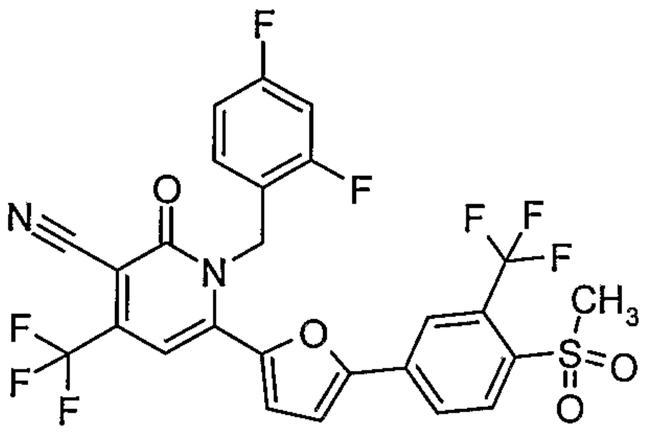
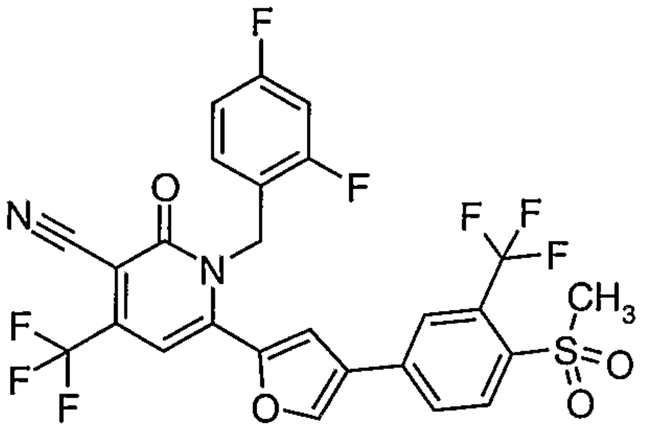
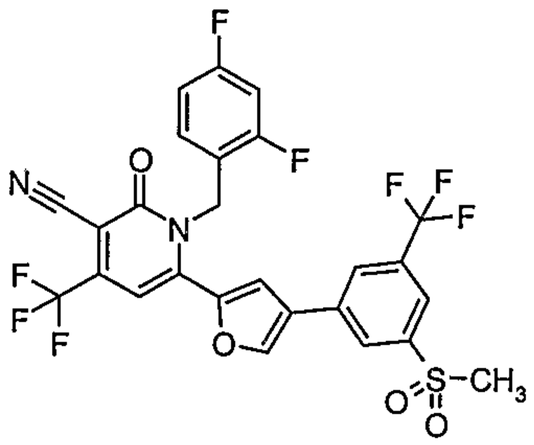
271		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-fluoro-4-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
272		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-fluoro-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
273		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methyloxy)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
274		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
275		6-{5-[3,5-bis(methylsulfonyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
276		6-[5-(3-chloro-4-methylphenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

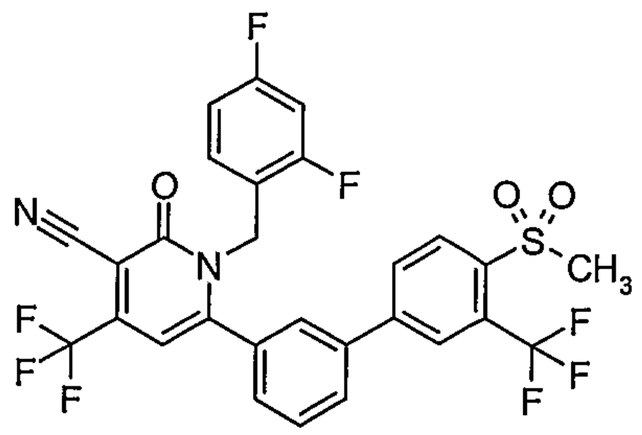
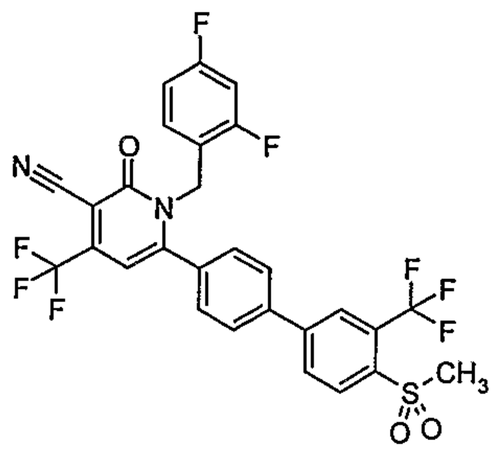
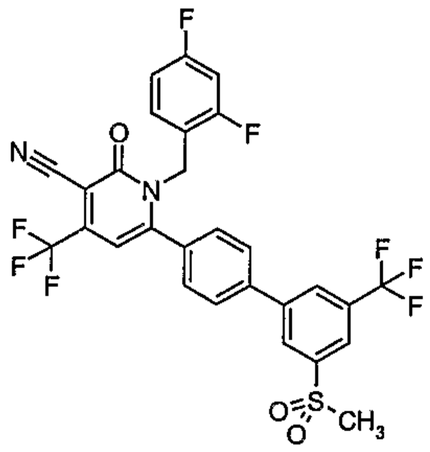
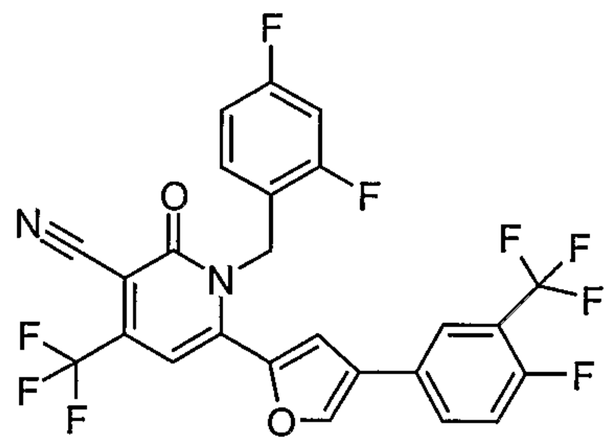
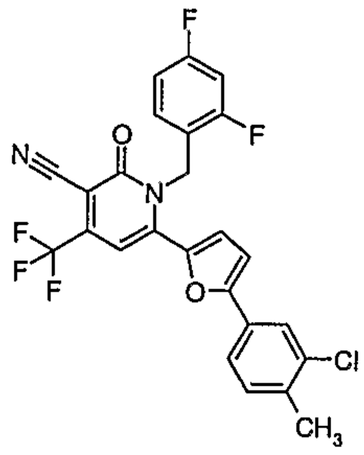
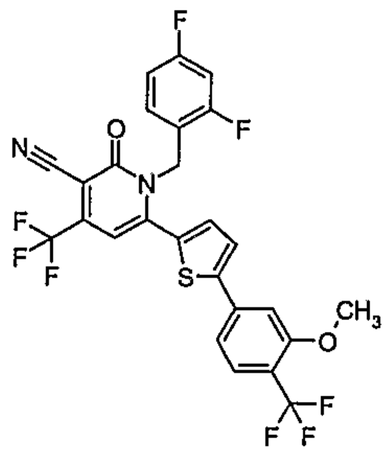
277		6-[4-(3-chloro-4-methylphenyl)furan-2-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
278		6-{5-[3-chloro-4-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
279		6-{4-[3-chloro-4-(trifluoromethyl)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
280		6-{4-[3-chloro-4-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
281		6-{5-[3-chloro-4-(trifluoromethyl)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
282		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-fluoro-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

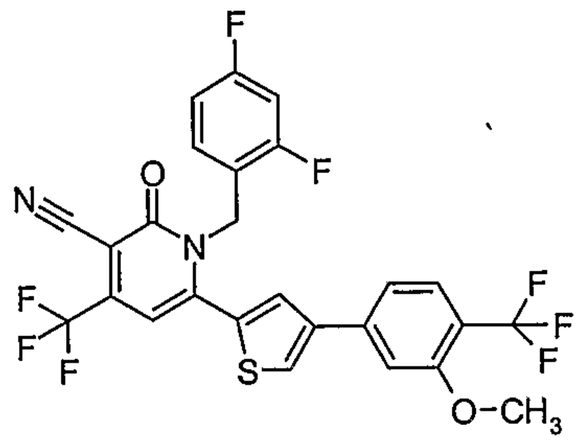
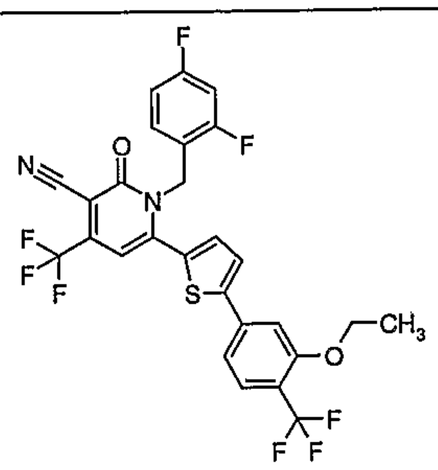
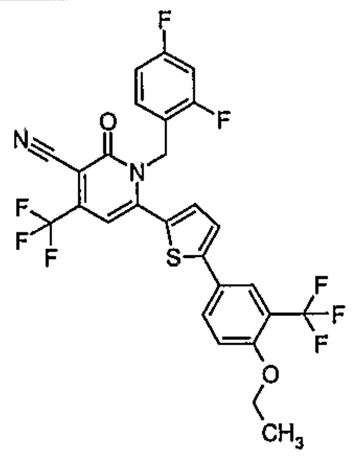
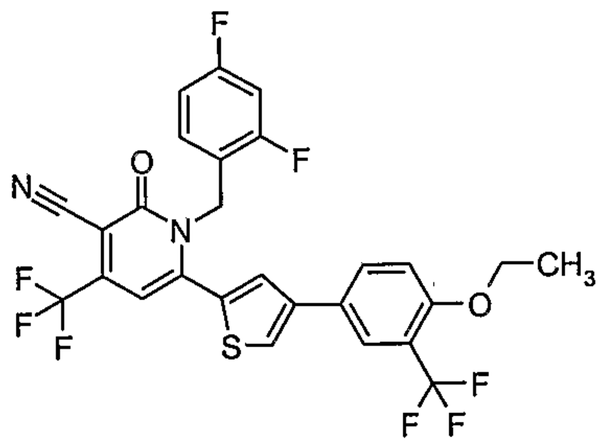
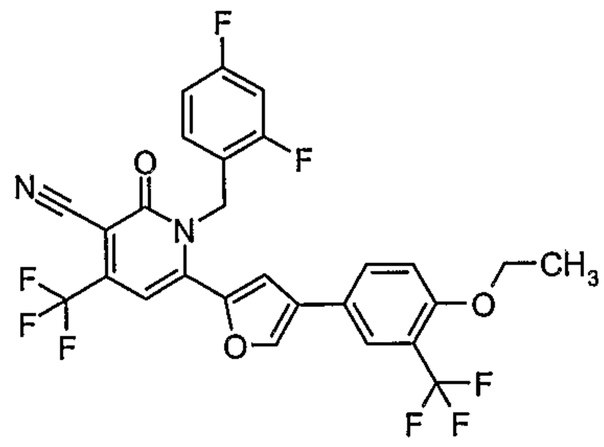
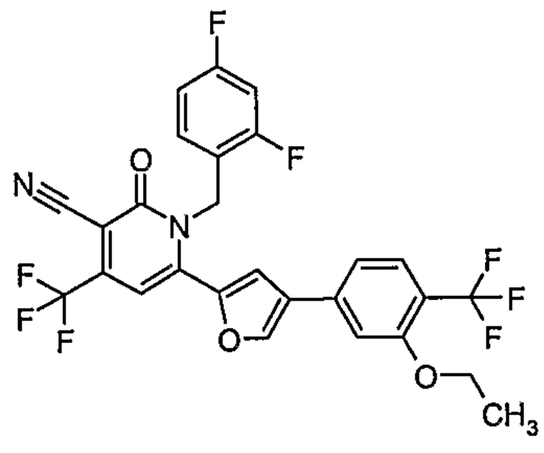
283		6-[4-(3-chloro-4-methylphenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
284		1-[(2,4-difluorophenyl)methyl]-6-[5-(2,3-dihydro-1-benzofuran-5-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
285		1-[(2,4-difluorophenyl)methyl]-6-[4-(2,3-dihydro-1-benzofuran-5-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
286		1-[(2,4-difluorophenyl)methyl]-6-[4-(2,3-dihydro-1-benzofuran-5-yl)furan-2-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
287		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylthio)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
288		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylthio)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

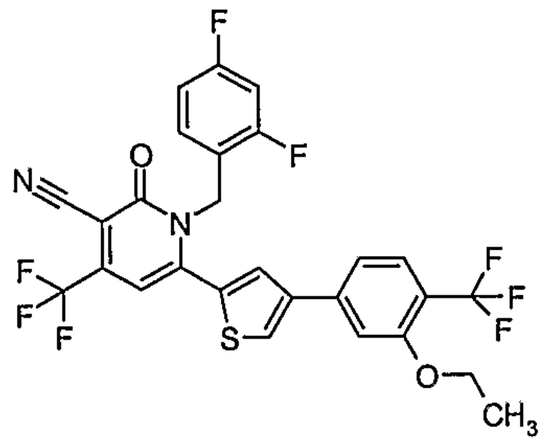
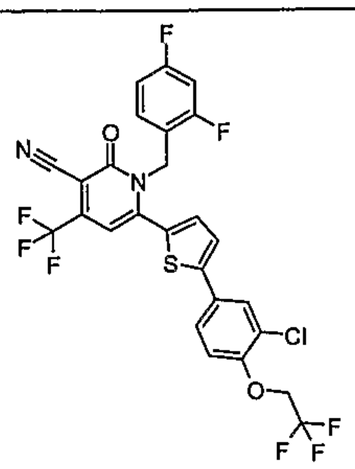
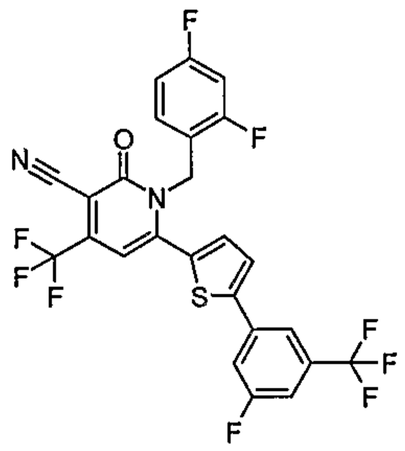
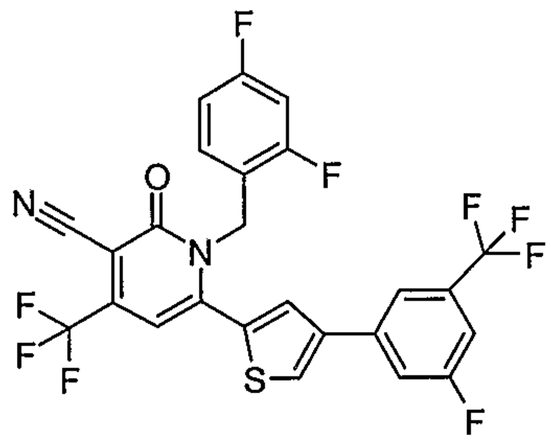
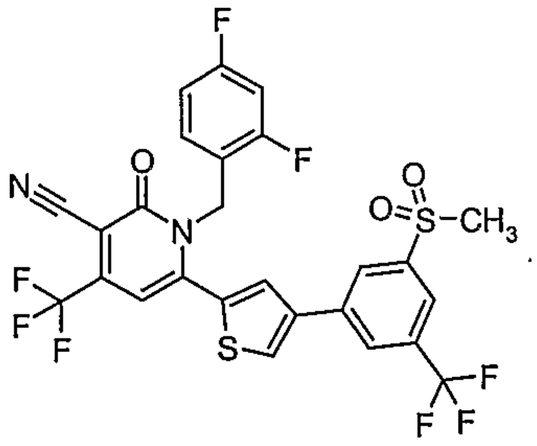
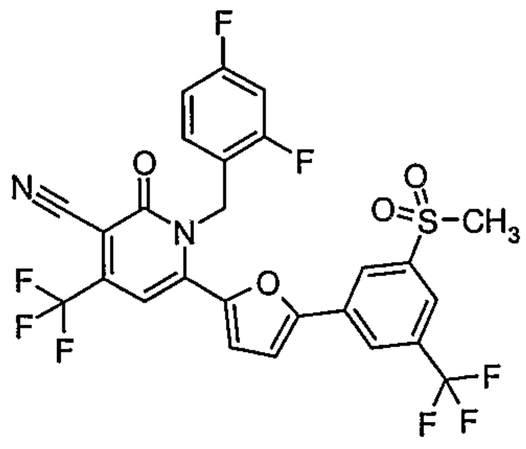
289		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylthio)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
290		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(methylthio)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
291		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylthio)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
292		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylthio)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
293		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylthio)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
294		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(methylthio)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

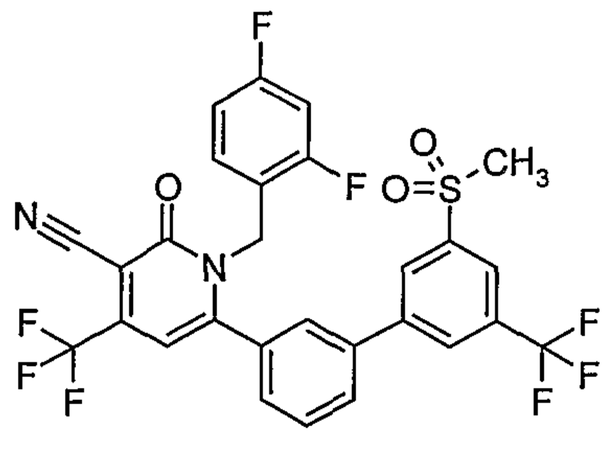
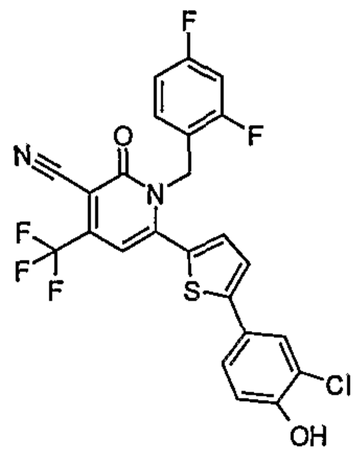
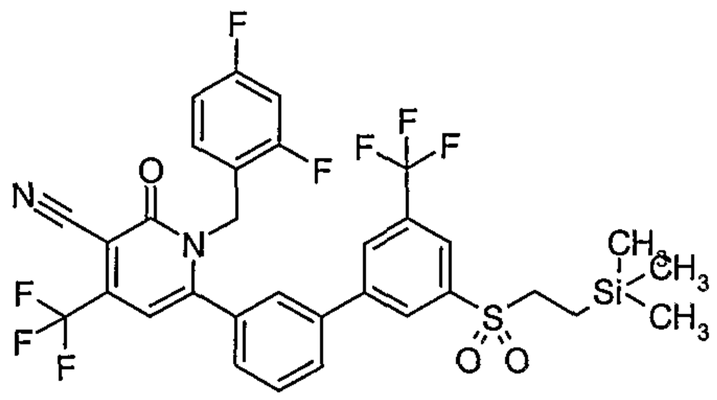
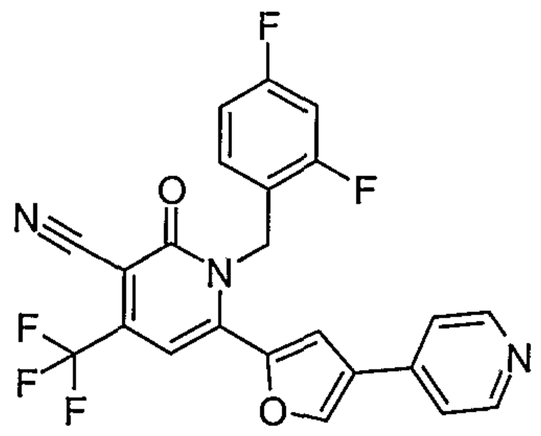
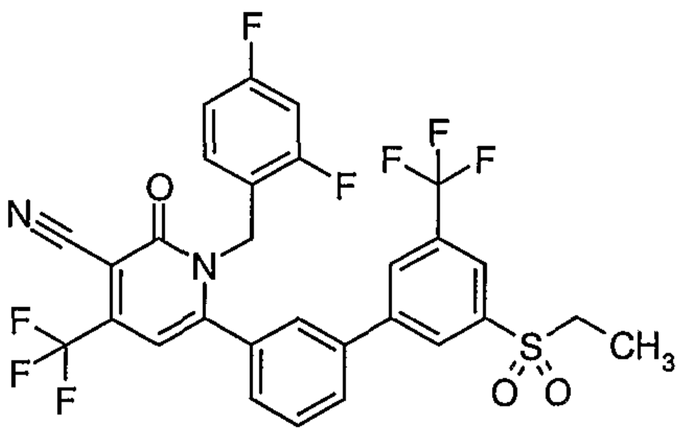
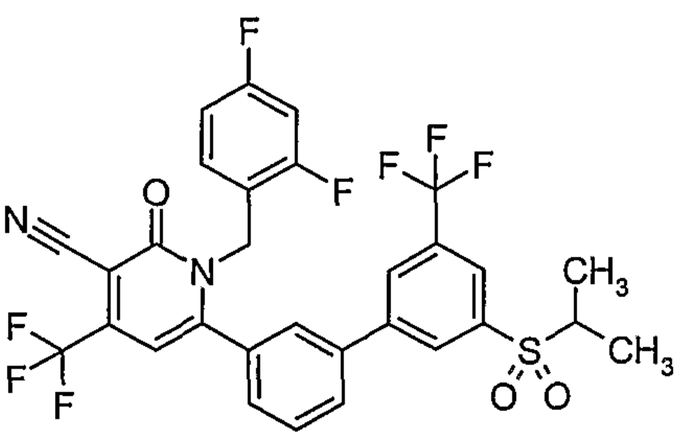
295		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylthio)-3'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
296		1-[(2,4-difluorophenyl)methyl]-6-[3'-(methylthio)-5'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
297		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylthio)-3'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
298		1-[(2,4-difluorophenyl)methyl]-6-[3'-(methylthio)-5'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
299		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-methyl-3-(methylthio)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
300		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-methyl-3-(methylthio)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

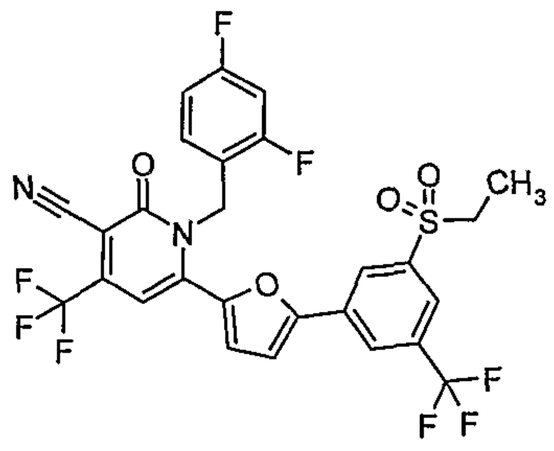
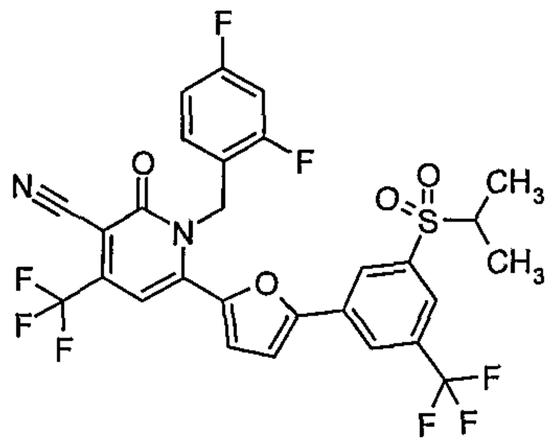
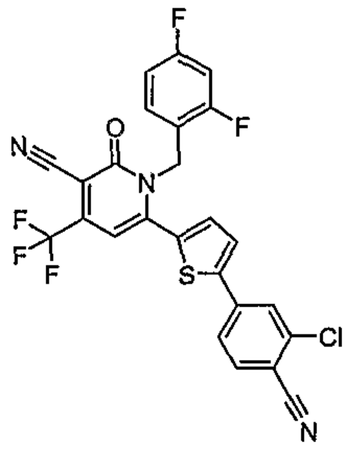
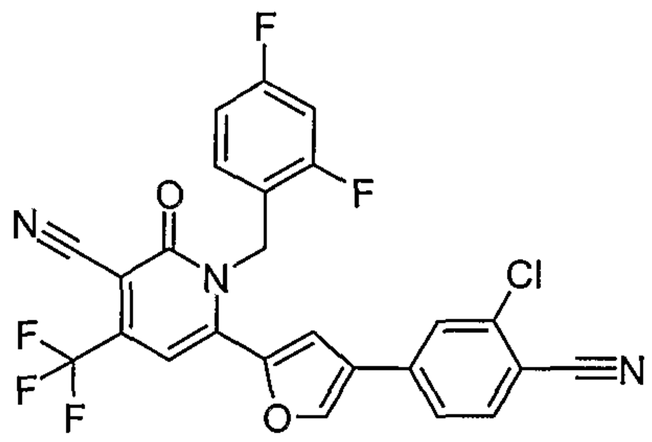
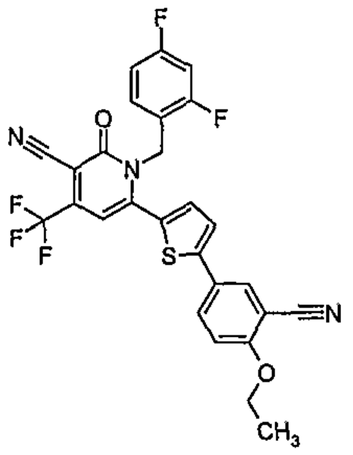
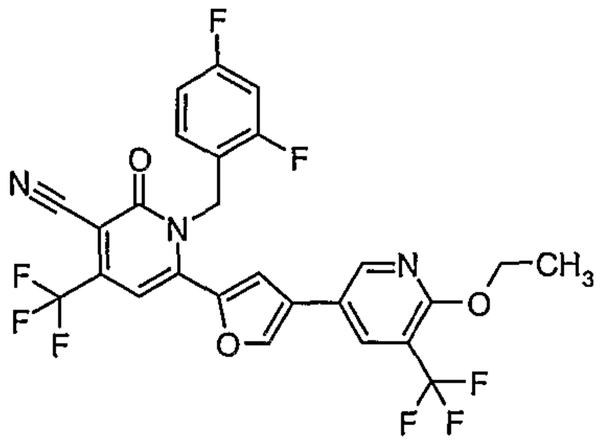
301		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfinyl)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
302		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
303		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
304		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
305		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
306		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(methylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

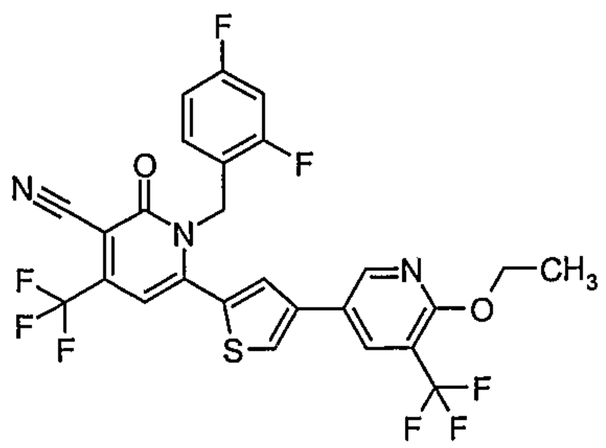
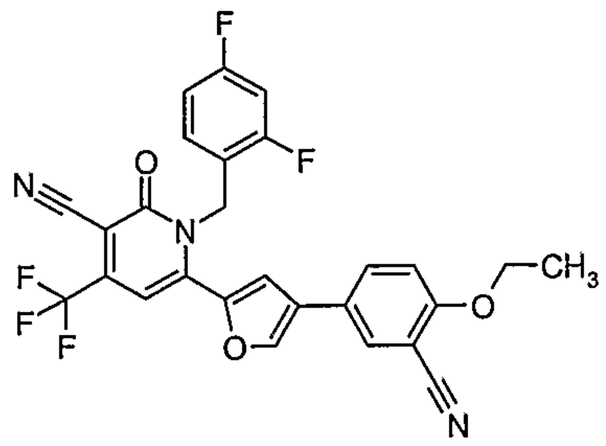
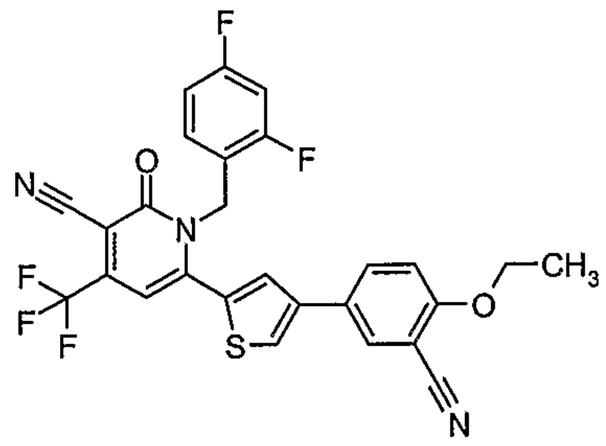
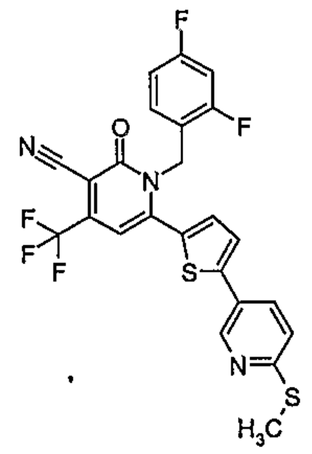
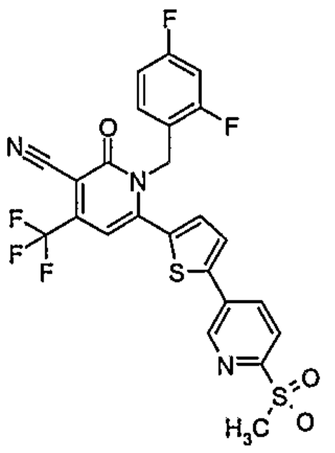
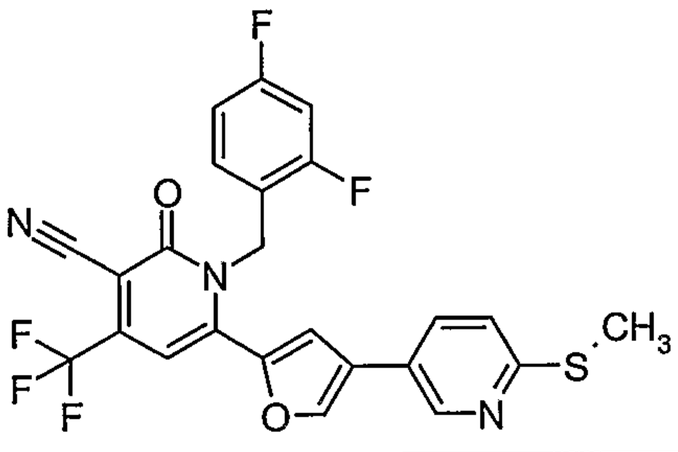
307		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylsulfonyl)-3'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
308		1-[(2,4-difluorophenyl)methyl]-6-[4'-(methylsulfonyl)-3'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
309		1-[(2,4-difluorophenyl)methyl]-6-[3'-(methylsulfonyl)-5'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
310		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-fluoro-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
311		6-[5-(3-chloro-4-methylphenyl)furan-2-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
312		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methyloxy)-4-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

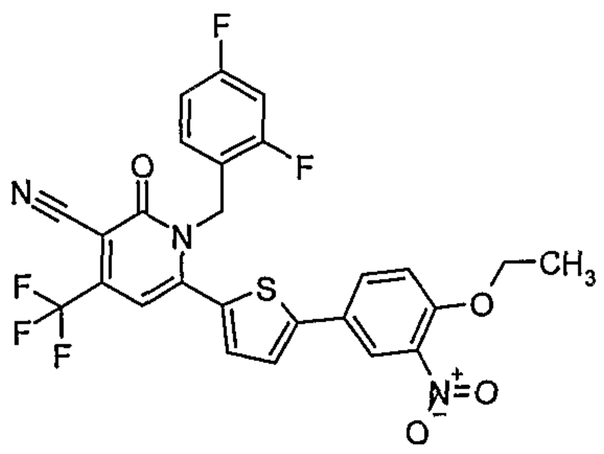
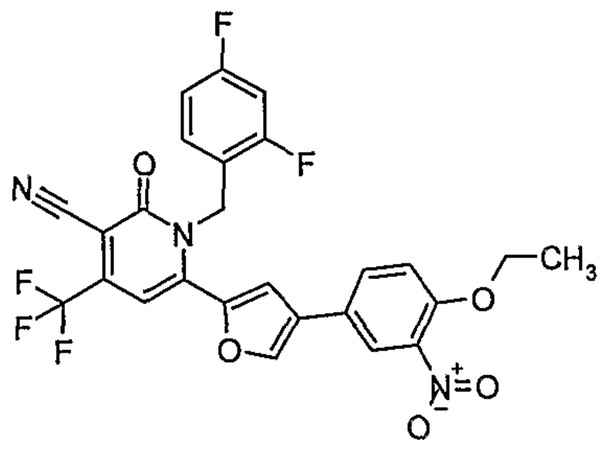
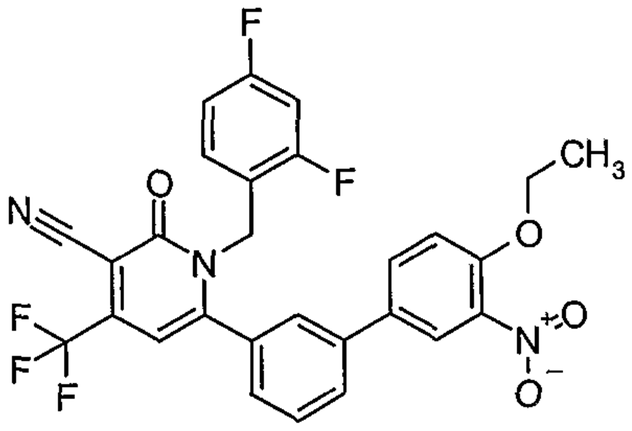
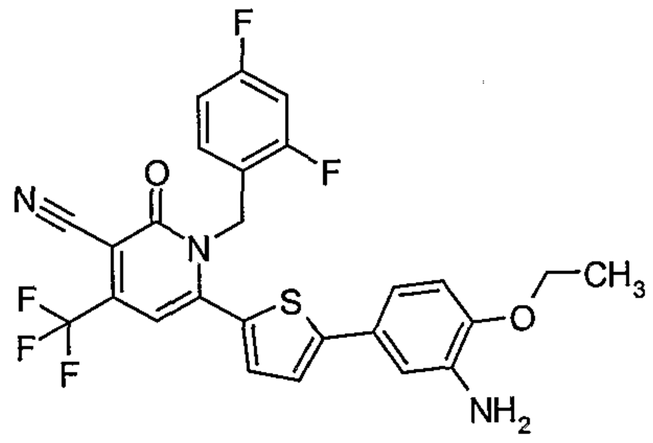
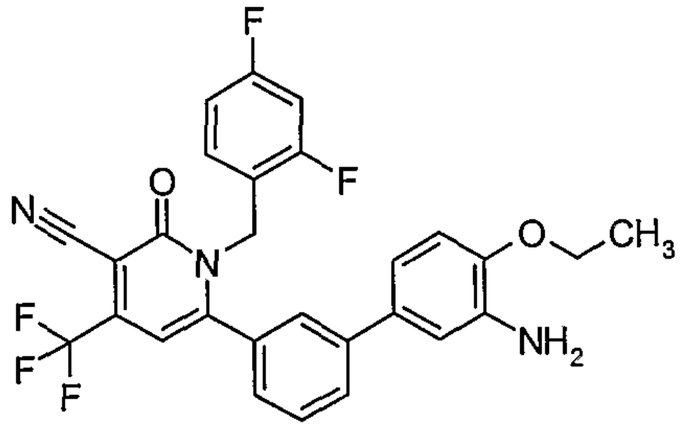
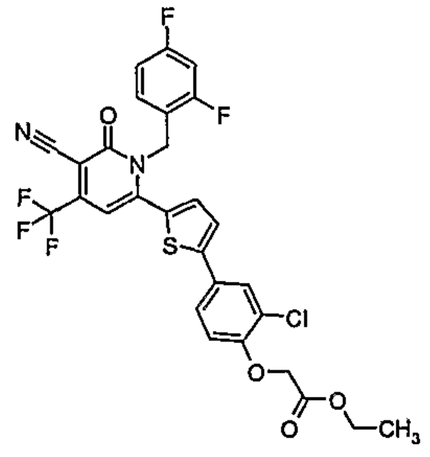
313		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(methyloxy)-4-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
314		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethyloxy)-4-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
315		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(ethyloxy)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
316		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(ethyloxy)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
317		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(ethyloxy)-3-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
318		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethyloxy)-4-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

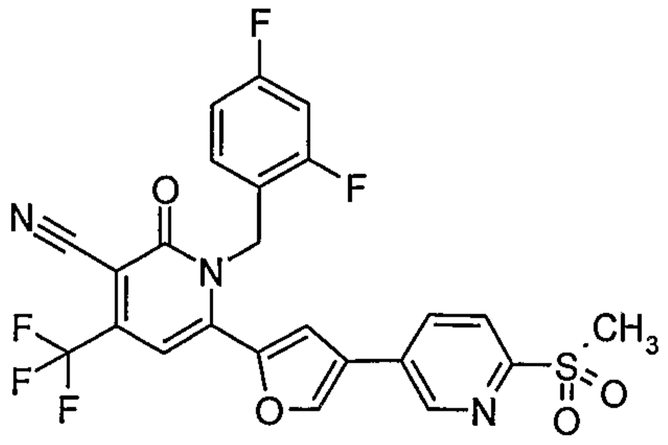
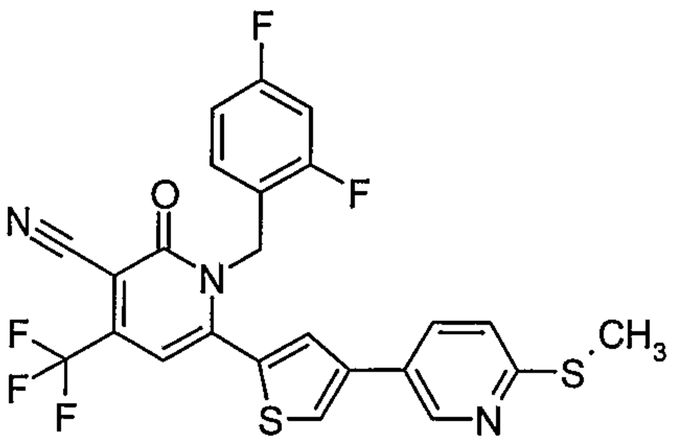
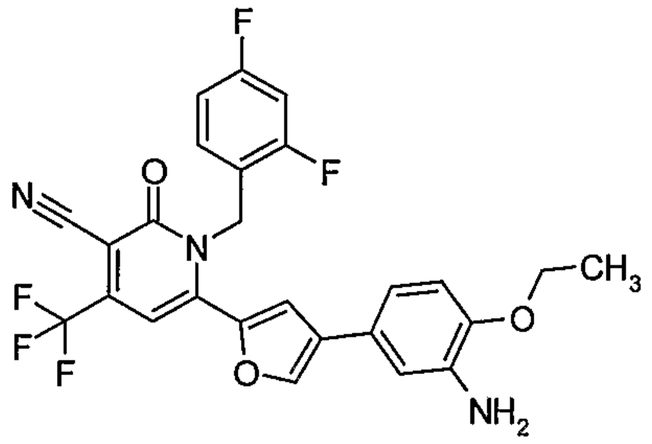
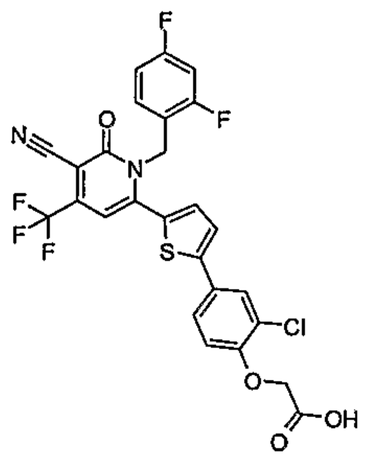
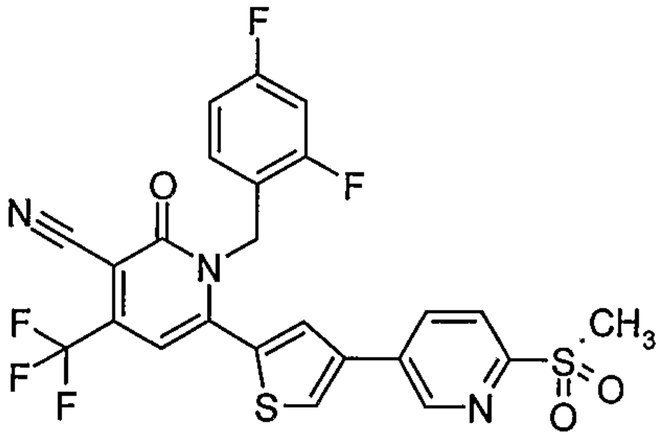
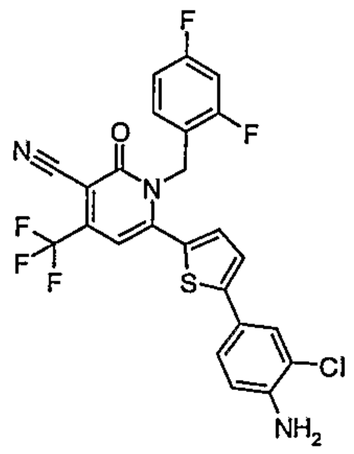
319		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethyloxy)-4-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
320		6-(5-{3-chloro-4-[(2,2,2-trifluoroethyl)oxy]phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
321		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-fluoro-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
322		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-fluoro-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
323		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(methylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
324		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

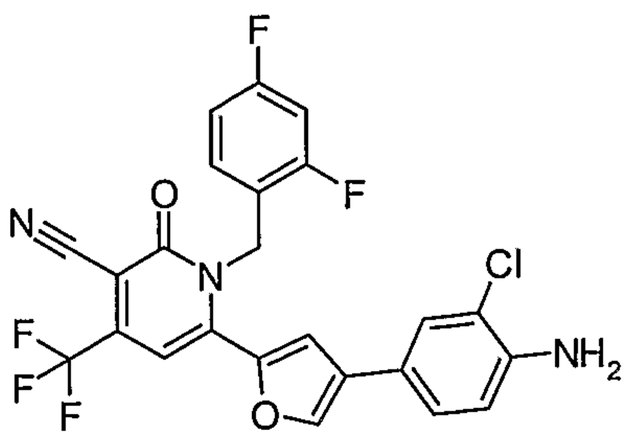
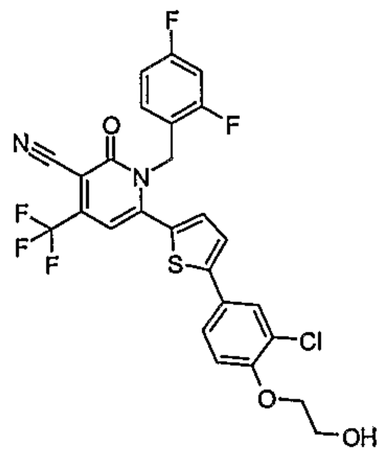
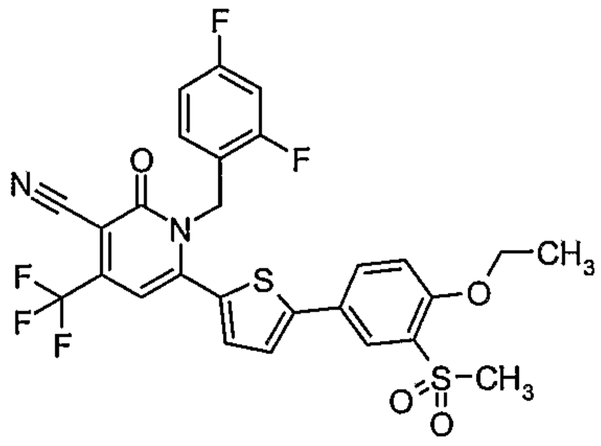
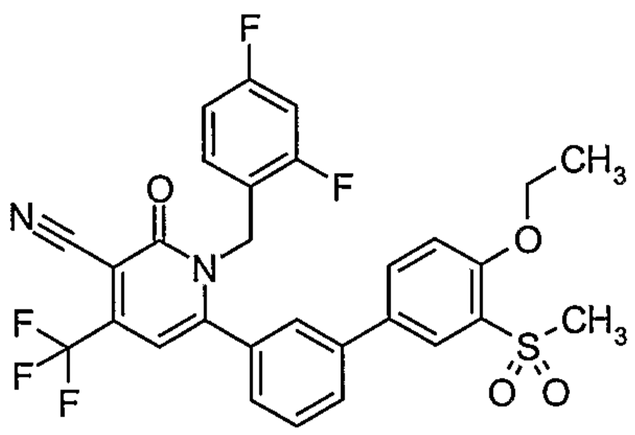
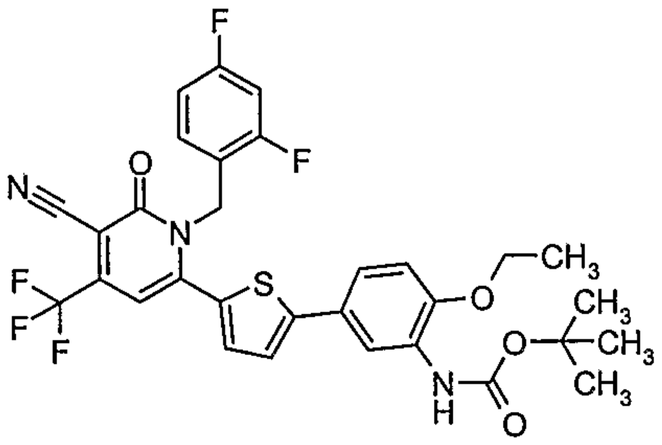
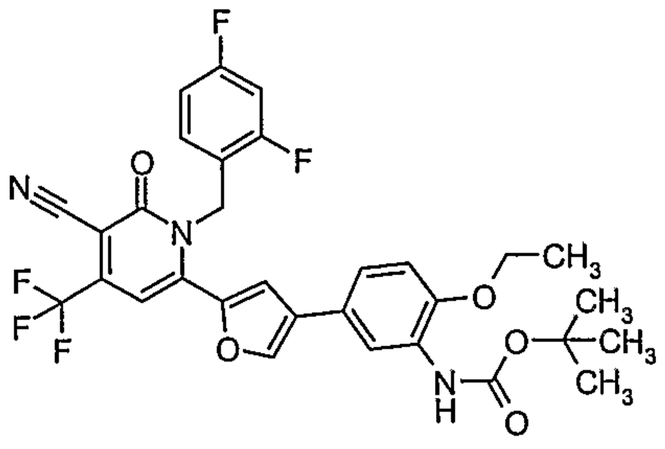
325		1-[(2,4-difluorophenyl)methyl]-6-[3'-(methylsulfonyl)-5'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
326		6-[5-(3-chloro-4-hydroxyphenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
327		1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-6-[3'-(trifluoromethyl)-5'-{[2-(trimethylsilyl)ethyl]sulfonyl}biphenyl-3-yl]-1,2-dihydropyridine-3-carbonitrile
328		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-pyridin-4-ylfuran-2-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
329		1-[(2,4-difluorophenyl)methyl]-6-[3'-(ethylsulfonyl)-5'-(trifluoromethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
330		1-[(2,4-difluorophenyl)methyl]-6-{3'-[(1-methylethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-3-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

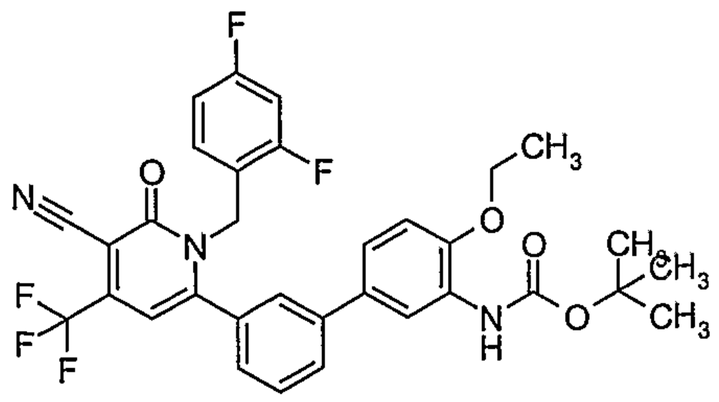
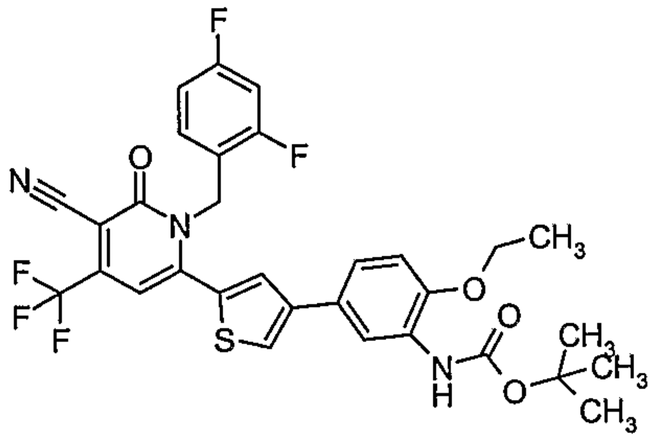
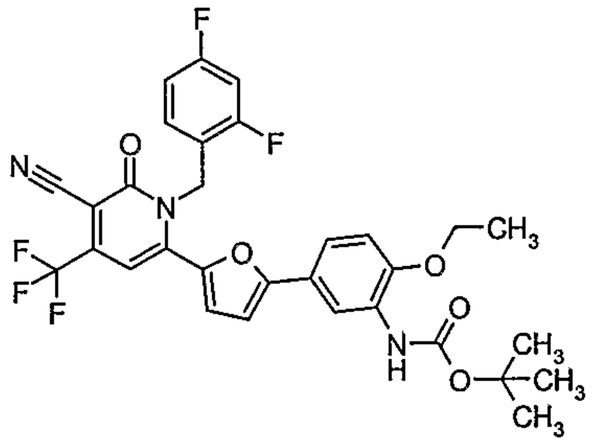
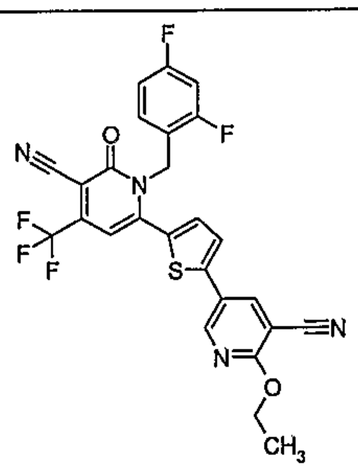
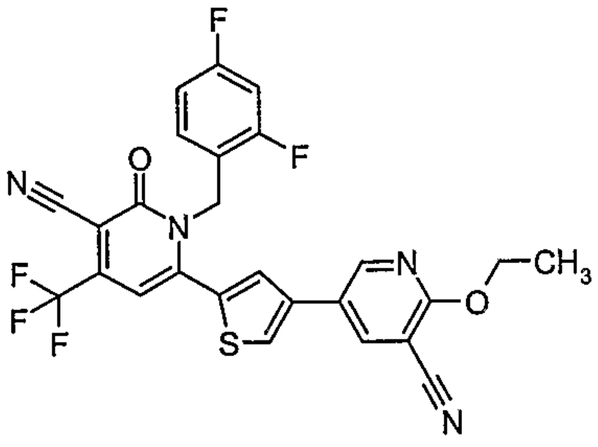
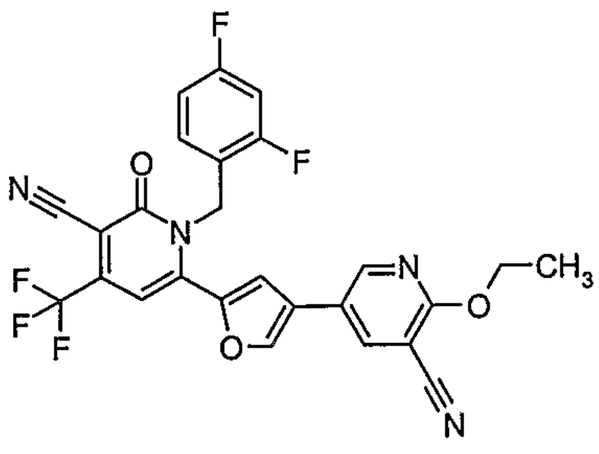
331		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
332		1-[(2,4-difluorophenyl)methyl]-6-(5-{3-[(1-methylethyl)sulfonyl]-5-(trifluoromethyl)phenyl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
333		6-[5-(3-chloro-4-cyanophenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
334		6-[4-(3-chloro-4-cyanophenyl)furan-2-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
335		6-{5-[3-cyano-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
336		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(trifluoromethyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

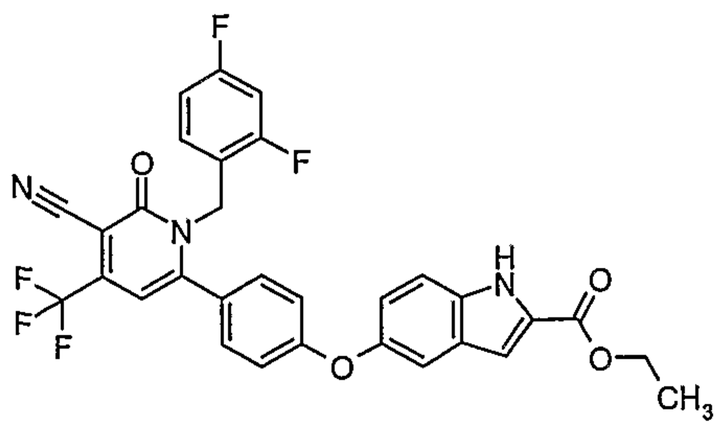
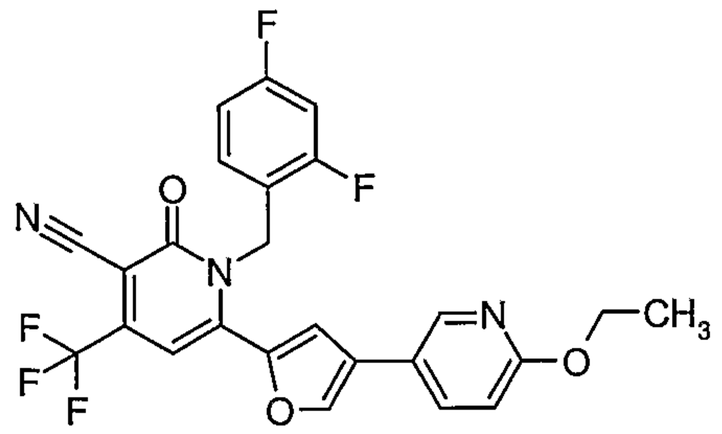
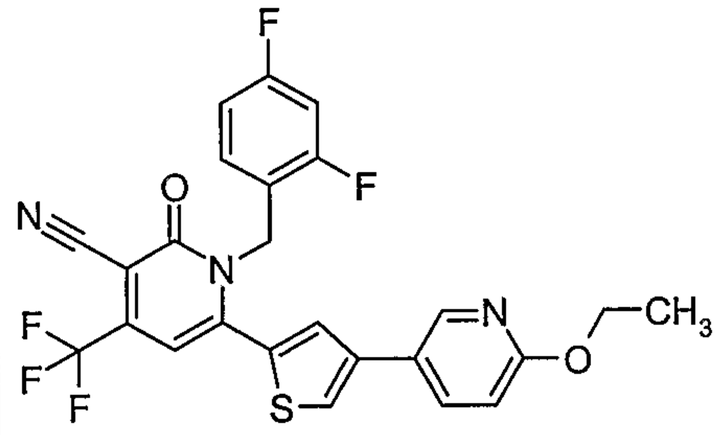
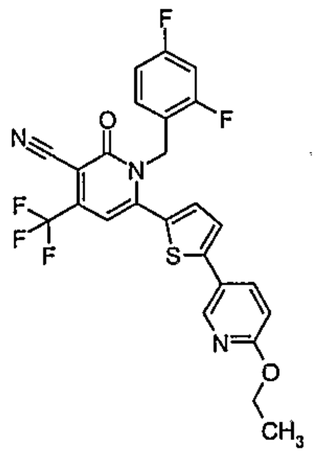
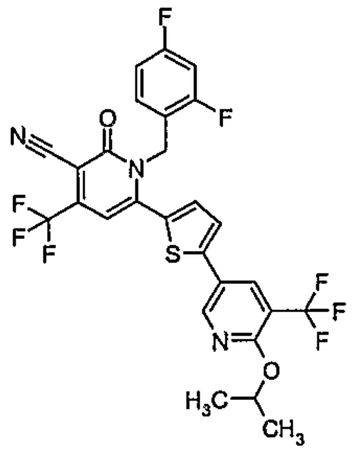
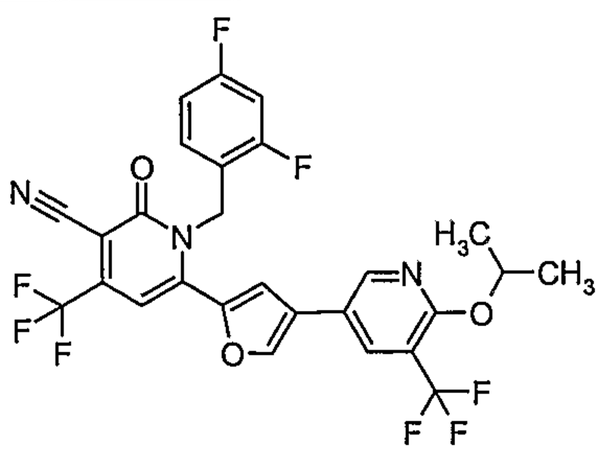
337		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(trifluoromethyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
338		6-{4-[3-cyano-4-(ethyloxy)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
339		6-{4-[3-cyano-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
340		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(methylthio)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
341		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
342		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(methylthio)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

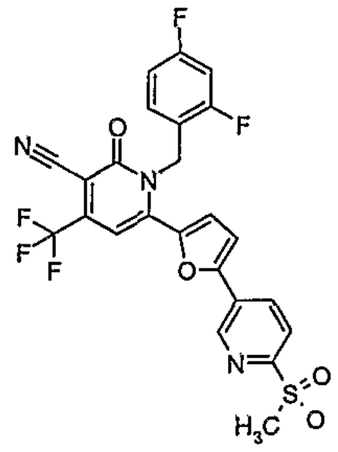
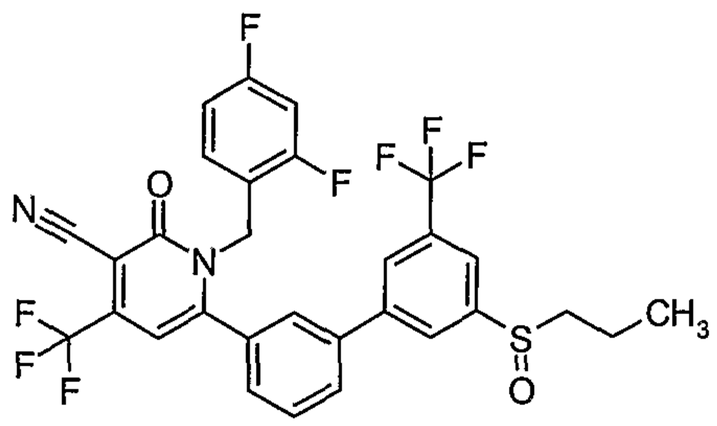
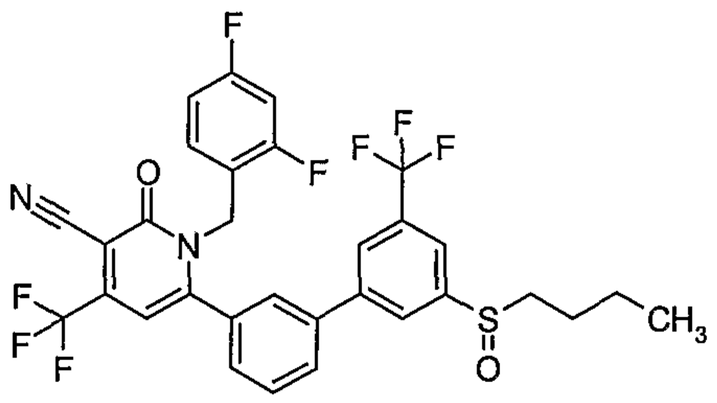
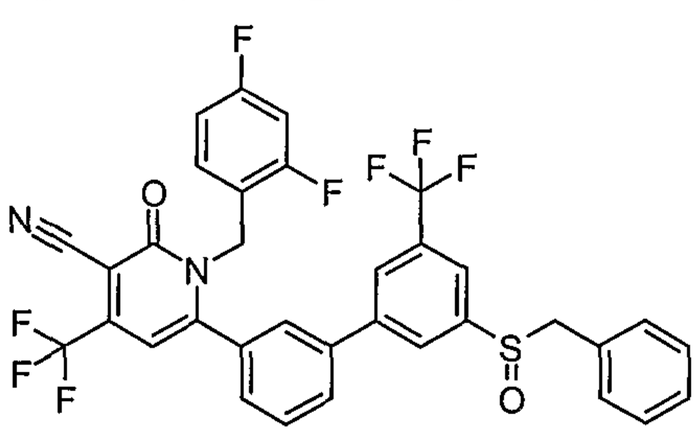
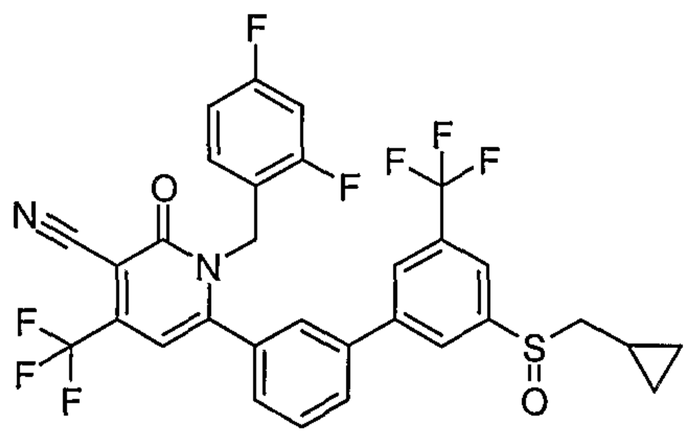
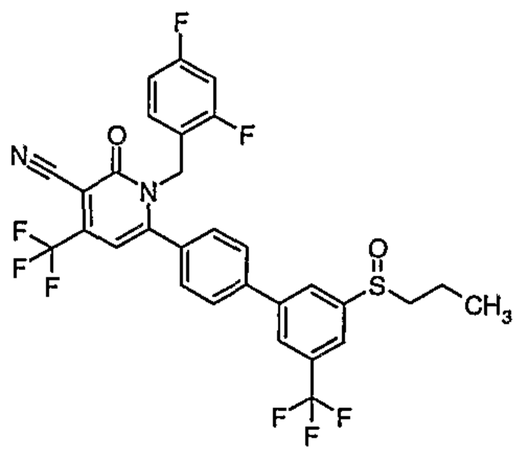
343		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(ethyloxy)-3-nitrophenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
344		1-[(2,4-difluorophenyl)methyl]-6-{4-[4-(ethyloxy)-3-nitrophenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
345		1-[(2,4-difluorophenyl)methyl]-6-[4'-(ethyloxy)-3'-nitrobiphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
346		6-{5-[3-amino-4-(ethyloxy)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
347		6-[3'-amino-4'-(ethyloxy)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
348		ethyl {[2-chloro-4-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)phenyl]oxy}acetate

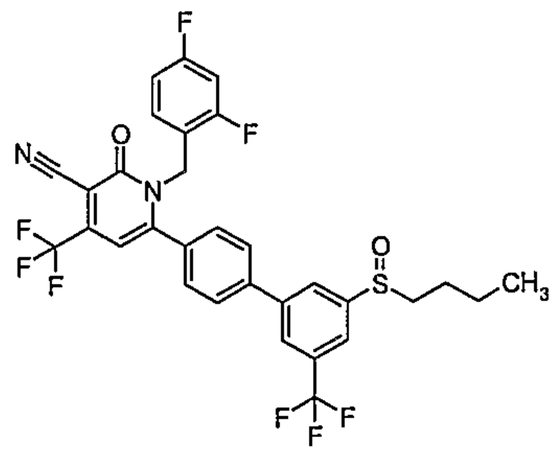
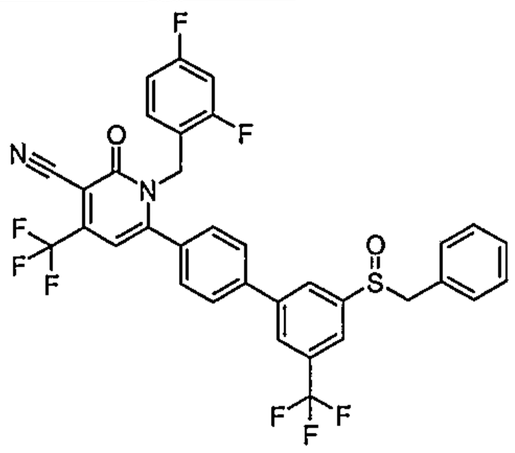
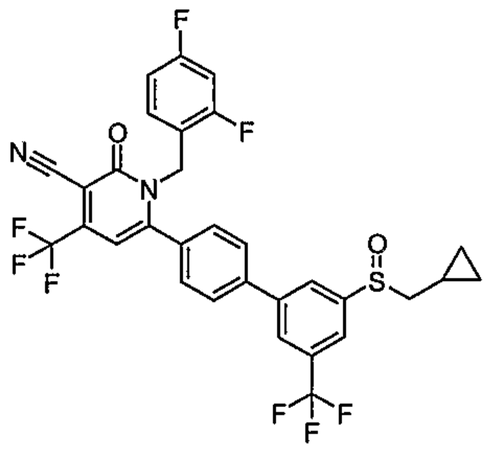
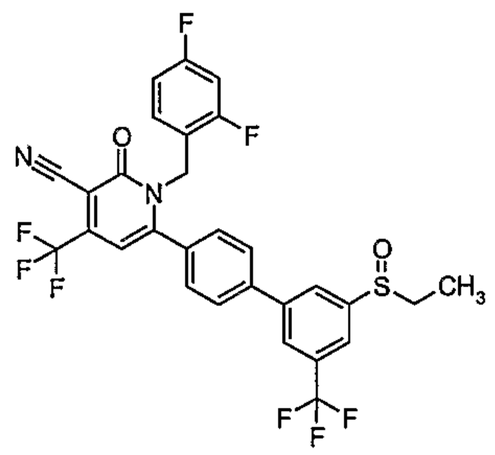
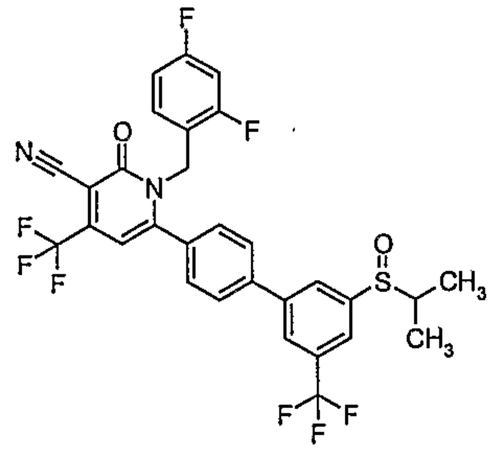
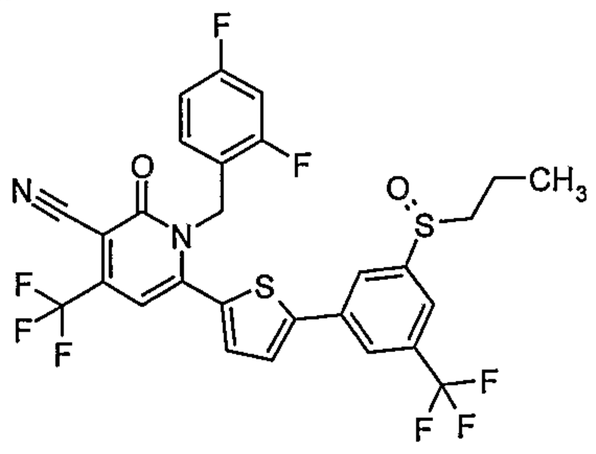
349		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
350		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(methylthio)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
351		6-{4-[3-amino-4-(ethyloxy)phenyl]furan-2-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
352		{[2-chloro-4-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)phenyl]oxy}acetic acid
353		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
354		6-[5-(4-amino-3-chlorophenyl)-2-thienyl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

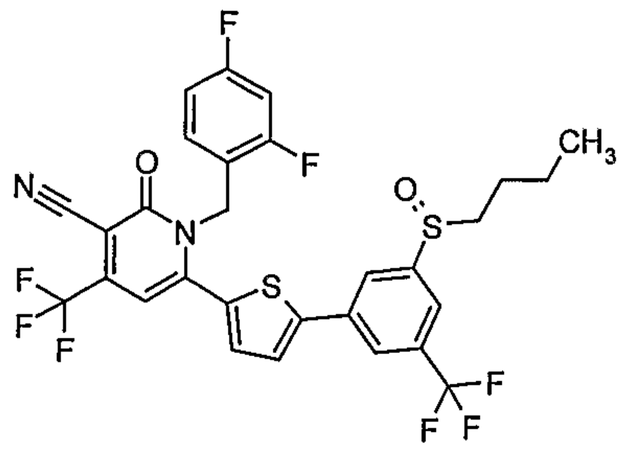
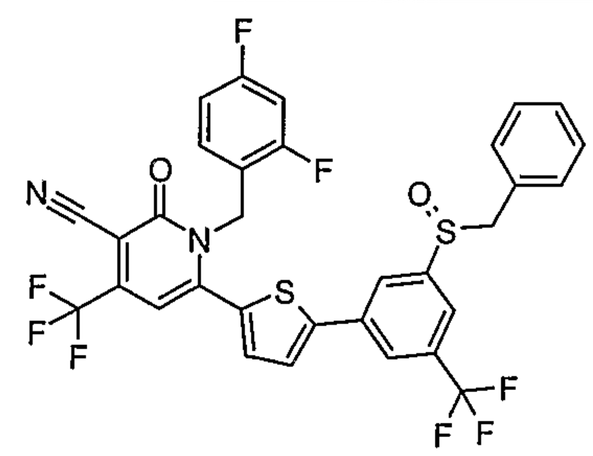
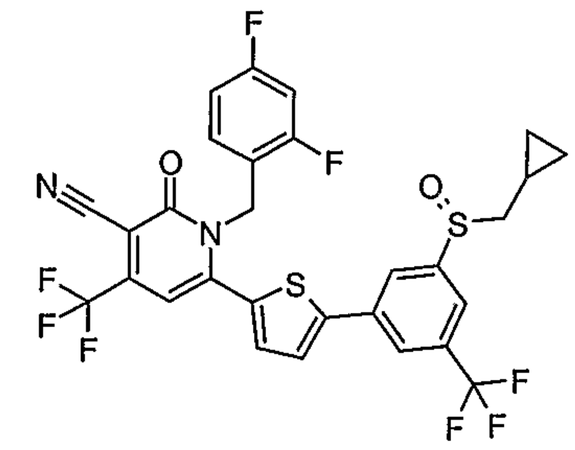
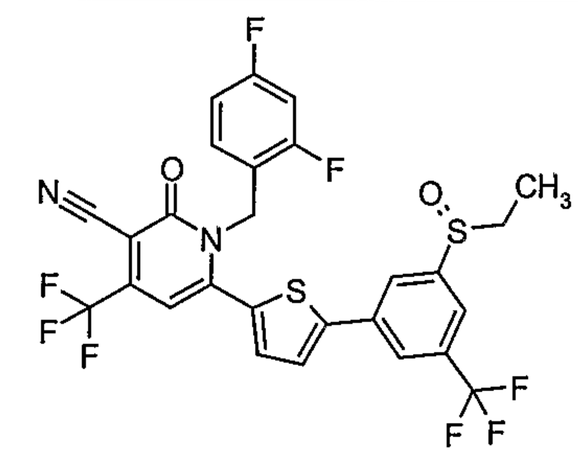
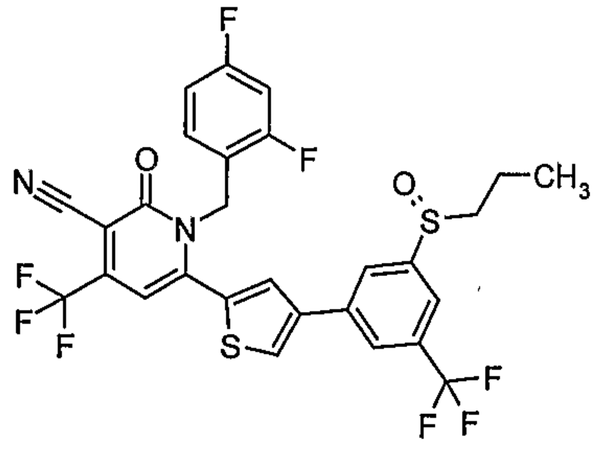
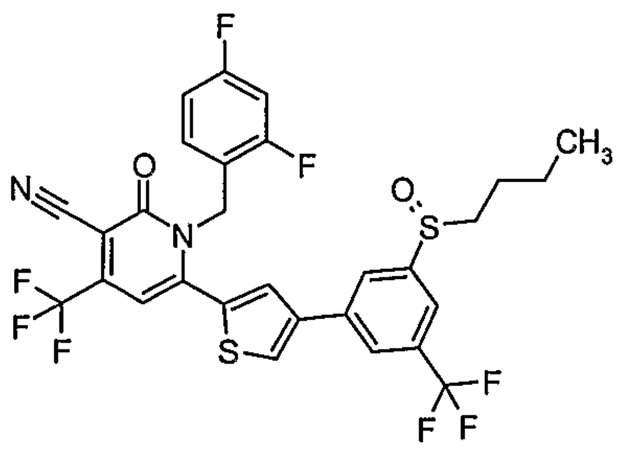
355		6-[4-(4-amino-3-chlorophenyl)furan-2-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
356		6-(5-{3-chloro-4-[(2-hydroxyethyl)oxy]phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
357		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(ethyloxy)-3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
358		1-[(2,4-difluorophenyl)methyl]-6-[4'-(ethyloxy)-3'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
359		1,1-dimethylethyl [5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(ethyloxy)phenyl]carbamate
360		1,1-dimethylethyl [5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-2-(ethyloxy)phenyl]carbamate

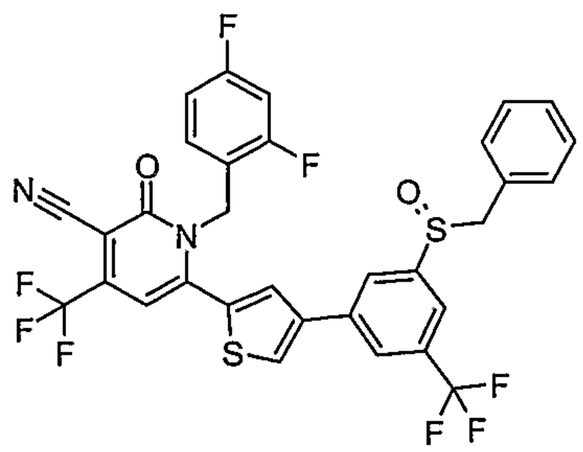
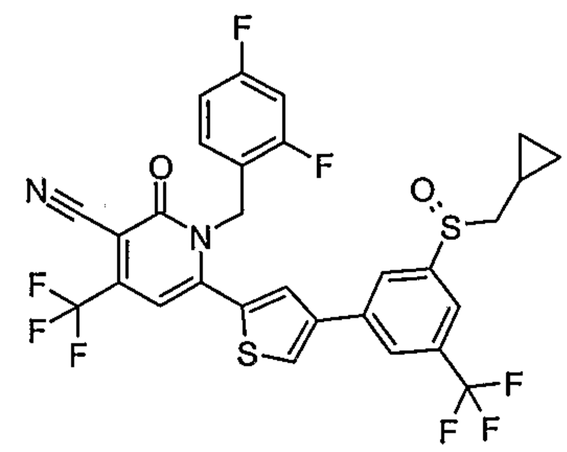
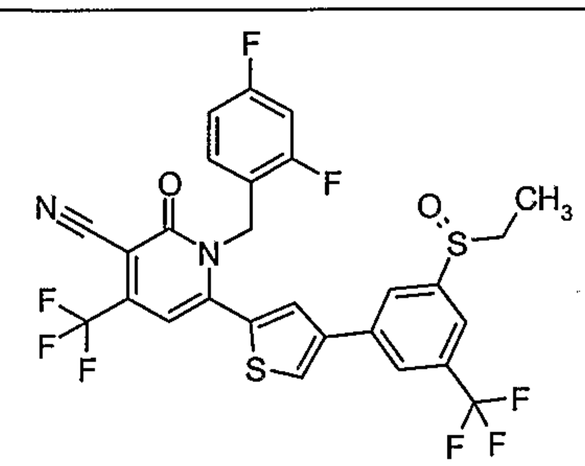
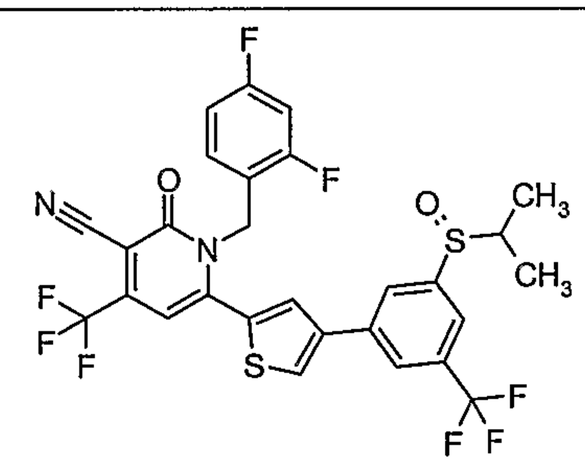
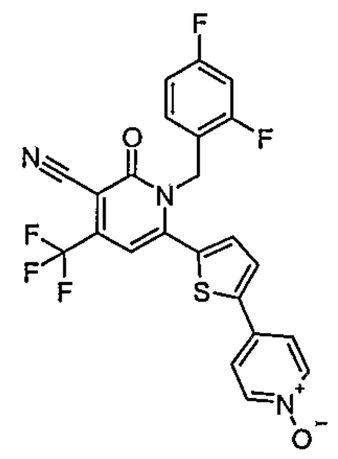
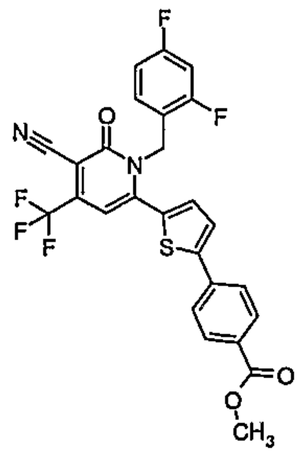
361		1,1-dimethylethyl [3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-4-(ethyloxy)biphenyl-3-yl]carbamate
362		1,1-dimethylethyl [5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-2-(ethyloxy)phenyl]carbamate
363		1,1-dimethylethyl [5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-2-yl)-2-(ethyloxy)phenyl]carbamate
364		5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(ethyloxy)pyridine-3-carbonitrile
365		5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-2-(ethyloxy)pyridine-3-carbonitrile
366		5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-2-(ethyloxy)pyridine-3-carbonitrile

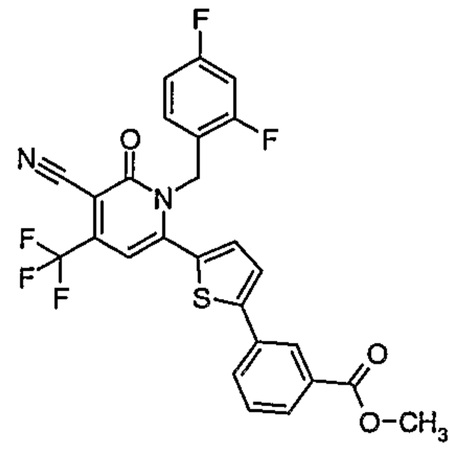
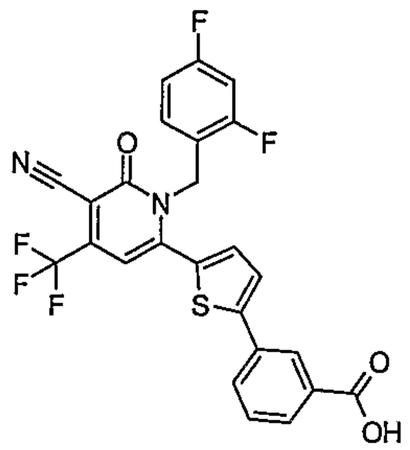
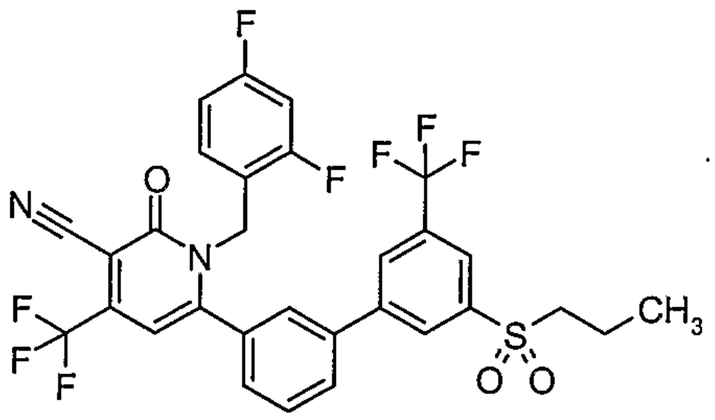
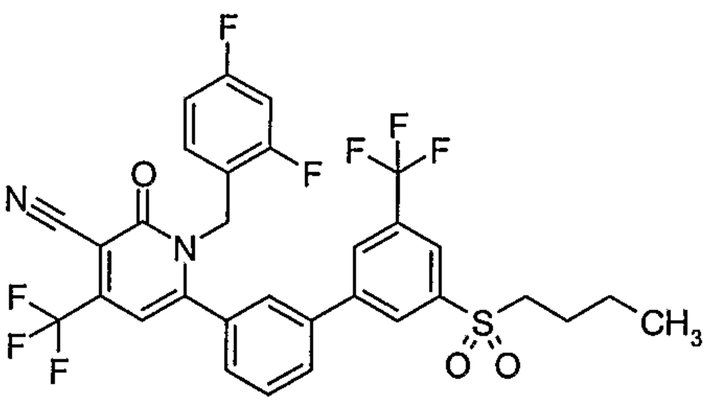
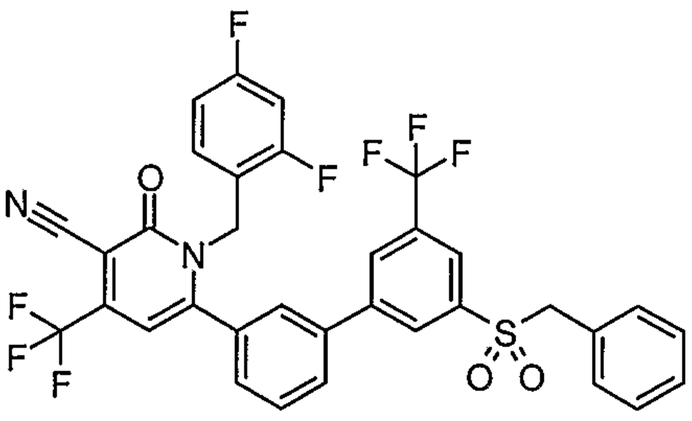
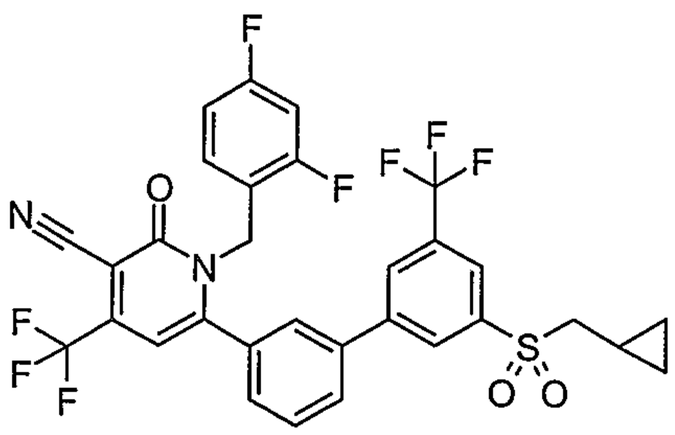
367		ethyl 5-[(4-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
368		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
369		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
370		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethyloxy)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
371		1-[(2,4-difluorophenyl)methyl]-6-(5-{6-[(1-methylethyl)oxy]-5-(trifluoromethyl)pyridin-3-yl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
372		1-[(2,4-difluorophenyl)methyl]-6-(4-{6-[(1-methylethyl)oxy]-5-(trifluoromethyl)pyridin-3-yl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

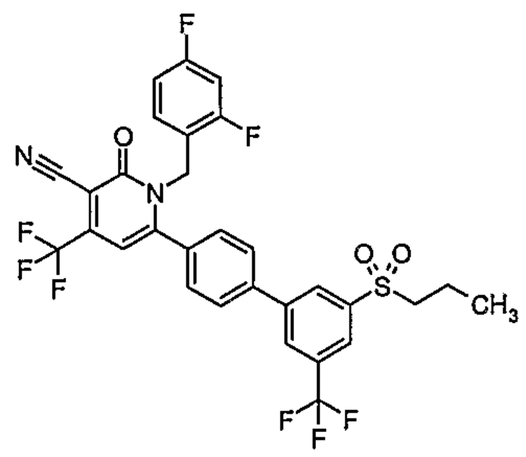
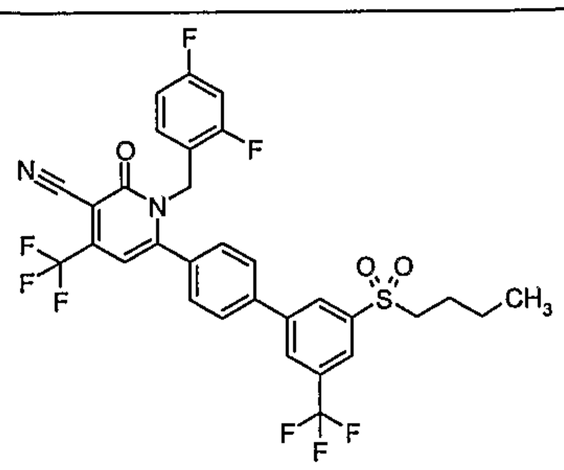
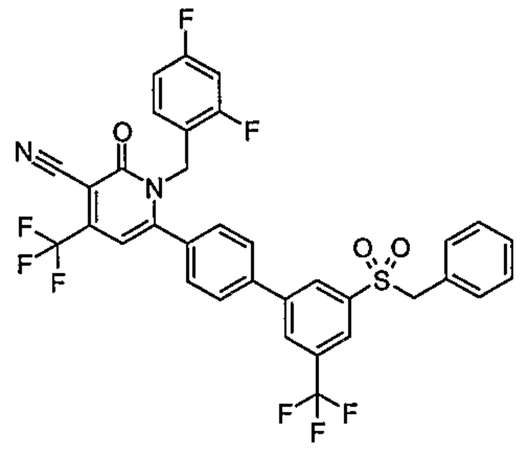
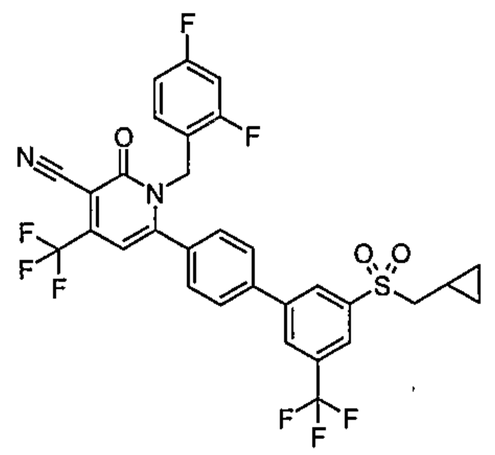
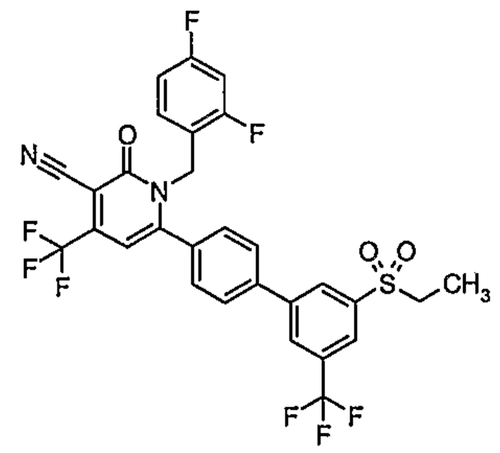
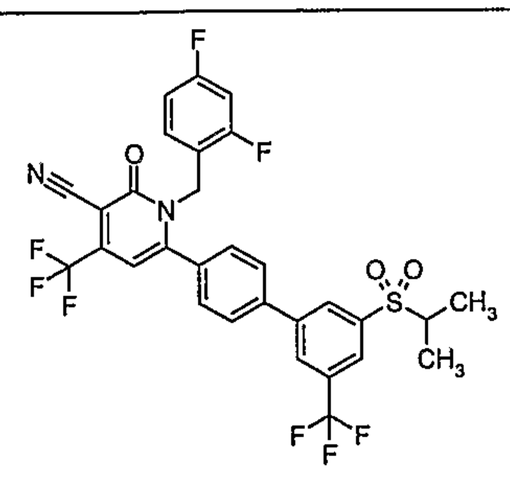
373		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
374		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3'-(propylsulfinyl)-5'-(trifluoromethyl)biphenyl-3-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
375		6-[3'-(butylsulfinyl)-5'-(trifluoromethyl)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
376		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{3'-[(phenylmethyl)sulfinyl]-5'-(trifluoromethyl)biphenyl-3-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
377		6-{3'-[(cyclopropylmethyl)sulfinyl]-5'-(trifluoromethyl)biphenyl-3-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
378		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3'-(propylsulfinyl)-5'-(trifluoromethyl)biphenyl-4-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

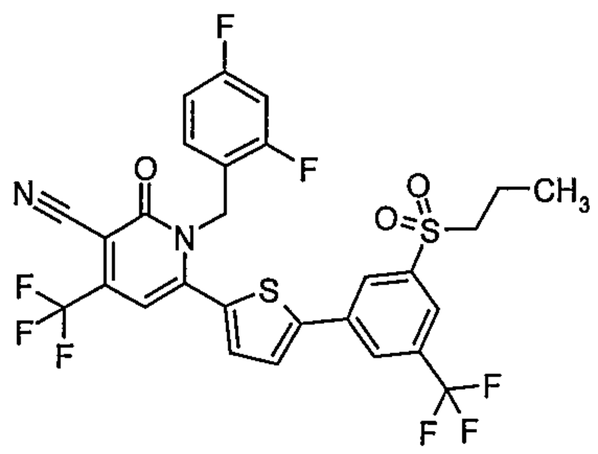
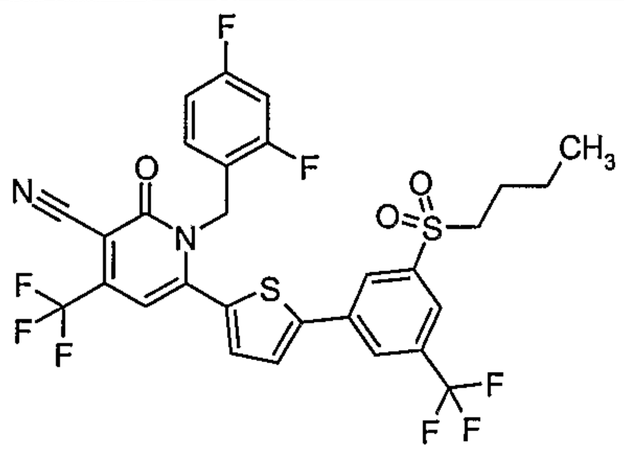
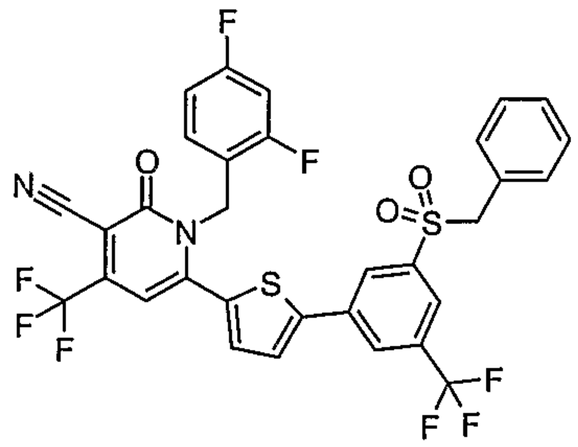
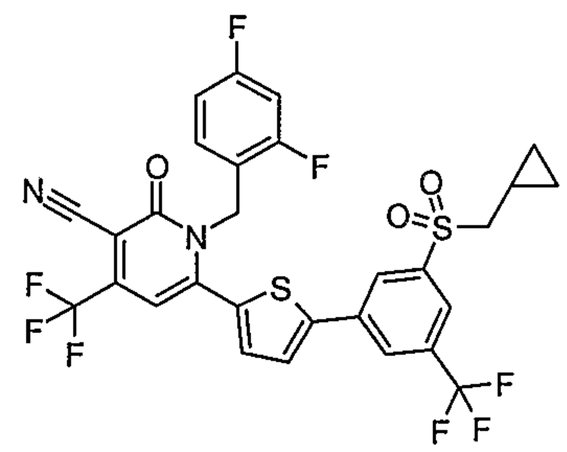
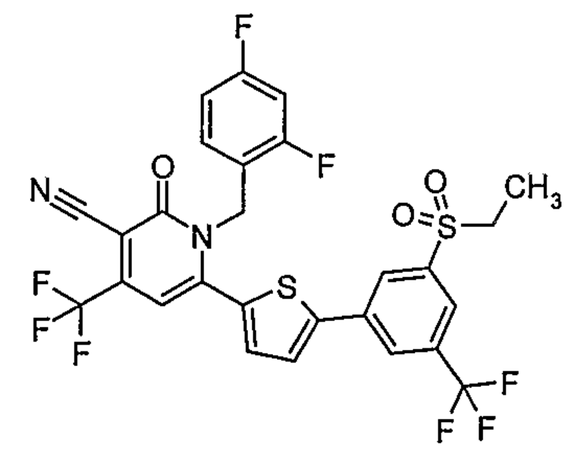
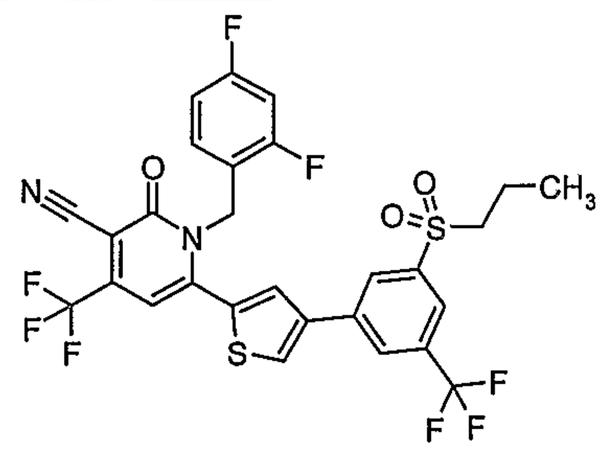
379		6-[3'-(butylsulfinyl)-5'-(trifluoromethyl)biphenyl-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
380		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{3'-[(phenylmethyl)sulfinyl]-5'-(trifluoromethyl)biphenyl-4-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
381		6-{3'-[(cyclopropylmethyl)sulfinyl]-5'-(trifluoromethyl)biphenyl-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
382		1-[(2,4-difluorophenyl)methyl]-6-[3'-(ethylsulfinyl)-5'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
383		1-[(2,4-difluorophenyl)methyl]-6-{3'-[(1-methylethyl)sulfinyl]-5'-(trifluoromethyl)biphenyl-4-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
384		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{5-[3-(propylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

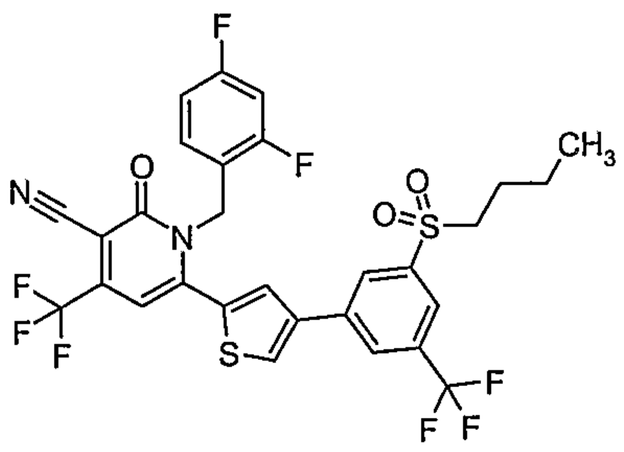
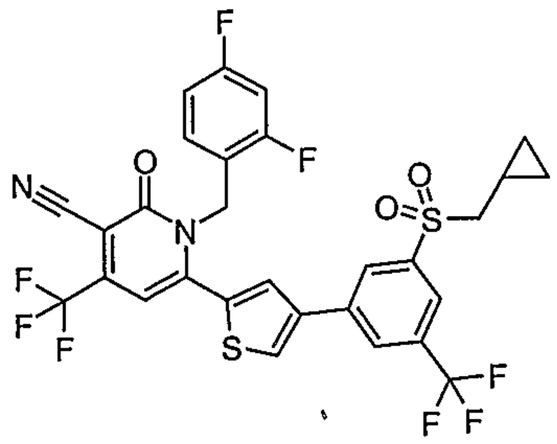
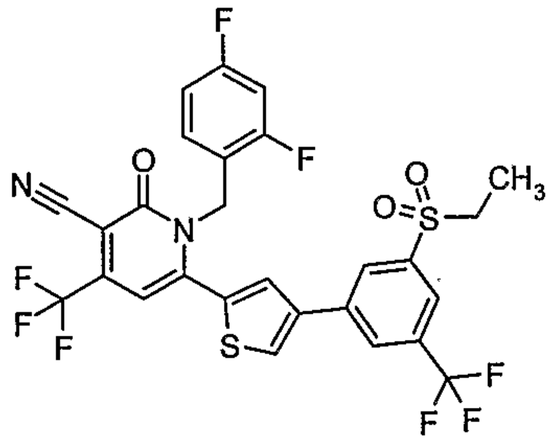
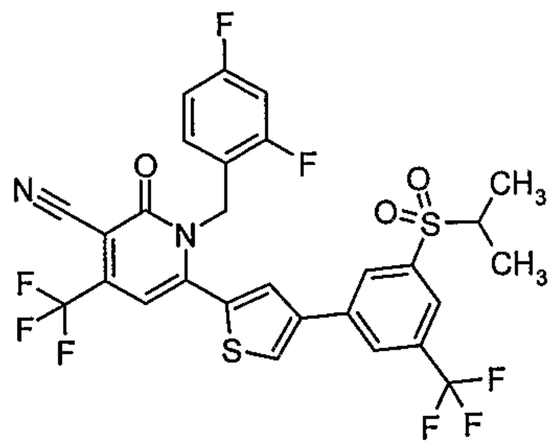
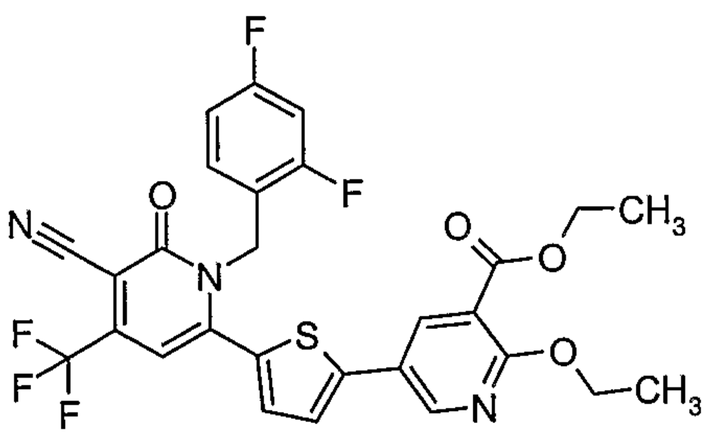
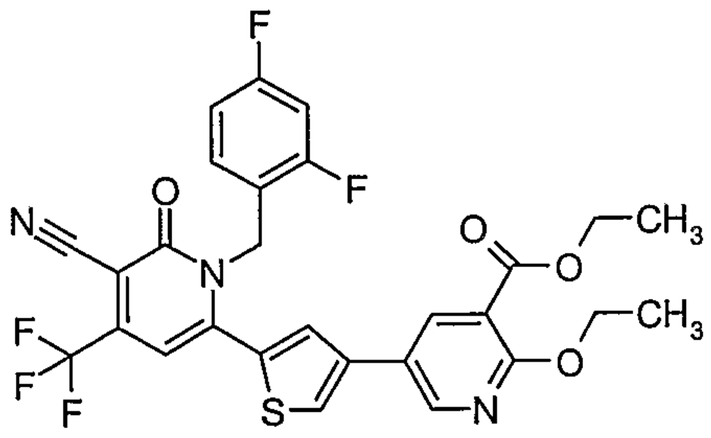
385		6-{5-[3-(butylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
386		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-{3-[(phenylmethyl)sulfinyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
387		6-(5-{3-[(cyclopropylmethyl)sulfinyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
388		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
389		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[3-(propylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
390		6-{4-[3-(butylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

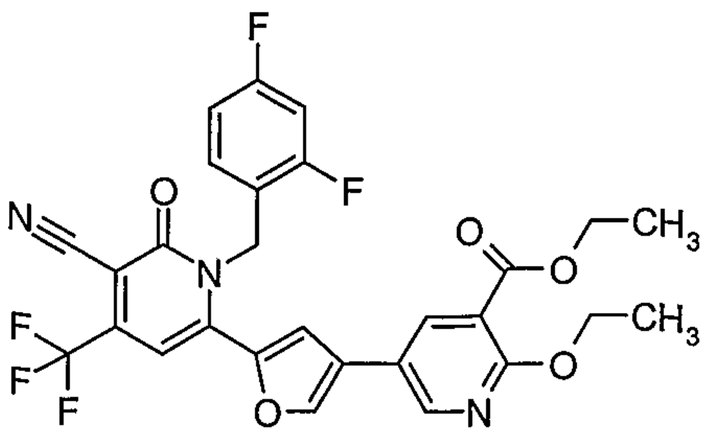
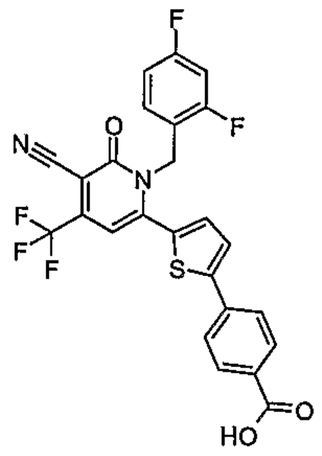
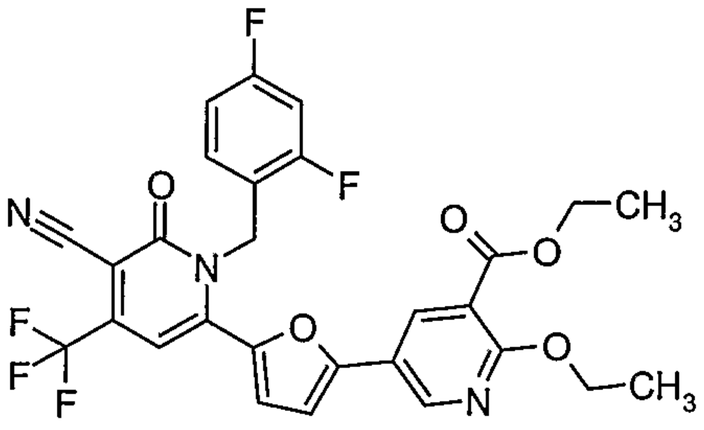
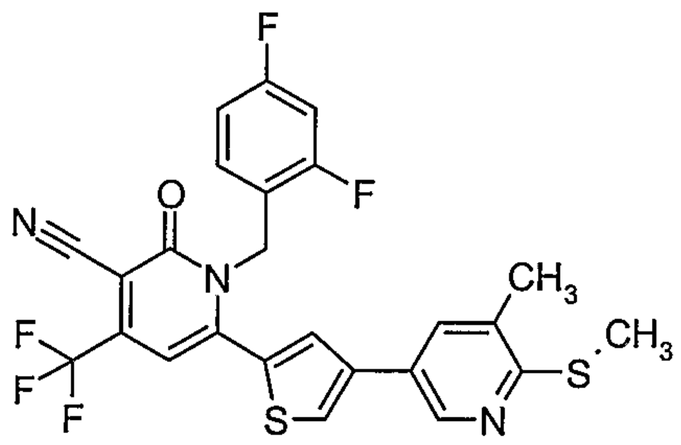
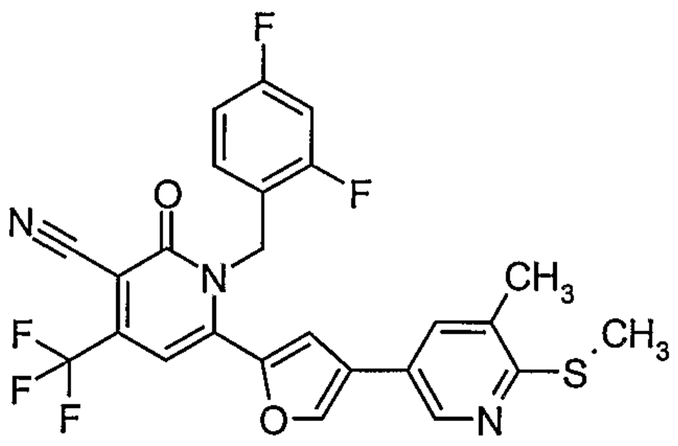
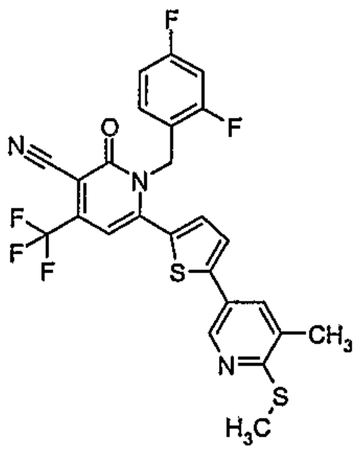
391		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(4-{3-[(phenylmethyl)sulfinyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
392		6-(4-{3-[(cyclopropylmethyl)sulfinyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
393		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethylsulfinyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
394		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-[(1-methylethyl)sulfinyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
395		1-[(2,4-difluorophenyl)methyl]-6-[5-(1-oxidopyridin-4-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
396		methyl 4-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)benzoate

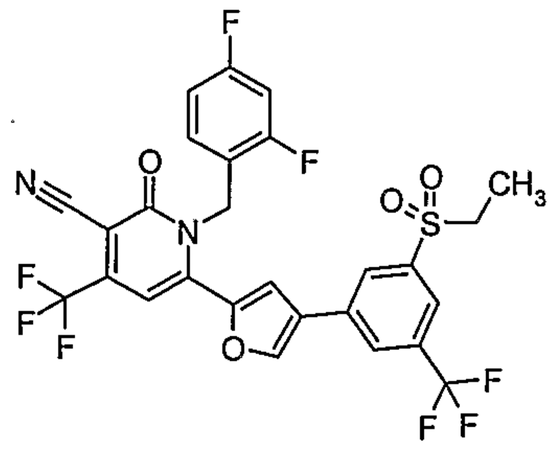
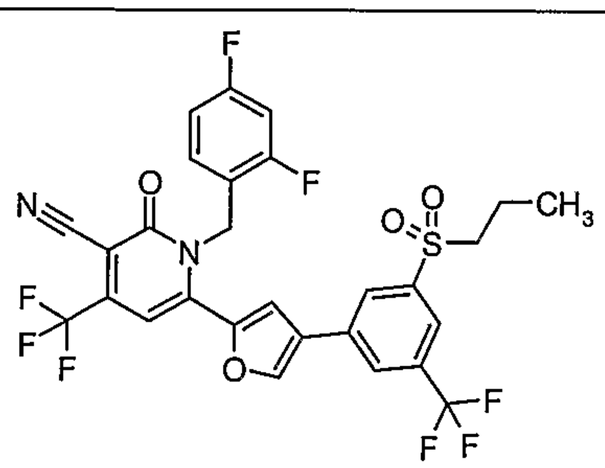
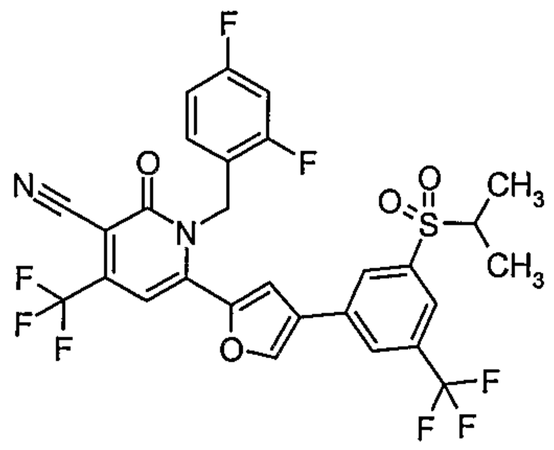
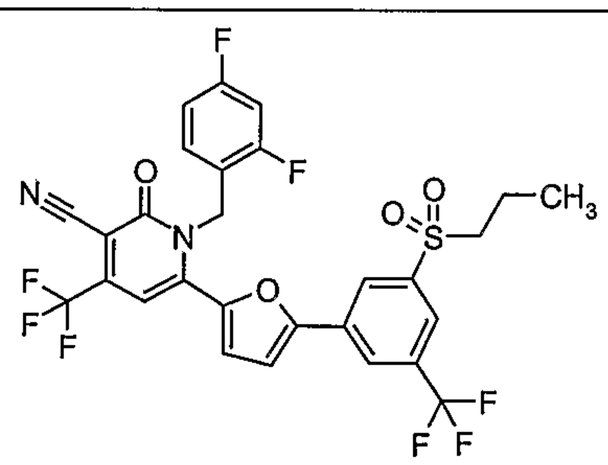
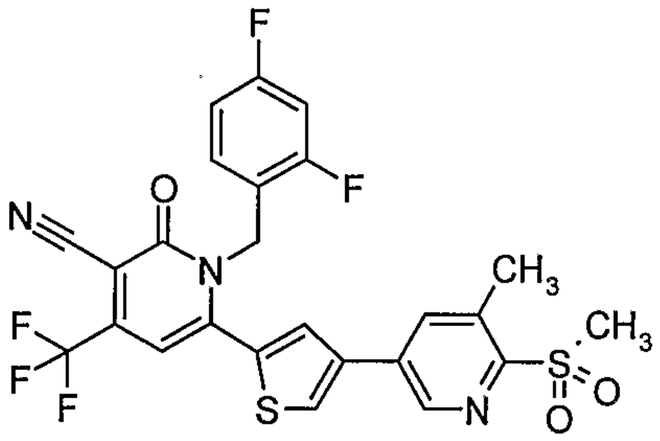
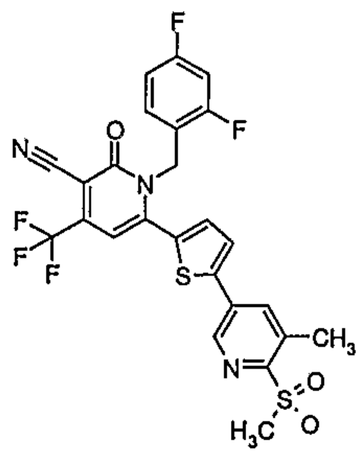
397		methyl 3-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)benzoate
398		3-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)benzoic acid
399		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3'-(propylsulfonyl)-5'-(trifluoromethyl)biphenyl-3-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
400		6-[3'-(butylsulfonyl)-5'-(trifluoromethyl)biphenyl-3-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
401		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{3'-[(phenylmethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-3-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
402		6-{3'-[(cyclopropylmethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-3-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

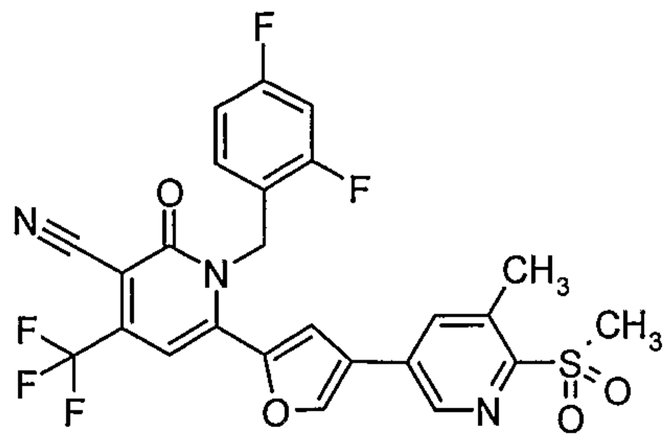
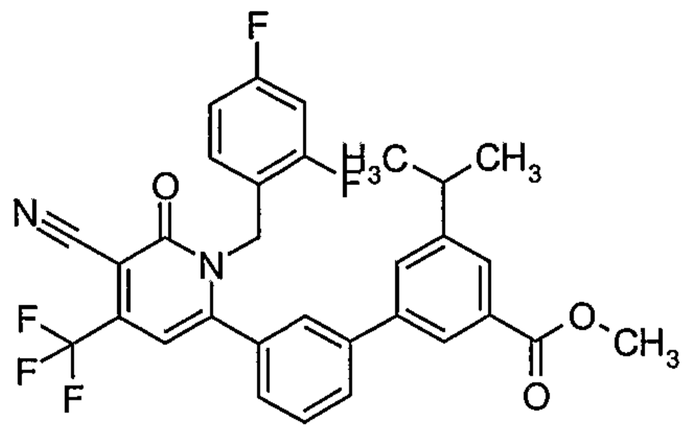
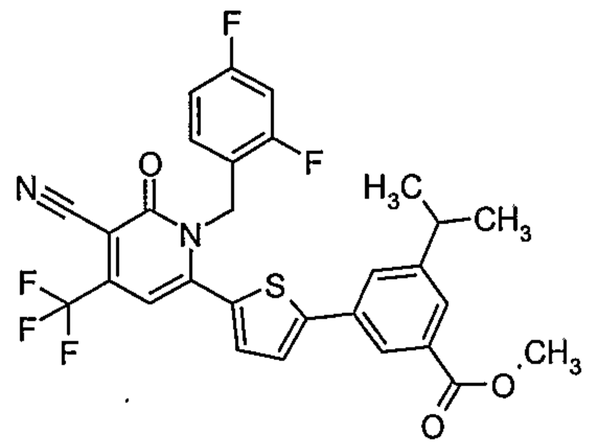
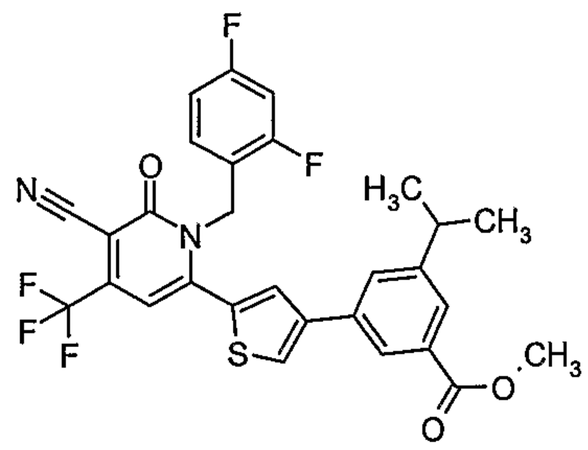
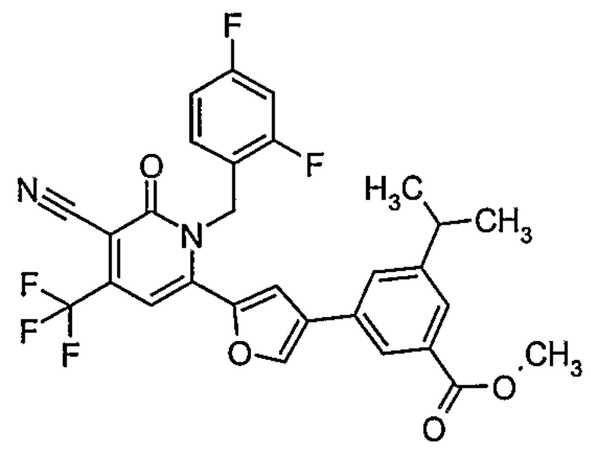
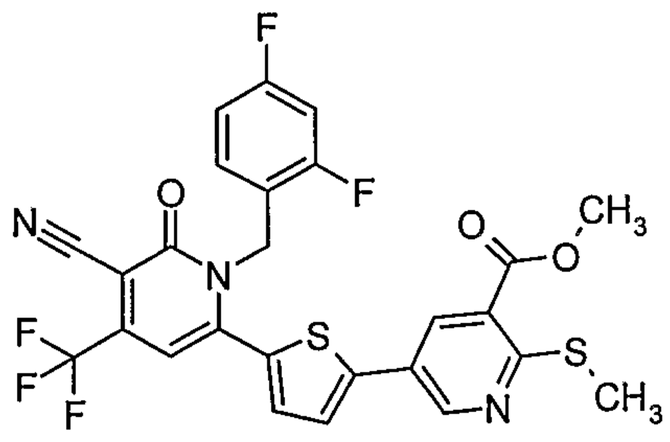
403		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-[3'-(propylsulfonyl)-5'-(trifluoromethyl)biphenyl-4-yl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
404		6-[3'-(butylsulfonyl)-5'-(trifluoromethyl)biphenyl-4-yl]-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
405		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{3'-[(phenylmethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-4-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
406		6-{3'-[(cyclopropylmethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-4-yl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
407		1-[(2,4-difluorophenyl)methyl]-6-[3'-(ethylsulfonyl)-5'-(trifluoromethyl)biphenyl-4-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
408		1-[(2,4-difluorophenyl)methyl]-6-{3'-[(1-methylethyl)sulfonyl]-5'-(trifluoromethyl)biphenyl-4-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

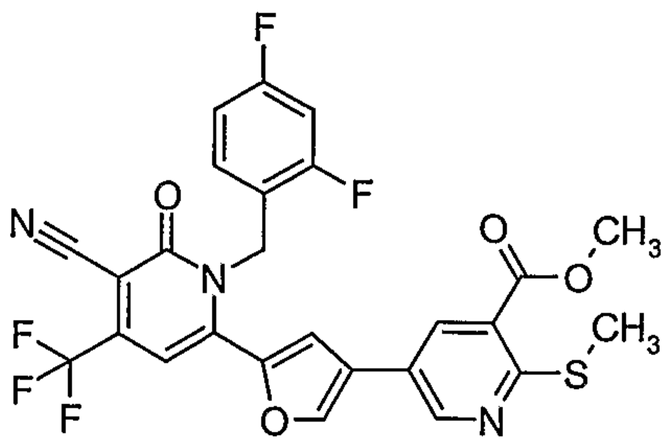
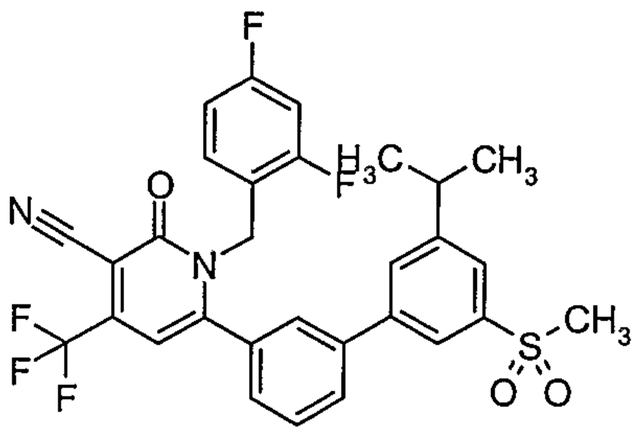
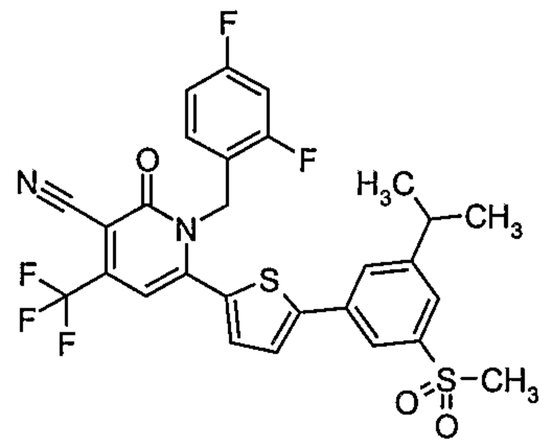
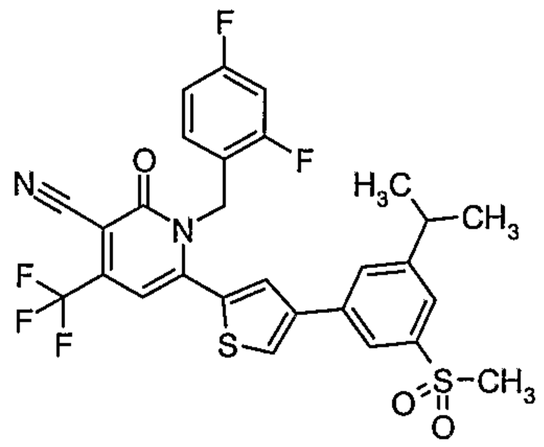
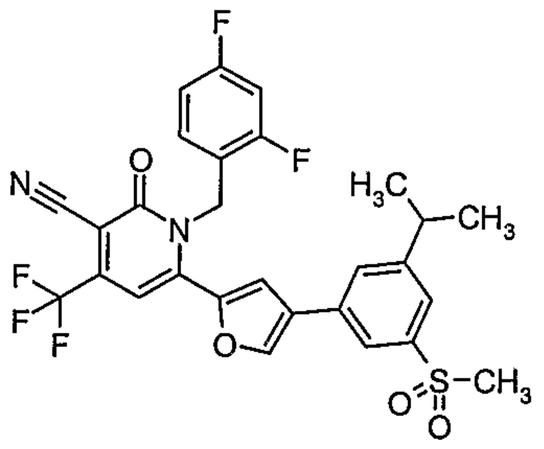
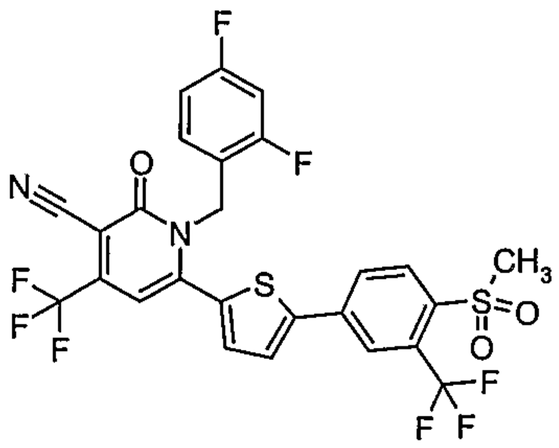
409		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{5-[3-(propylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
410		6-{5-[3-(butylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
411		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-(5-{3-[(phenylmethyl)sulfonyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
412		6-(5-{3-[(cyclopropylmethyl)sulfonyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
413		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
414		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[3-(propylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

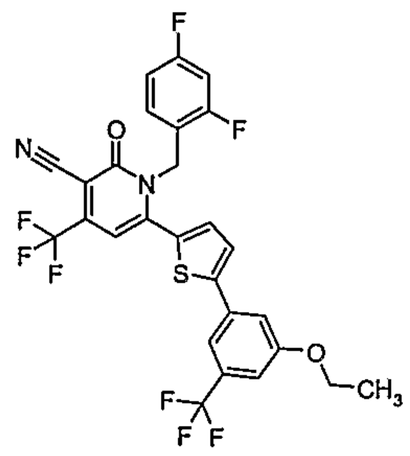
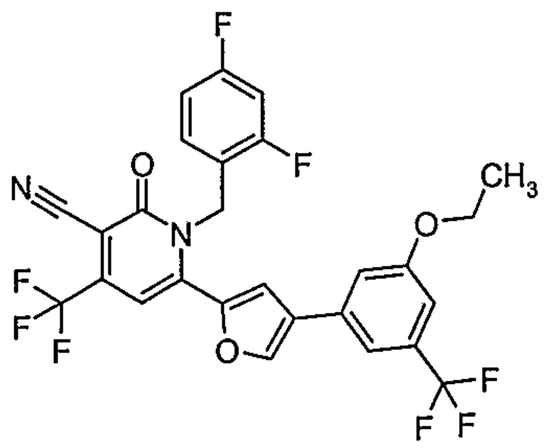
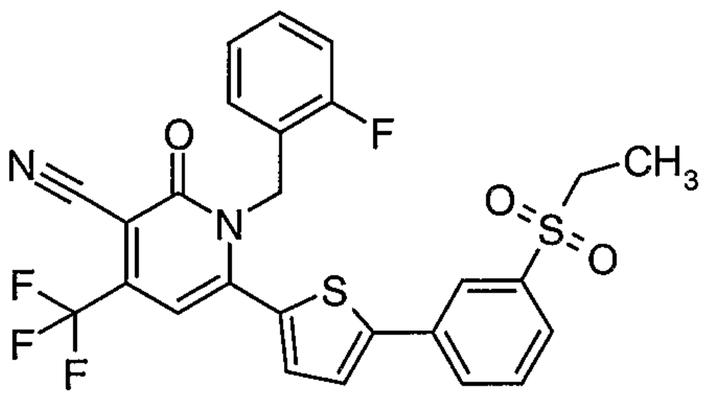
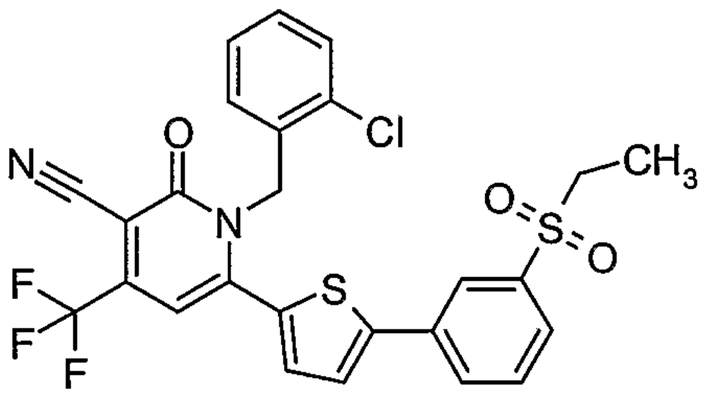
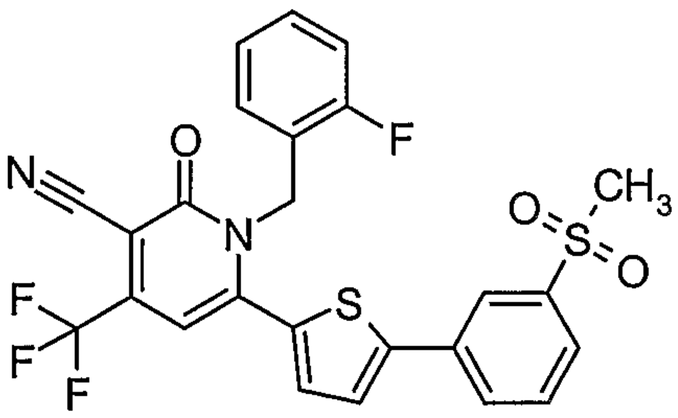
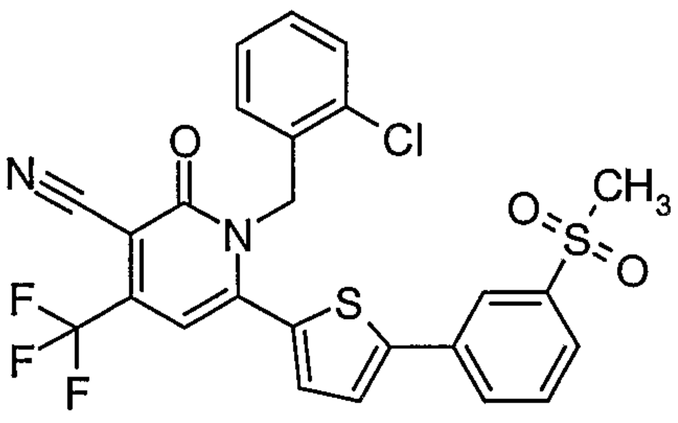
415		6-{4-[3-(butylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
416		6-(4-{3-[(cyclopropylmethyl)sulfonyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-1-[(2,4-difluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
417		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
418		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-[(1-methylethyl)sulfonyl]-5-(trifluoromethyl)phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
419		ethyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(ethyloxy)pyridine-3-carboxylate
420		ethyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-2-(ethyloxy)pyridine-3-carboxylate

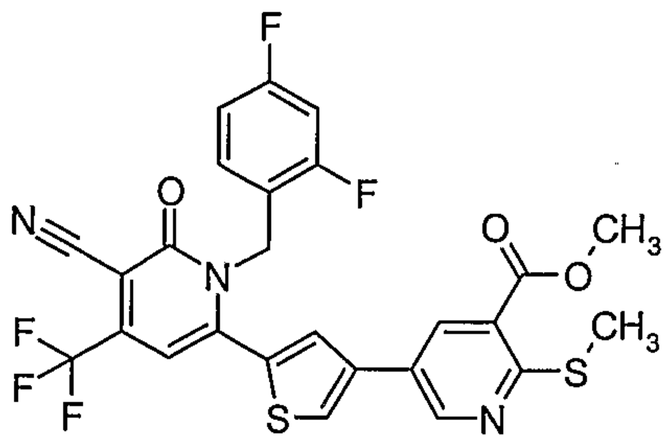
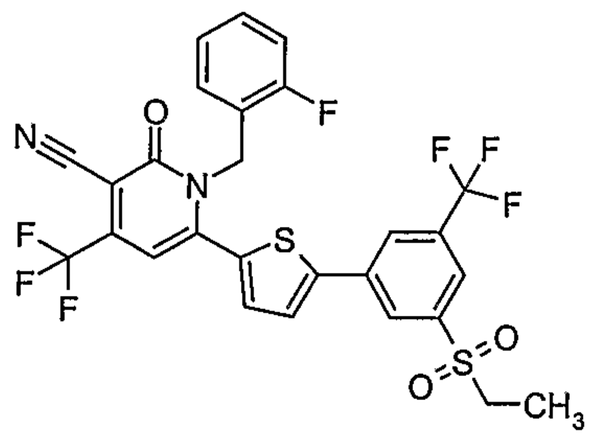
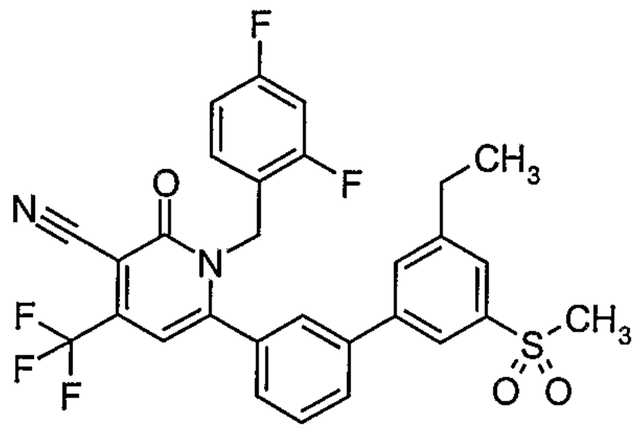
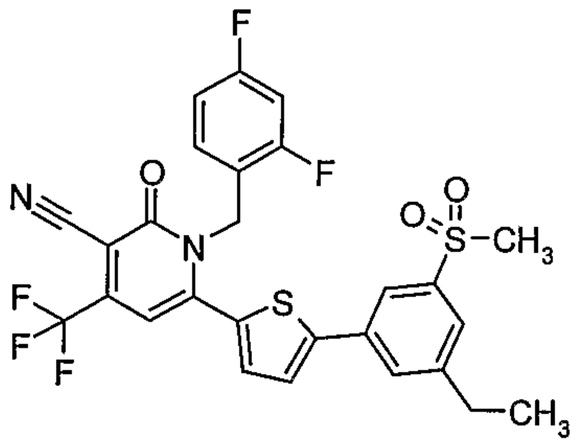
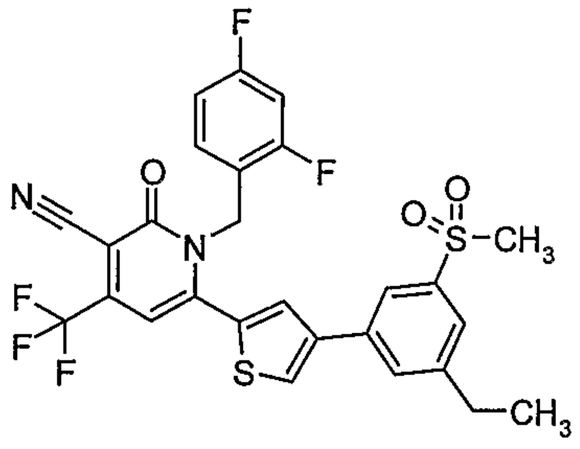
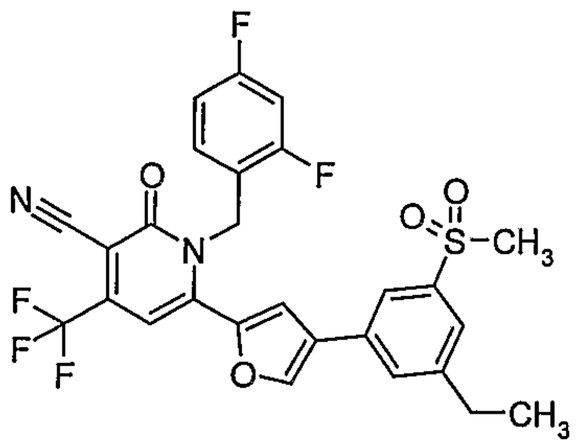
421		ethyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-2-(ethyloxy)pyridine-3-carboxylate
422		4-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)benzoic acid
423		ethyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-2-yl)-2-(ethyloxy)pyridine-3-carboxylate
424		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-methyl-6-(methylthio)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
425		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-methyl-6-(methylthio)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
426		1-[(2,4-difluorophenyl)methyl]-6-{5-[5-methyl-6-(methylthio)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

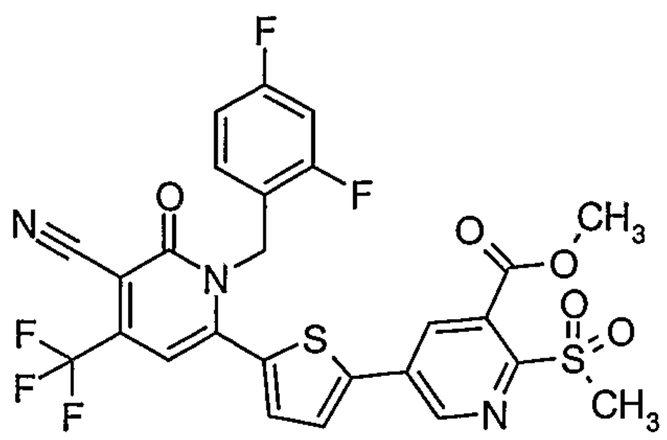
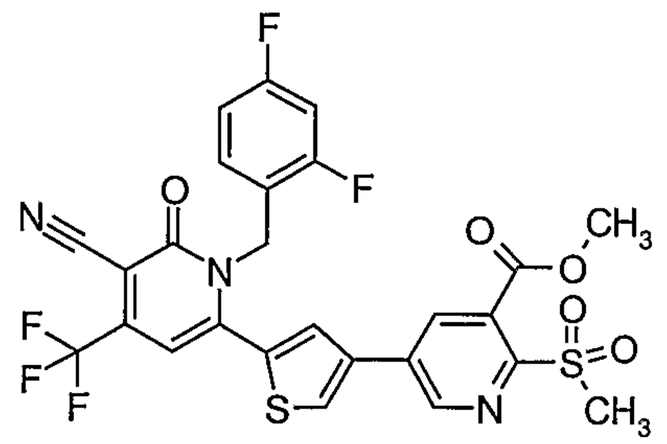
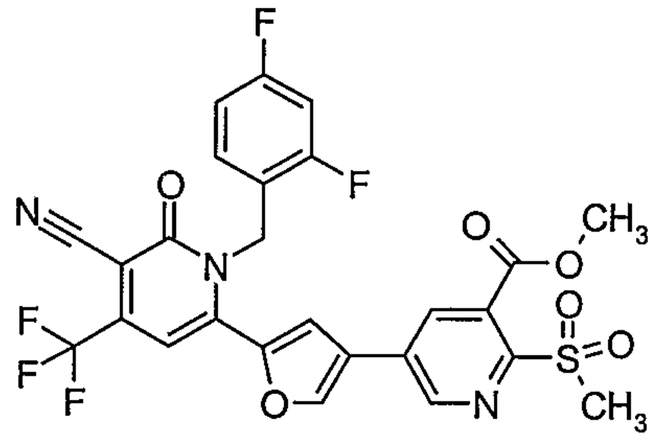
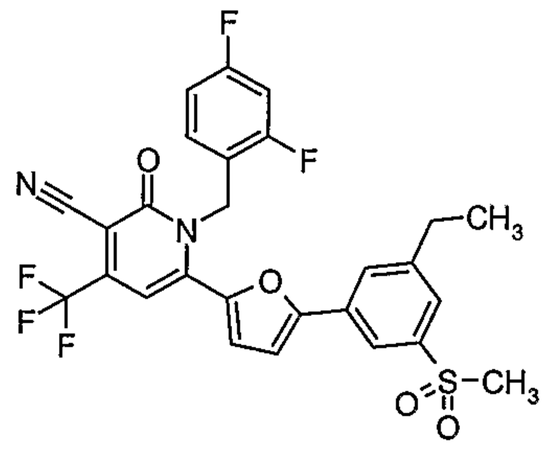
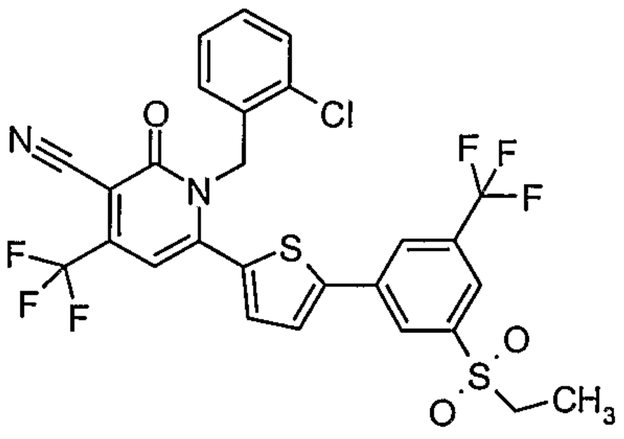
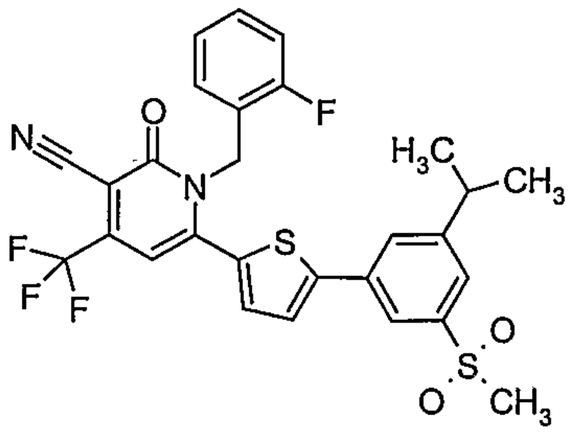
427		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
428		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{4-[3-(propylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
429		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-[(1-methylethyl)sulfonyl]-5-(trifluoromethyl)phenyl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
430		1-[(2,4-difluorophenyl)methyl]-2-oxo-6-{5-[3-(propylsulfonyl)-5-(trifluoromethyl)phenyl]furan-2-yl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
431		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
432		1-[(2,4-difluorophenyl)methyl]-6-{5-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

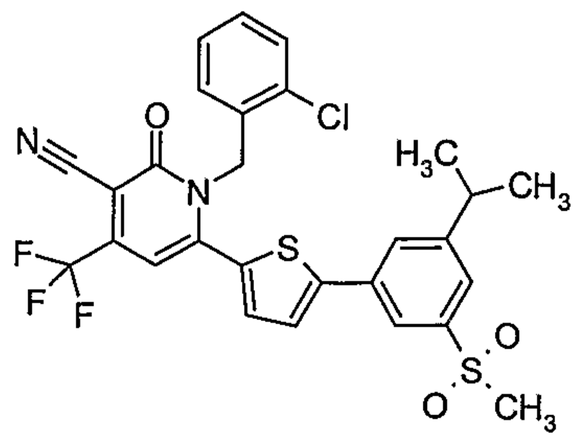
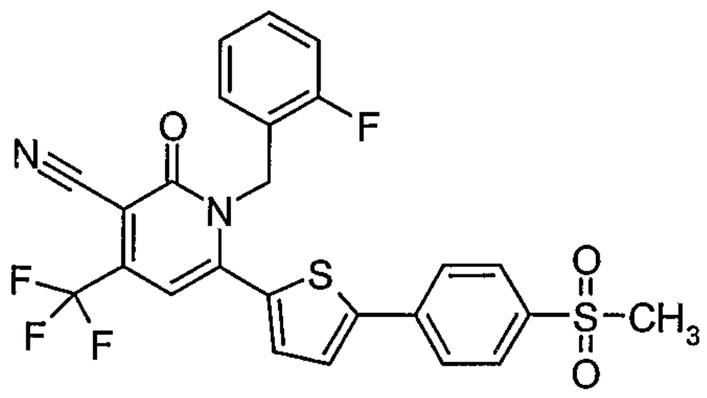
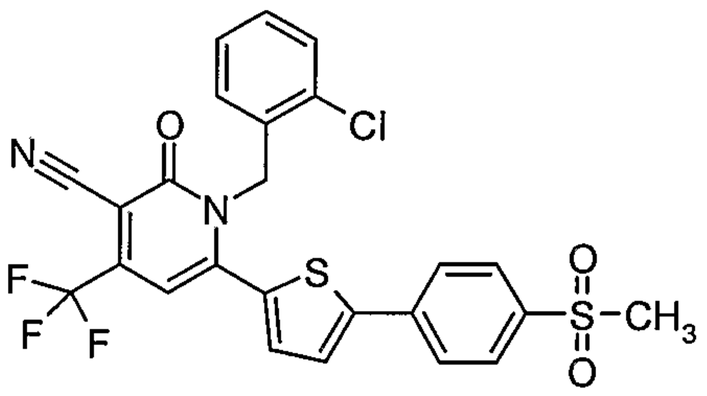
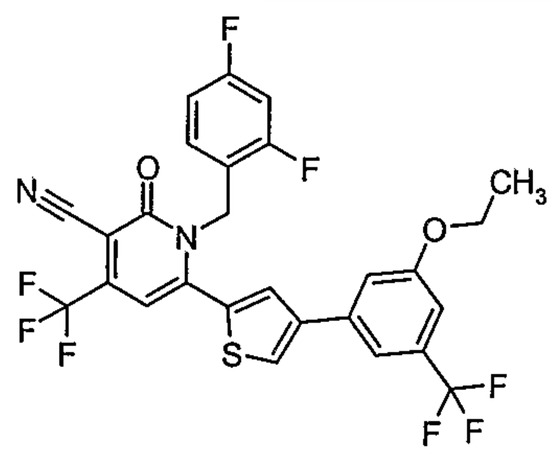
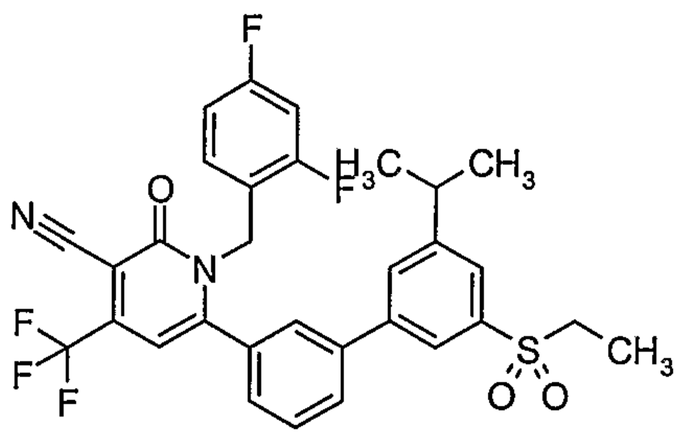
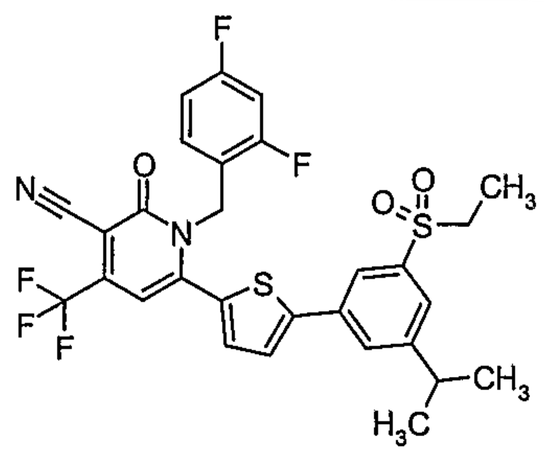
433		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
434		methyl 3'-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-5-(1-methylethyl)biphenyl-3-carboxylate
435		methyl 3-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-5-(1-methylethyl)benzoate
436		methyl 3-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-5-(1-methylethyl)benzoate
437		methyl 3-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-5-(1-methylethyl)benzoate
438		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(methylthio)pyridine-3-carboxylate

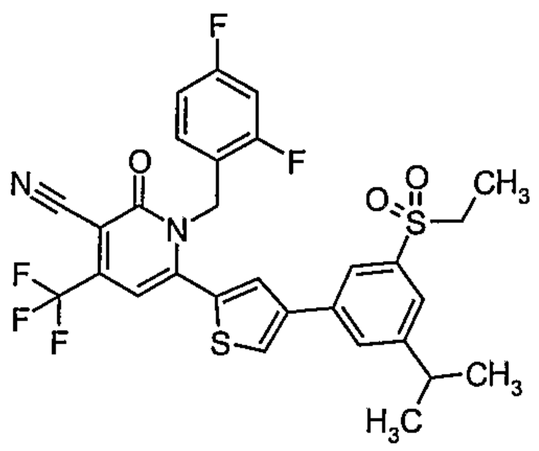
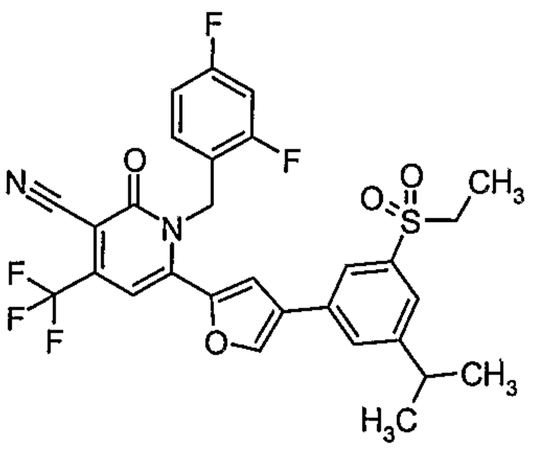
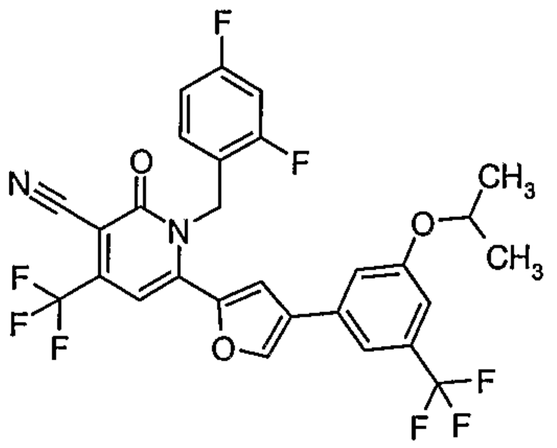
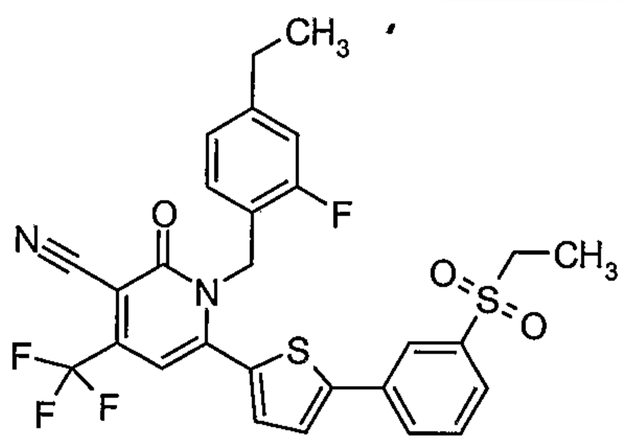
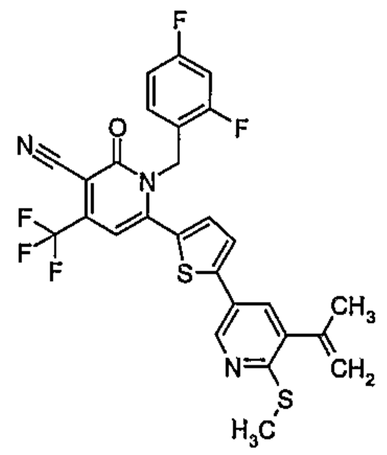
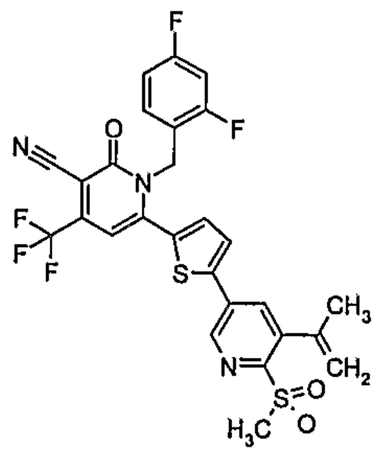
439		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-2-(methylthio)pyridine-3-carboxylate
440		1-[(2,4-difluorophenyl)methyl]-6-[3'-(1-methylethyl)-5'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
441		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
442		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
443		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
444		1-[(2,4-difluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)-3-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

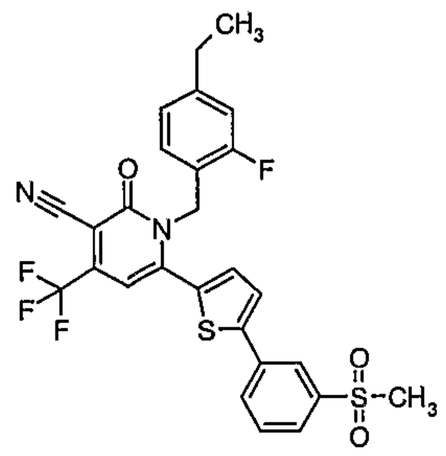
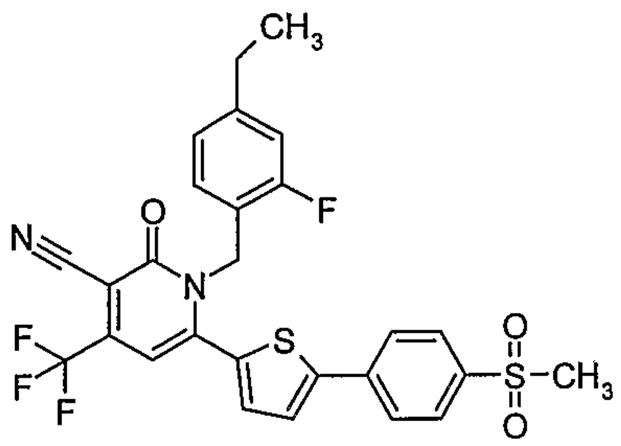
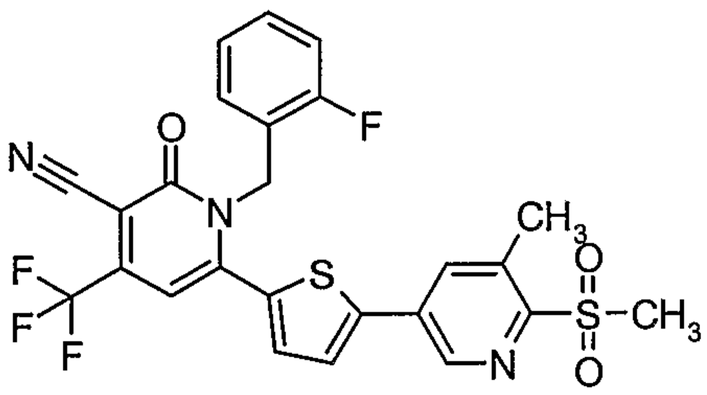
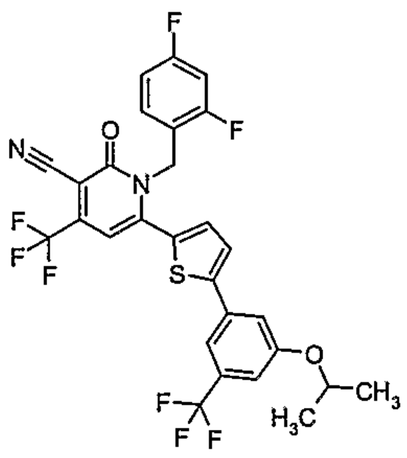
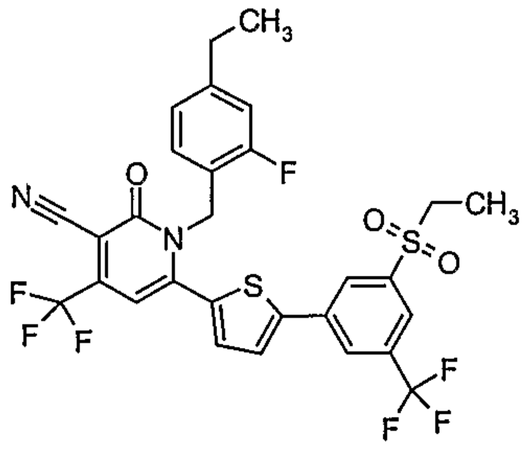
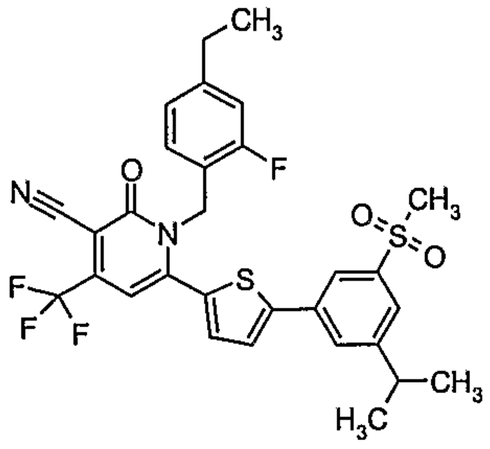
445		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethyloxy)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
446		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethyloxy)-5-(trifluoromethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
447		6-{5-[3-(ethylsulfonyl)phenyl]-2-thienyl}-1-[(2-fluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
448		1-[(2-chlorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
449		1-[(2-fluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
450		1-[(2-chlorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

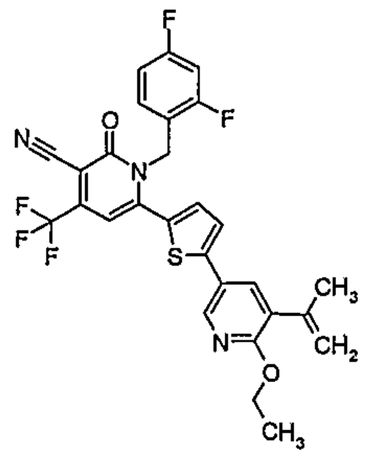
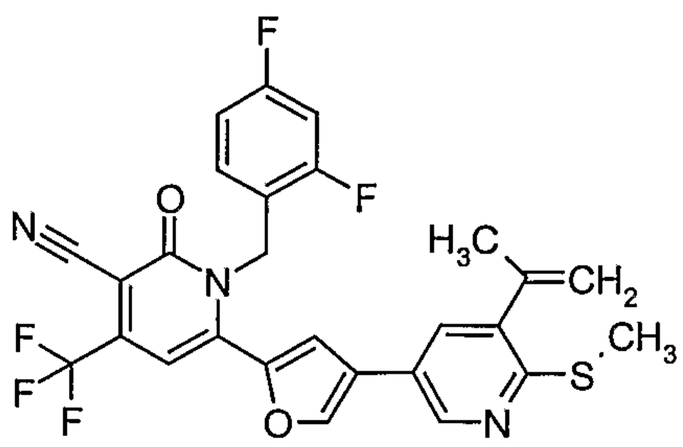
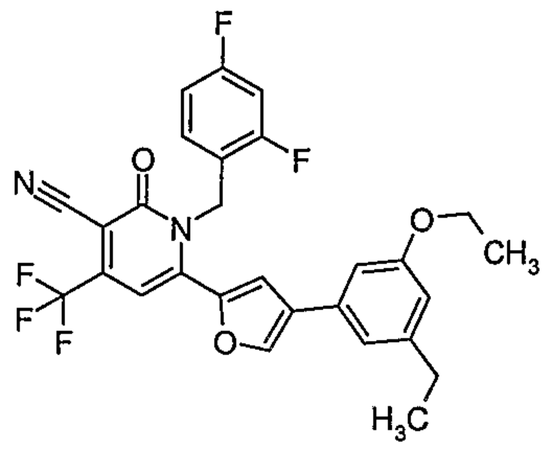
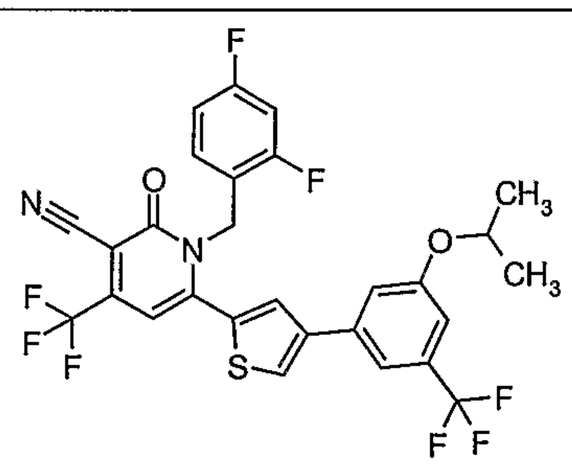
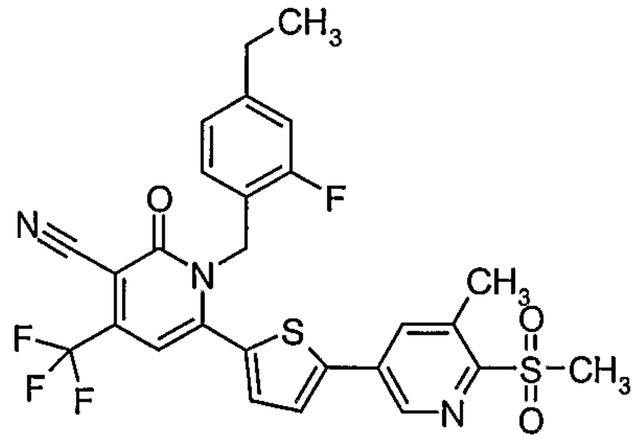
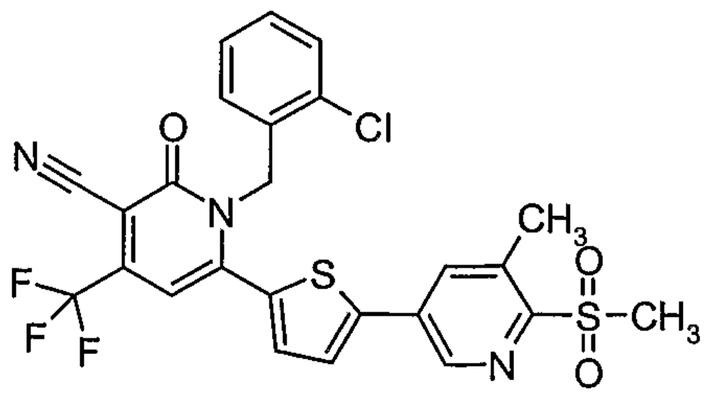
451		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-2-(methylthio)pyridine-3-carboxylate
452		6-{5-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-1-[(2-fluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
453		1-[(2,4-difluorophenyl)methyl]-6-[3'-ethyl-5'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
454		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-ethyl-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
455		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
456		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

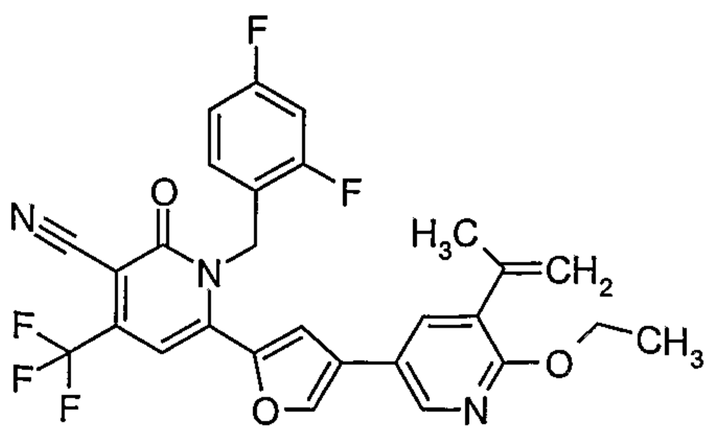
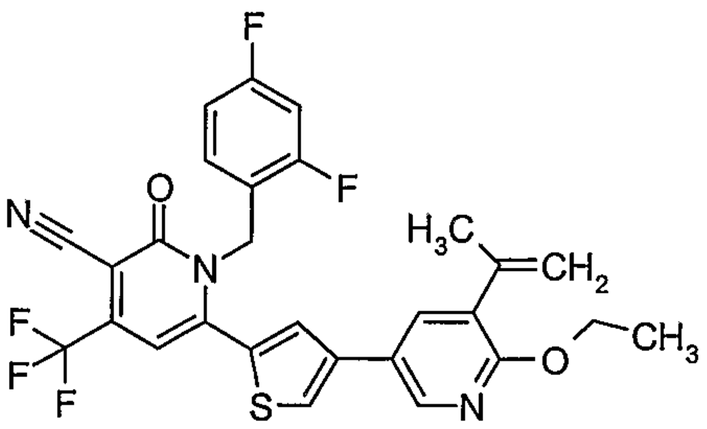
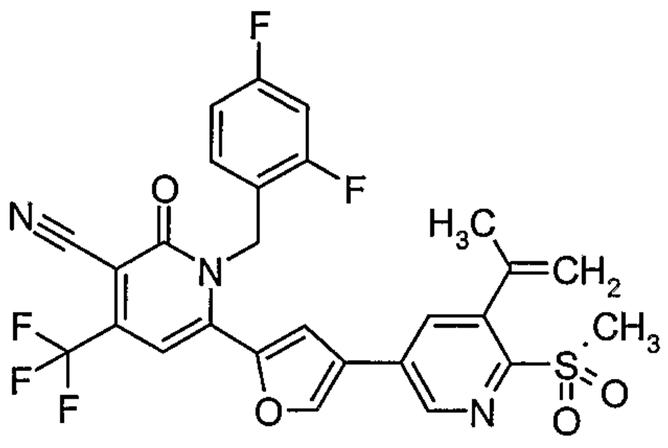
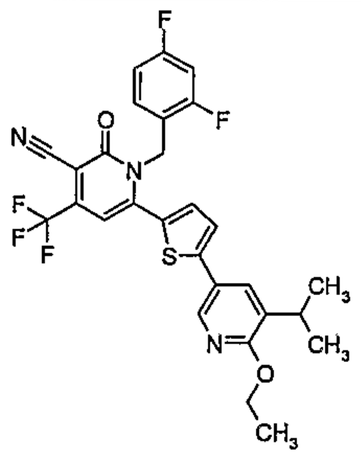
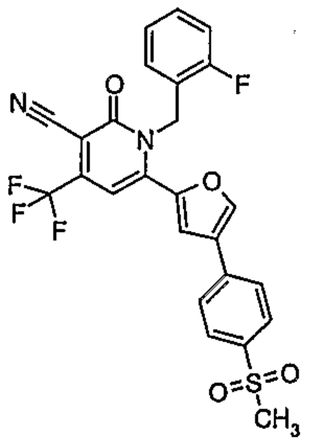
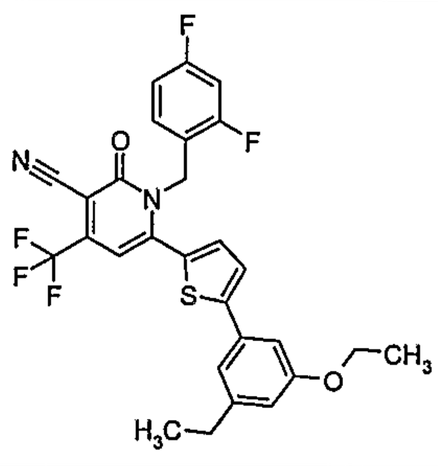
457		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(methylsulfonyl)pyridine-3-carboxylate
458		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-3-thienyl)-2-(methylsulfonyl)pyridine-3-carboxylate
459		methyl 5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}furan-3-yl)-2-(methylsulfonyl)pyridine-3-carboxylate
460		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-ethyl-5-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
461		1-[(2-chlorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
462		1-[(2-fluorophenyl)methyl]-6-{5-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

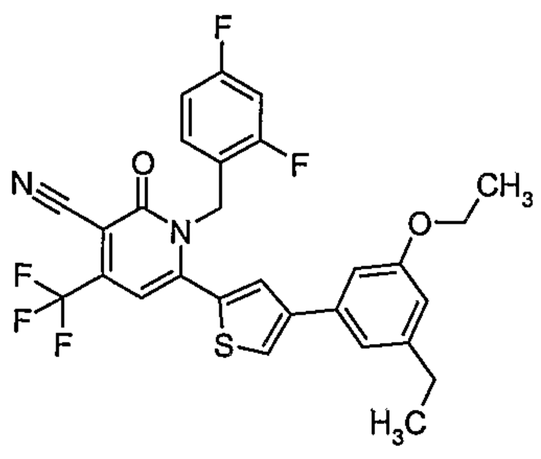
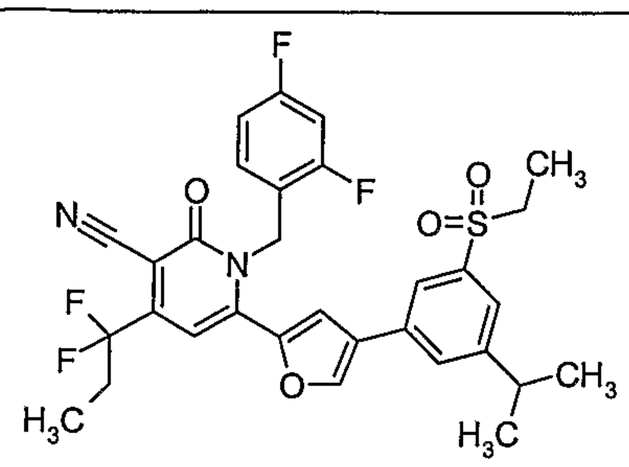
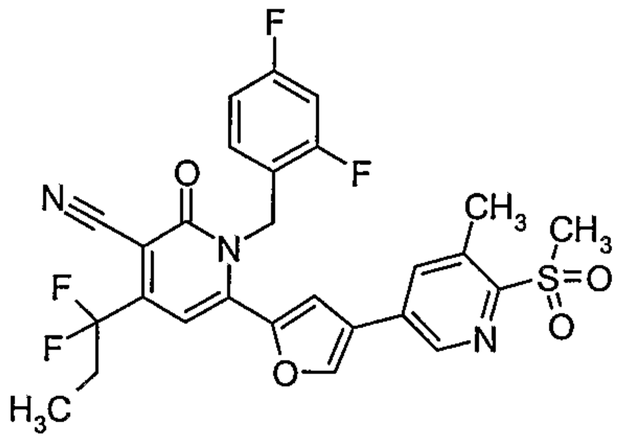
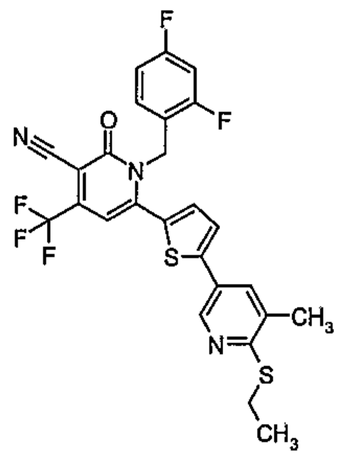
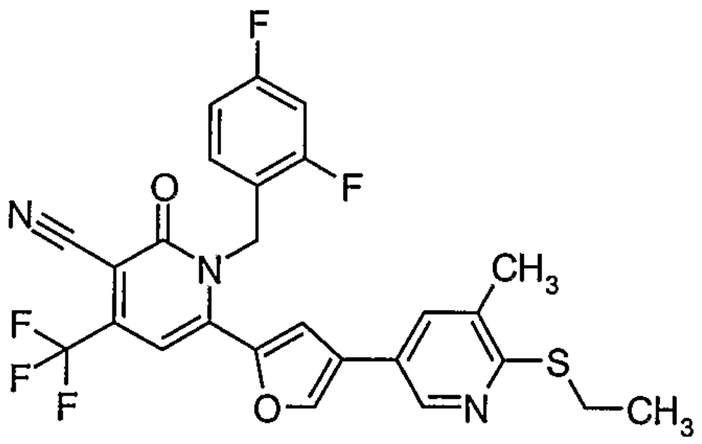
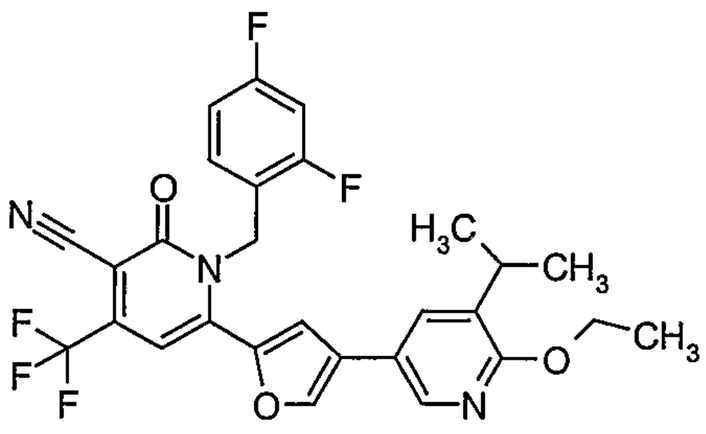
463		1-[(2-chlorophenyl)methyl]-6-{5-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
464		1-[(2-fluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
465		1-[(2-chlorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
466		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethyloxy)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
467		1-[(2,4-difluorophenyl)methyl]-6-[3'-(ethylsulfonyl)-5'-(1-methylethyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
468		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)-5-(1-methylethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

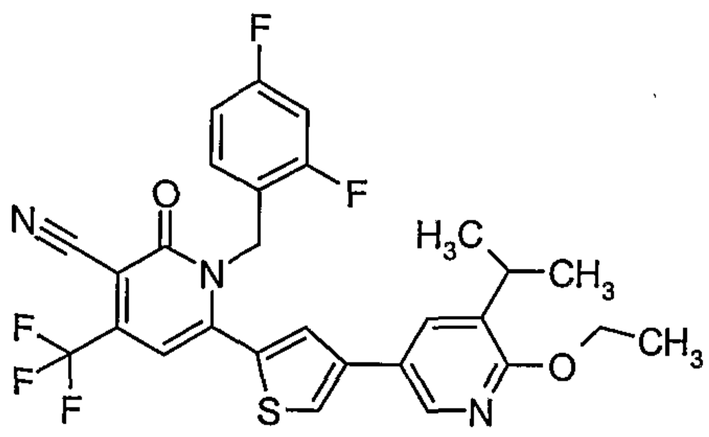
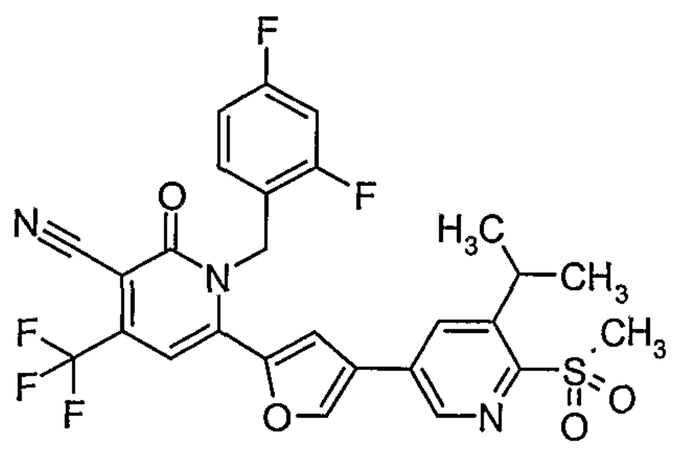
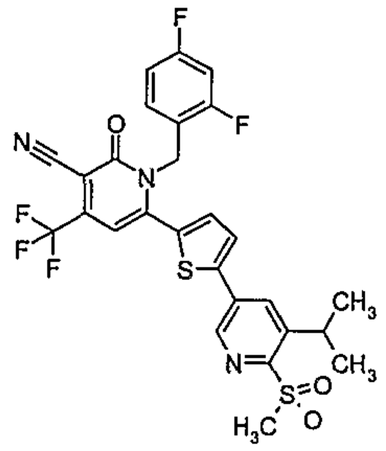
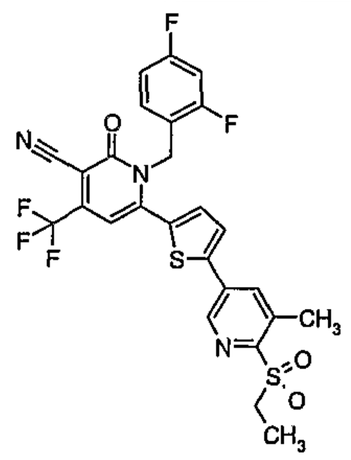
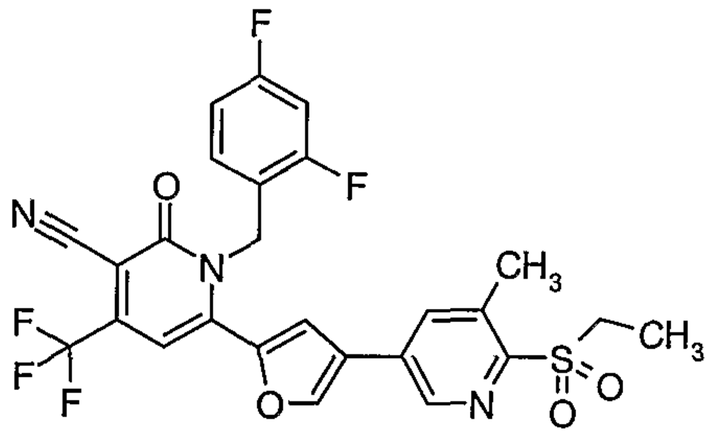
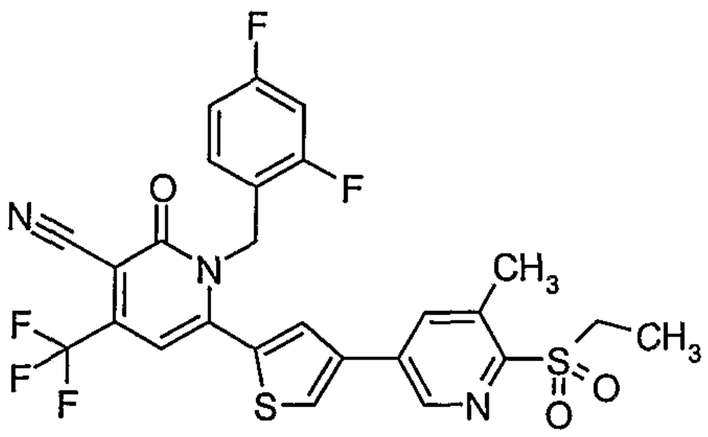
469		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethylsulfonyl)-5-(1-methylethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
470		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(ethylsulfonyl)-5-(1-methylethyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
471		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-[(1-methylethyl)oxy]-5-(trifluoromethyl)phenyl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
472		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
473		1-[(2,4-difluorophenyl)methyl]-6-{5-[5-(1-methylethenyl)-6-(methylthio)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
474		1-[(2,4-difluorophenyl)methyl]-6-{5-[5-(1-methylethenyl)-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

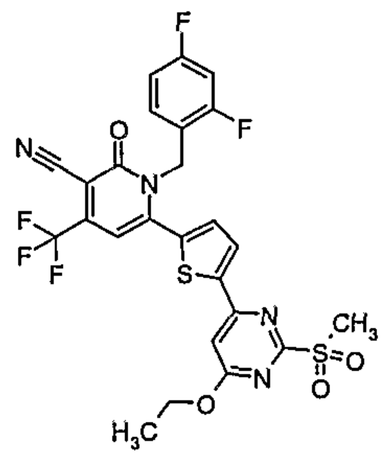
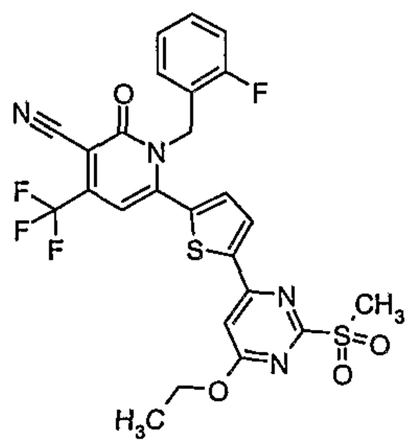
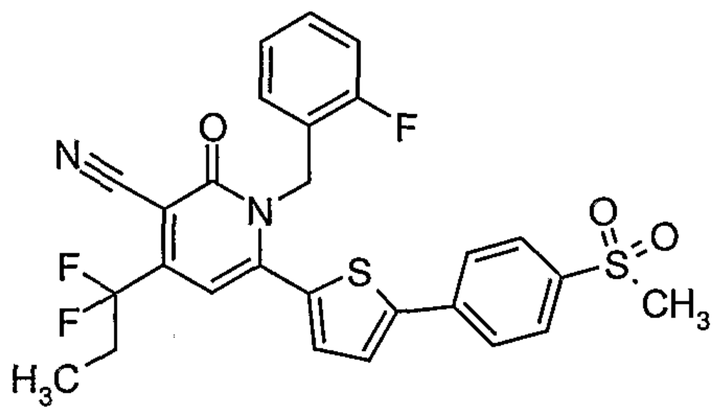
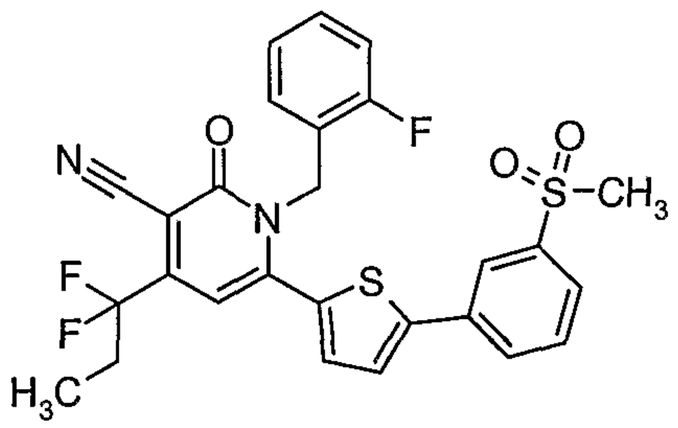
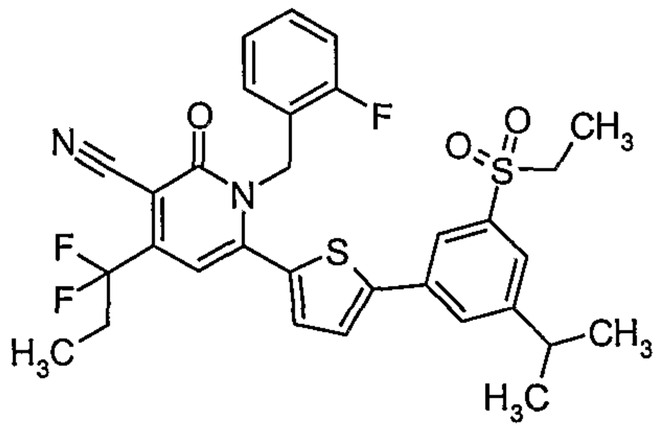
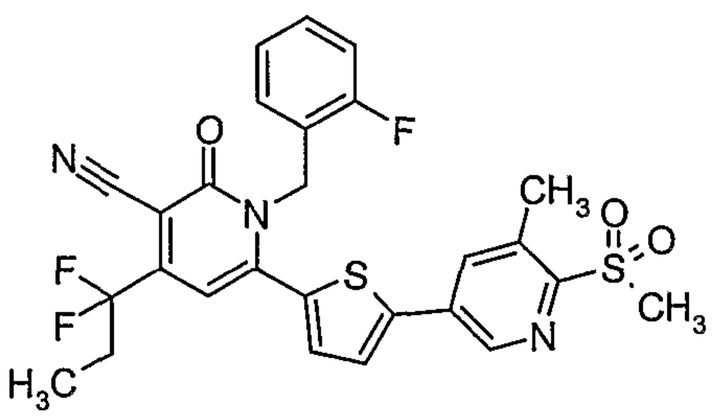
475		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
476		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
477		1-[(2-fluorophenyl)methyl]-6-{5-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
478		1-[(2,4-difluorophenyl)methyl]-6-(5-{3-[(1-methylethyl)oxy]-5-(trifluoromethyl)phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
479		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[3-(ethylsulfonyl)-5-(trifluoromethyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
480		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[3-(1-methylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

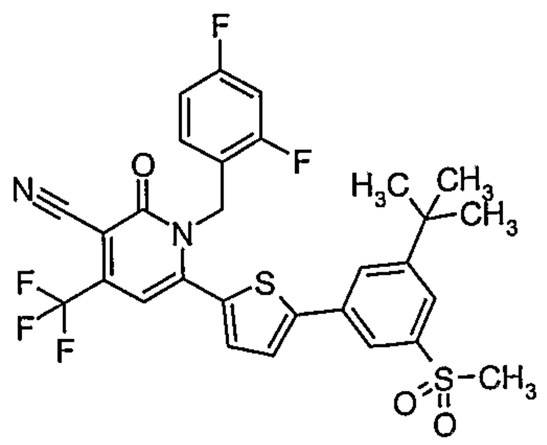
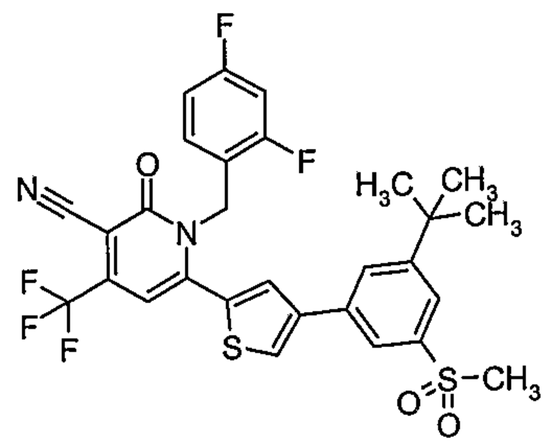
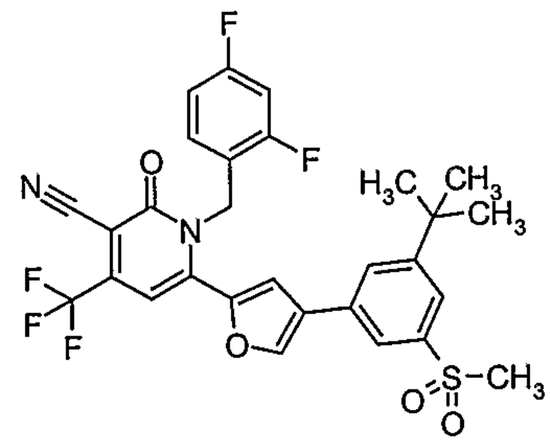
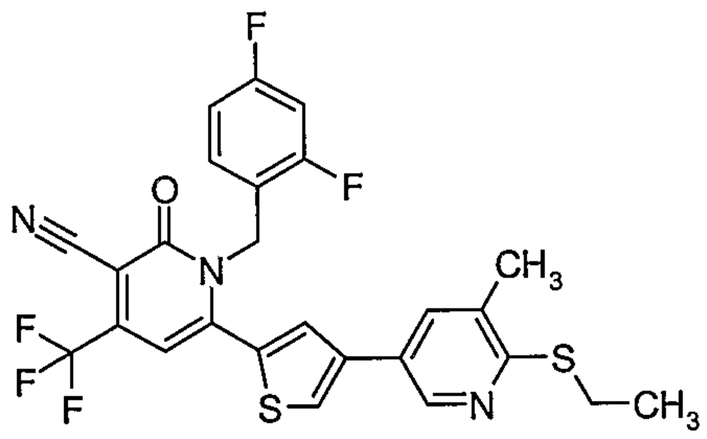
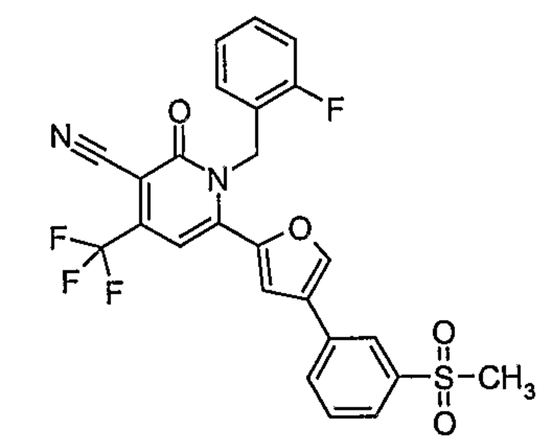
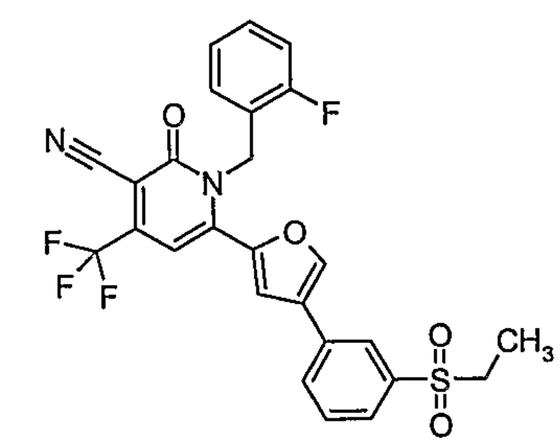
481		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethyloxy)-5-(1-methylethenyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
482		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-(1-methylethenyl)-6-(methylthio)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
483		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(ethyloxy)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
484		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-[(1-methylethyl)oxy]-5-(trifluoromethyl)phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
485		1-[(4-ethyl-2-fluorophenyl)methyl]-6-{5-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
486		1-[(2-chlorophenyl)methyl]-6-{5-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

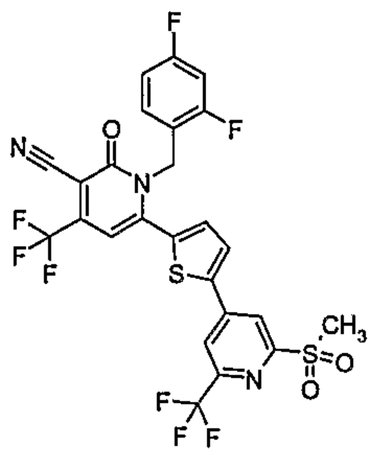
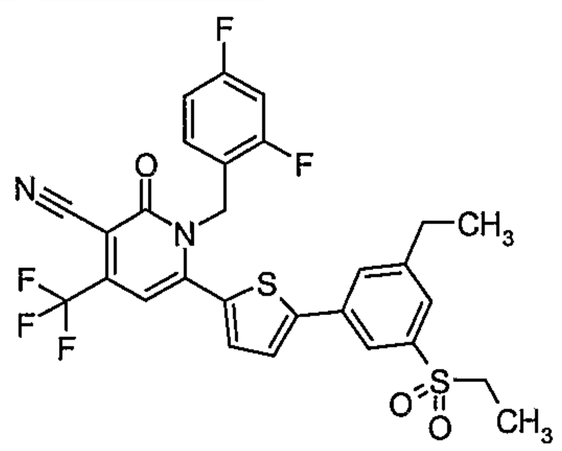
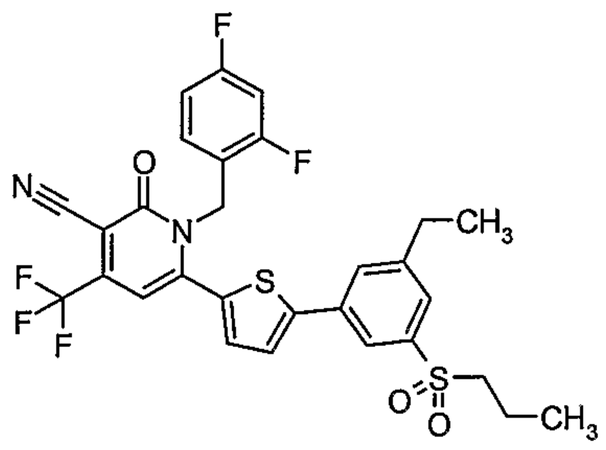
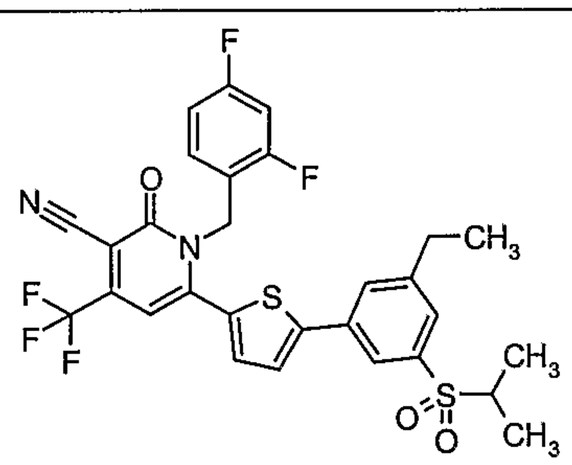
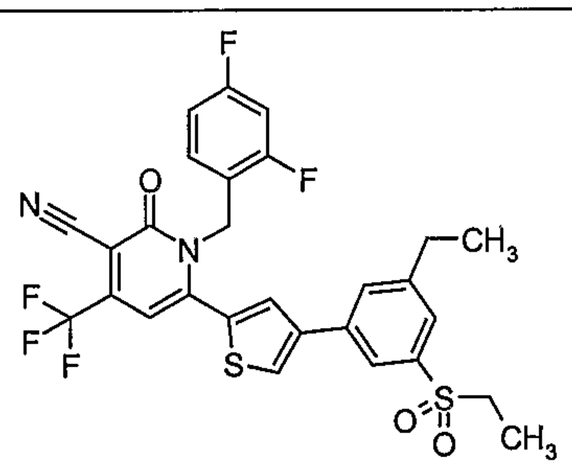
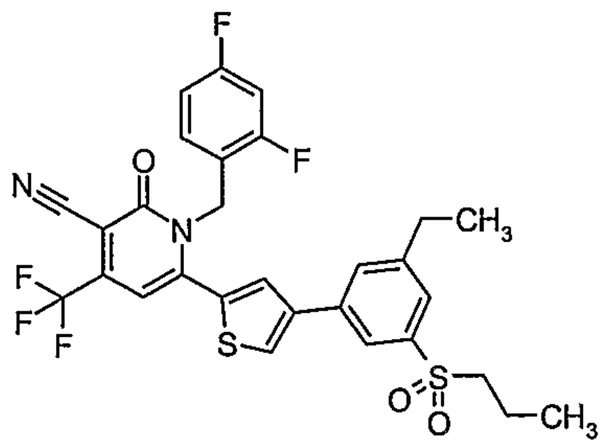
487		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(1-methylethenyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
488		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(1-methylethenyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
489		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-(1-methylethenyl)-6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
490		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethyloxy)-5-(1-methylethyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
491		1-[(2-fluorophenyl)methyl]-6-{4-[4-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
492		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-ethyl-5-(ethyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

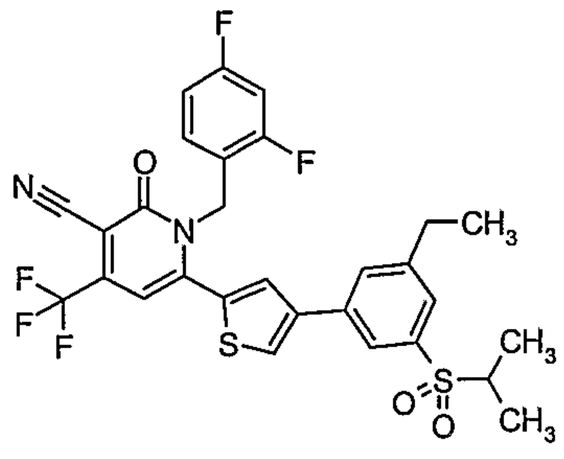
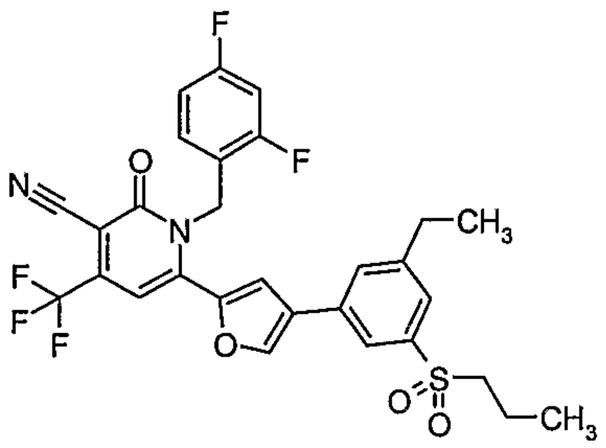
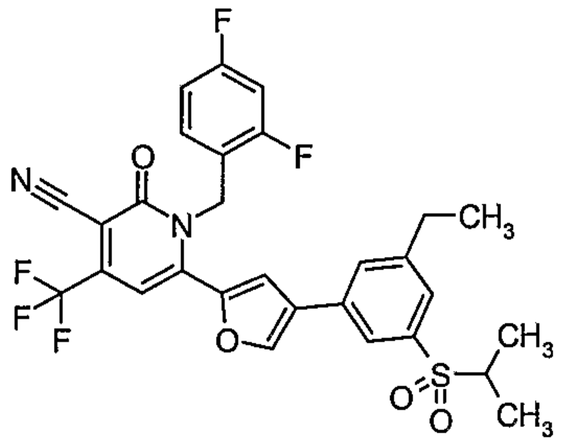
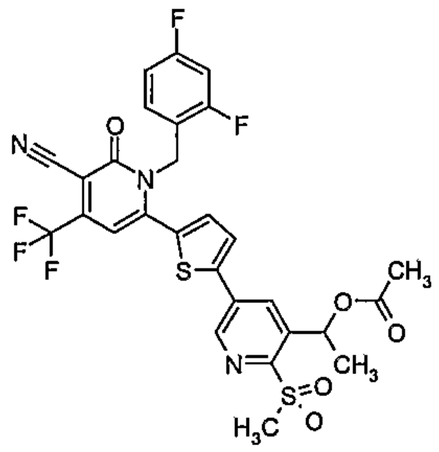
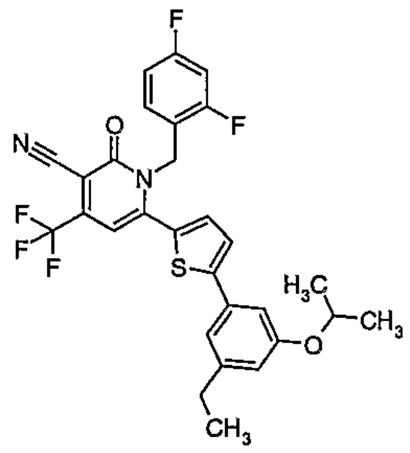
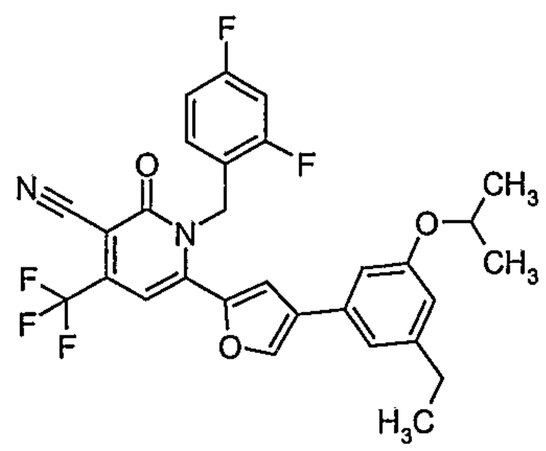
493		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(ethyloxy)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
494		1-[(2,4-difluorophenyl)methyl]-4-(1,1-difluoropropyl)-6-{4-[3-(ethylsulfonyl)-5-(1-methylethyl)phenyl]furan-2-yl}-2-oxo-1,2-dihydropyridine-3-carbonitrile
495		1-[(2,4-difluorophenyl)methyl]-4-(1,1-difluoropropyl)-6-{4-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-1,2-dihydropyridine-3-carbonitrile
496		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethylthio)-5-methylpyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
497		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethylthio)-5-methylpyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
498		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(1-methylethyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

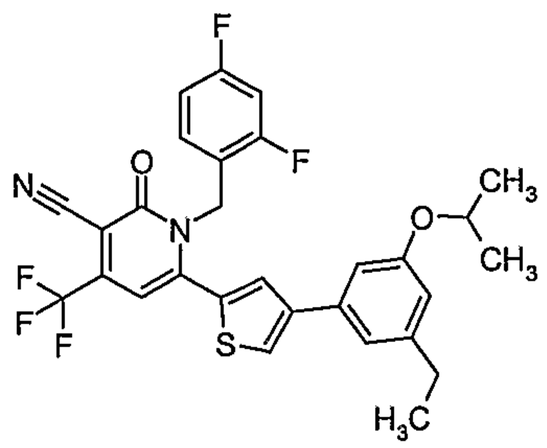
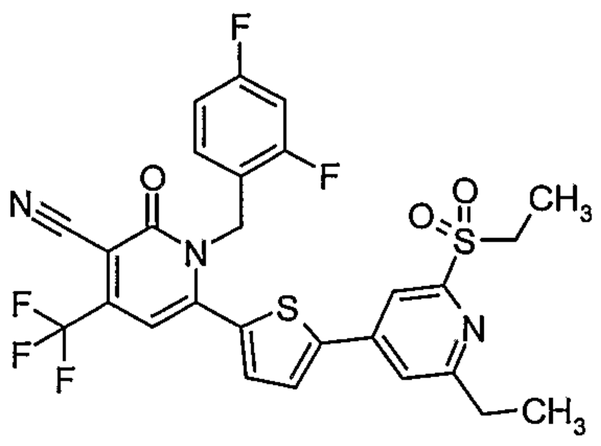
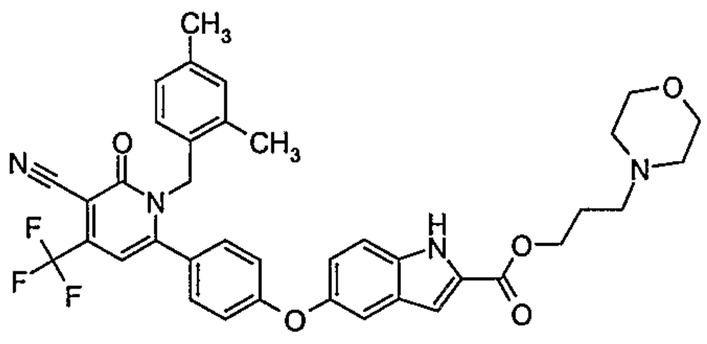
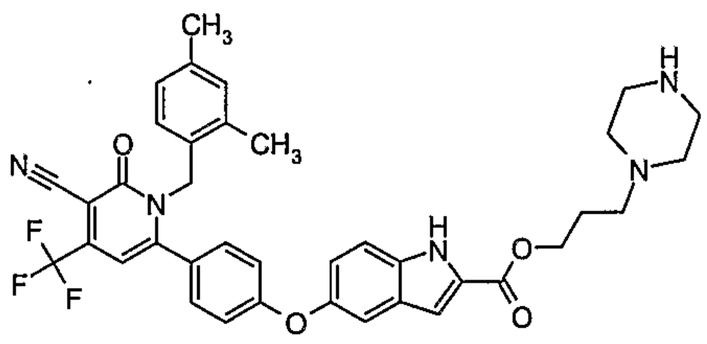
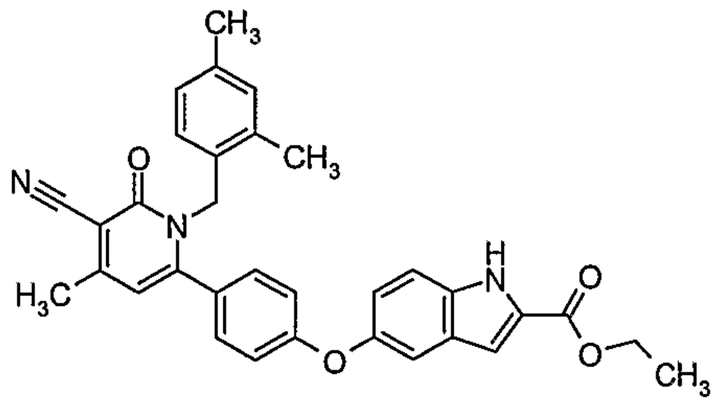
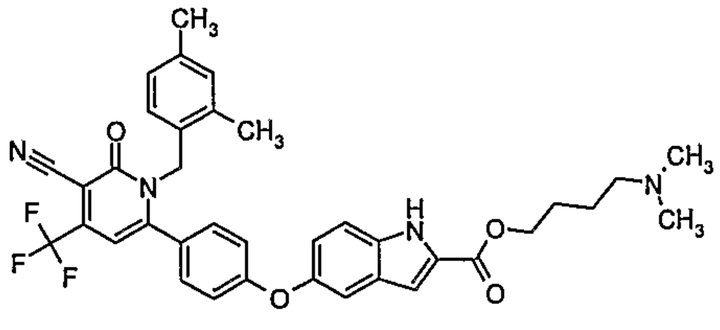
499		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethyloxy)-5-(1-methylethyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
500		1-[(2,4-difluorophenyl)methyl]-6-{4-[5-(1-methylethyl)-6-(methylsulfonyl)pyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
501		1-[(2,4-difluorophenyl)methyl]-6-{5-[5-(1-methylethyl)-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
502		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethylsulfonyl)-5-methylpyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
503		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethylsulfonyl)-5-methylpyridin-3-yl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
504		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethylsulfonyl)-5-methylpyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

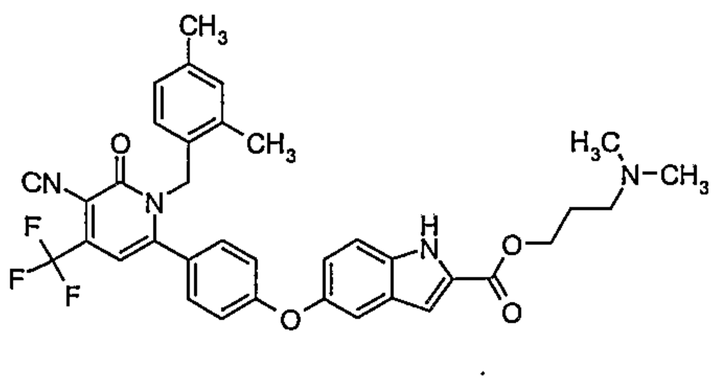
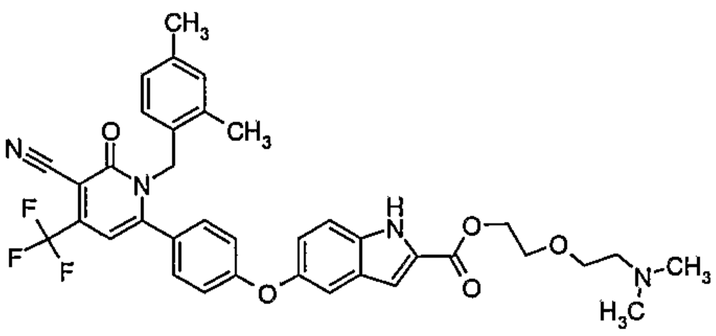
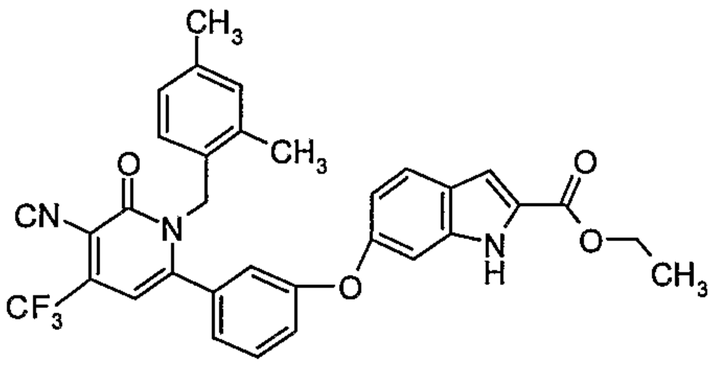
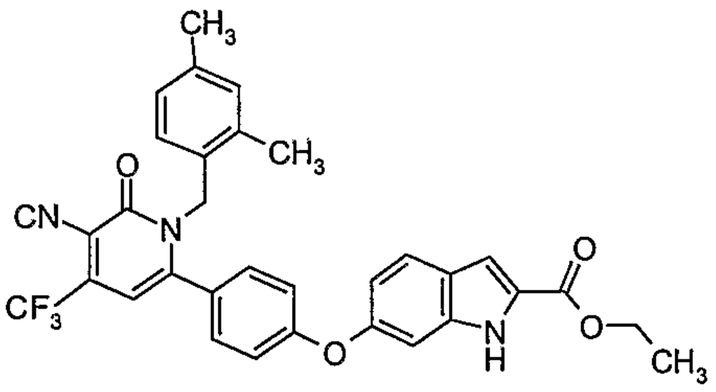
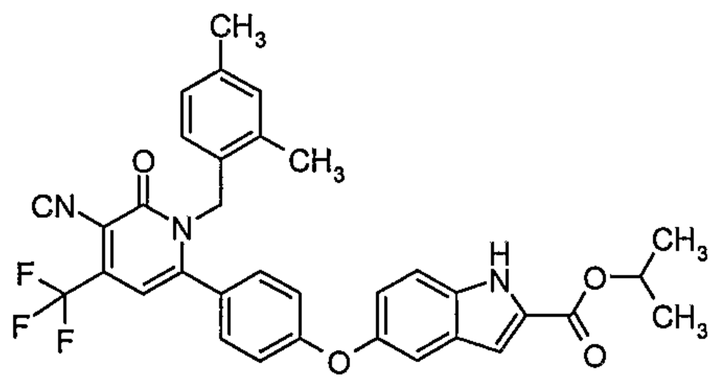
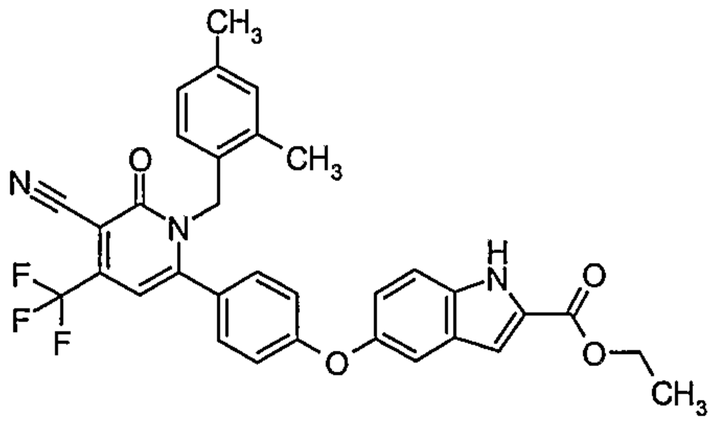
505		1-[(2,4-difluorophenyl)methyl]-6-{5-[6-(ethyloxy)-2-(methylsulfonyl)pyrimidin-4-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
506		6-{5-[6-(ethyloxy)-2-(methylsulfonyl)pyrimidin-4-yl]-2-thienyl}-1-[(2-fluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
507		4-(1,1-difluoropropyl)-1-[(2-fluorophenyl)methyl]-6-{5-[4-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-1,2-dihydropyridine-3-carbonitrile
508		4-(1,1-difluoropropyl)-1-[(2-fluorophenyl)methyl]-6-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-1,2-dihydropyridine-3-carbonitrile
509		4-(1,1-difluoropropyl)-6-{5-[3-(ethylsulfonyl)-5-(1-methylethyl)phenyl]-2-thienyl}-1-[(2-fluorophenyl)methyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile
510		4-(1,1-difluoropropyl)-1-[(2-fluorophenyl)methyl]-6-{5-[5-methyl-6-(methylsulfonyl)pyridin-3-yl]-2-thienyl}-2-oxo-1,2-dihydropyridine-3-carbonitrile

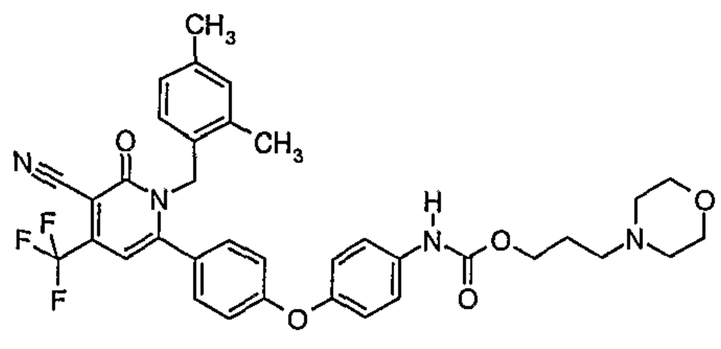
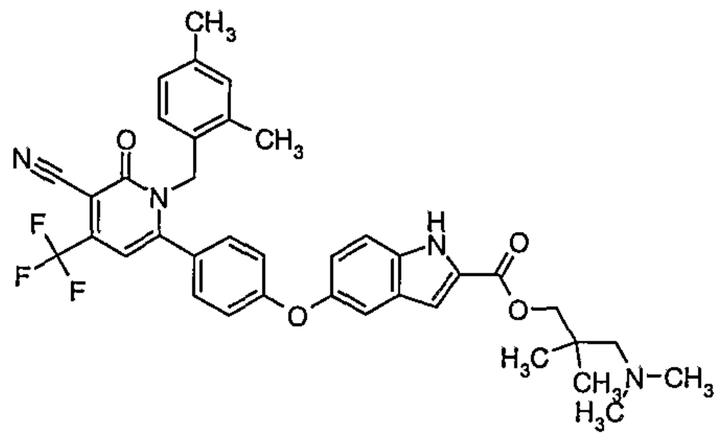
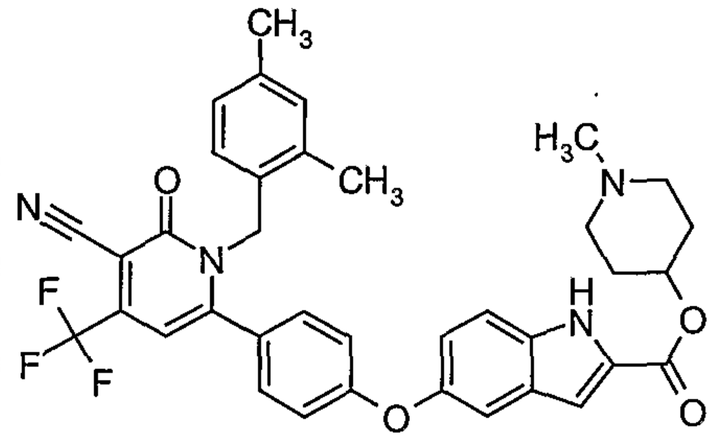
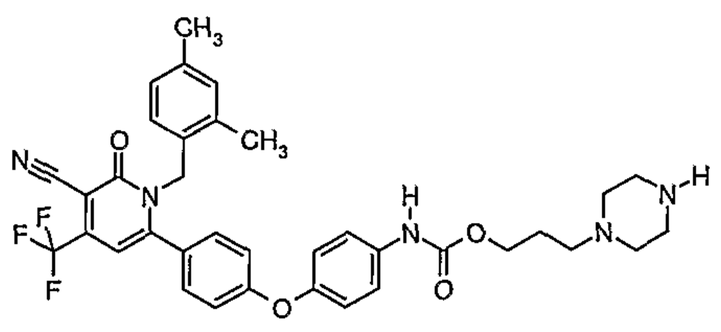
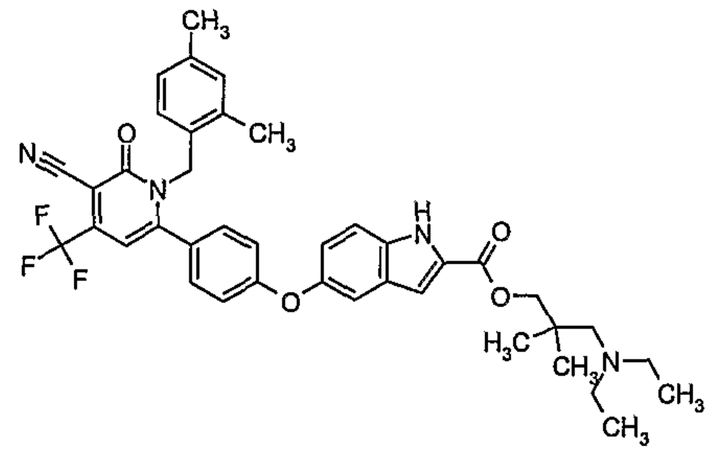
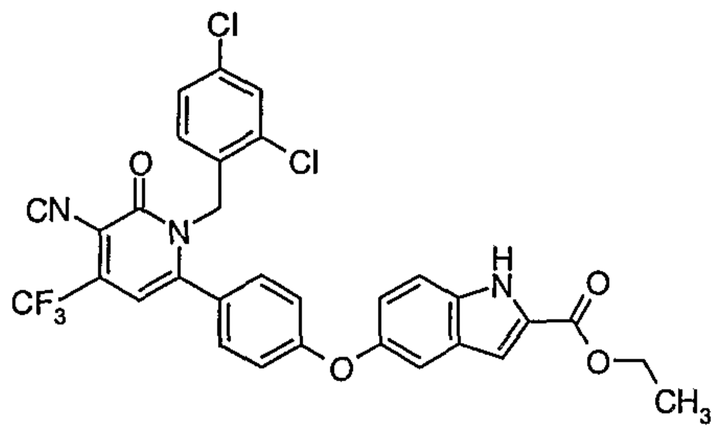
511		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-(1,1-dimethylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
512		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(1,1-dimethylethyl)-5-(methylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
513		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-(1,1-dimethylethyl)-5-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
514		1-[(2,4-difluorophenyl)methyl]-6-{4-[6-(ethylthio)-5-methylpyridin-3-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
515		1-[(2-fluorophenyl)methyl]-6-{4-[3-(methylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
516		6-{4-[3-(ethylsulfonyl)phenyl]furan-2-yl}-1-[(2-fluorophenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

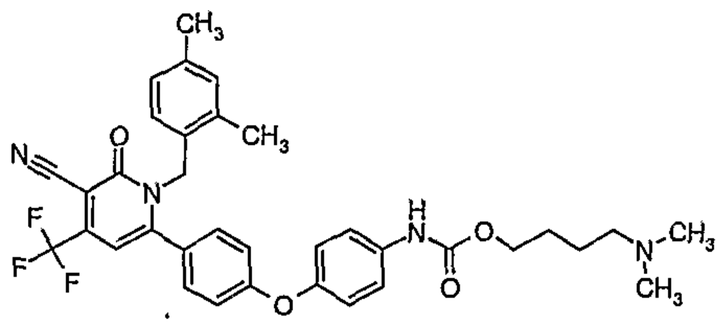
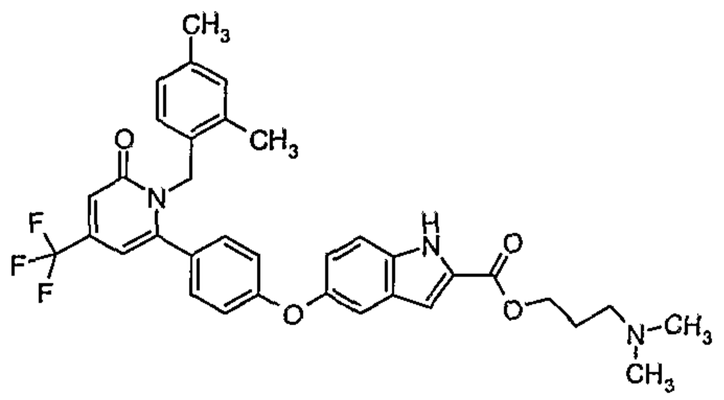
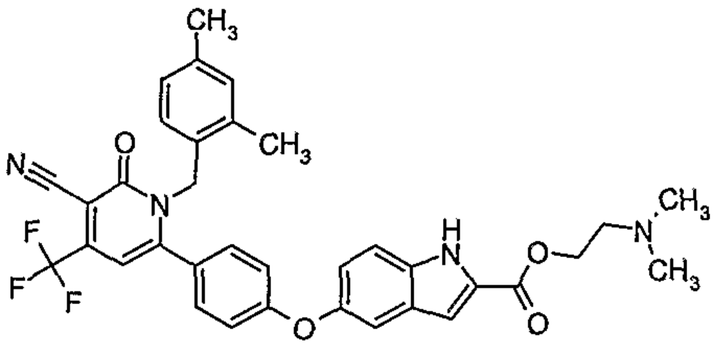
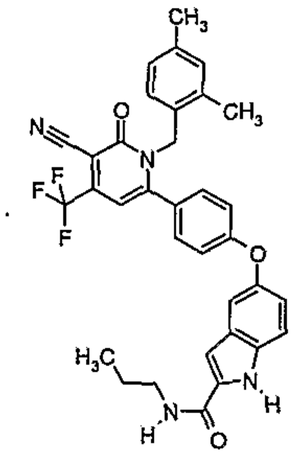
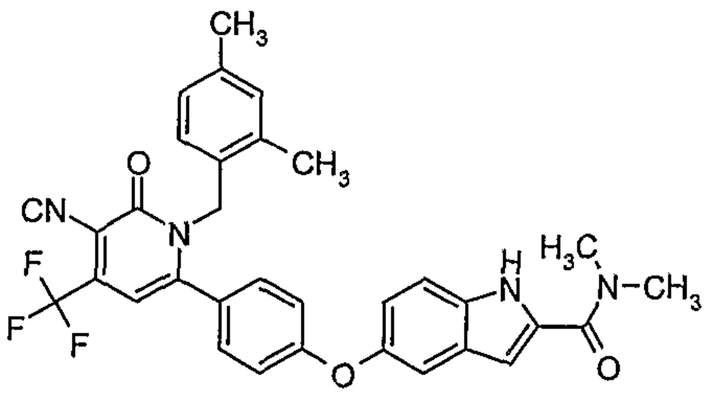
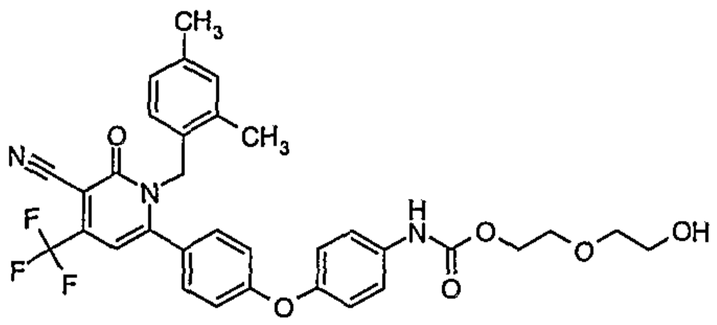
517		1-[(2,4-difluorophenyl)methyl]-6-{5-[2-(methylsulfonyl)-6-(trifluoromethyl)pyridin-4-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
518		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-ethyl-5-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
519		1-[(2,4-difluorophenyl)methyl]-6-{5-[3-ethyl-5-(propylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
520		1-[(2,4-difluorophenyl)methyl]-6-(5-{3-ethyl-5-[(1-methylethyl)sulfonyl]phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
521		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(ethylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
522		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(propylsulfonyl)phenyl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

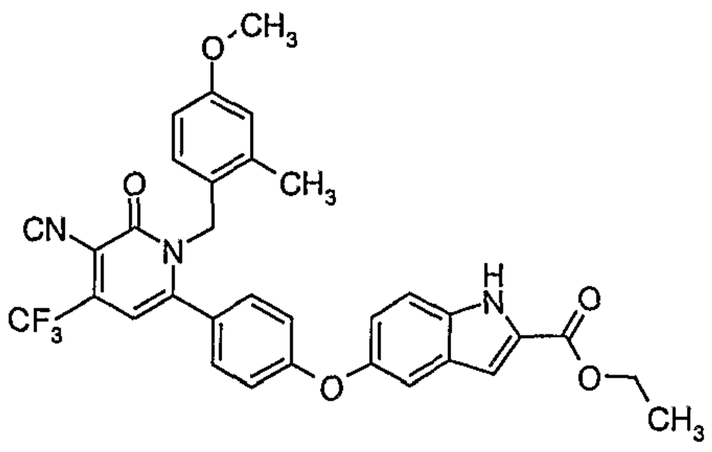
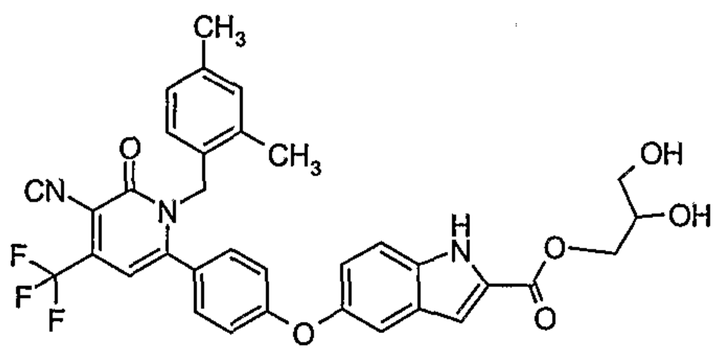
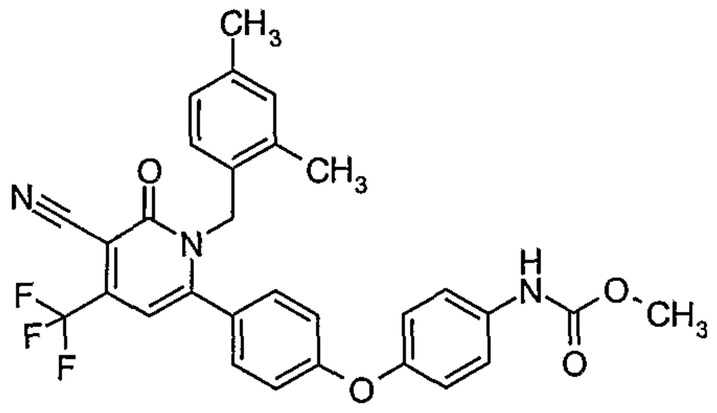
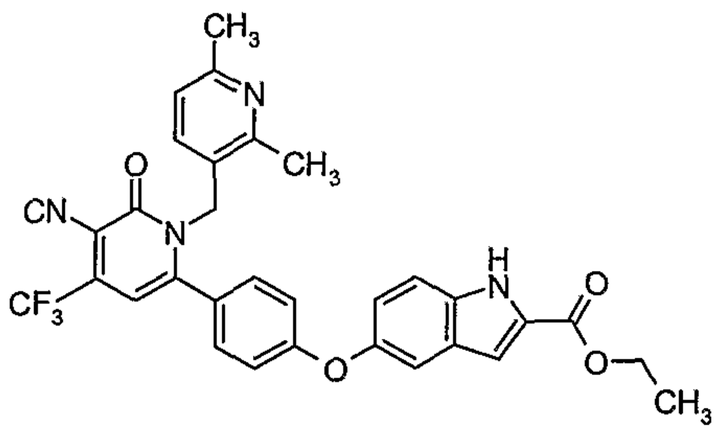
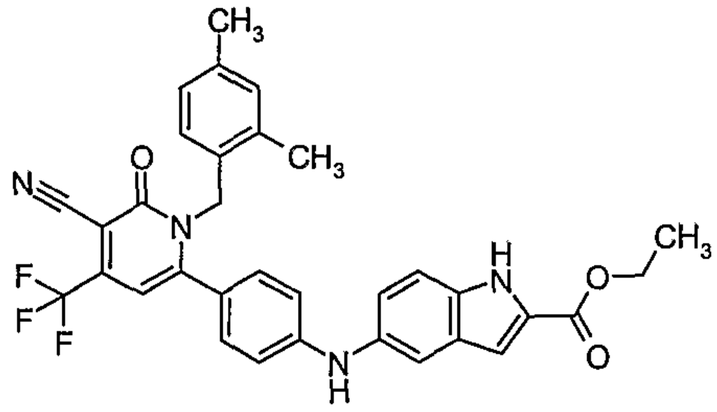
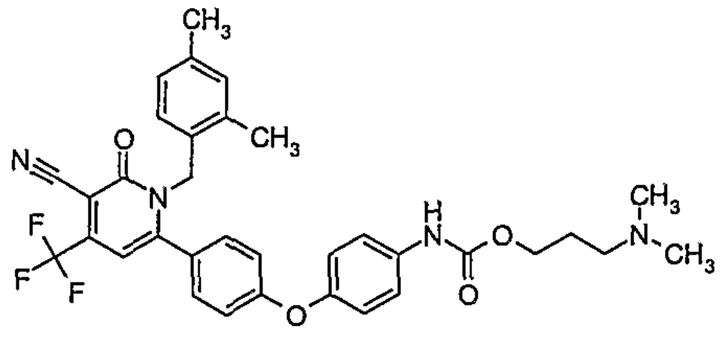
523		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-ethyl-5-[(1-methylethyl)sulfonyl]phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
524		1-[(2,4-difluorophenyl)methyl]-6-{4-[3-ethyl-5-(propylsulfonyl)phenyl]furan-2-yl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
525		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-ethyl-5-[(1-methylethyl)sulfonyl]phenyl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
526		1-[5-(5-{5-cyano-1-[(2,4-difluorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-2-(methylsulfonyl)pyridin-3-yl]ethyl acetate
527		1-[(2,4-difluorophenyl)methyl]-6-(5-{3-ethyl-5-[(1-methylethyl)oxy]phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
528		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-ethyl-5-[(1-methylethyl)oxy]phenyl}furan-2-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

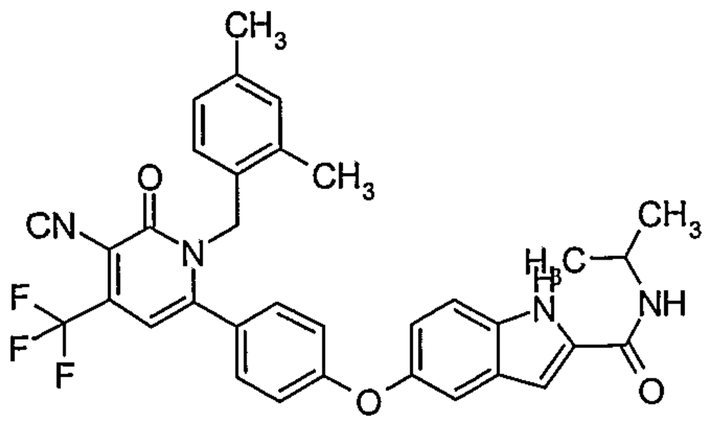
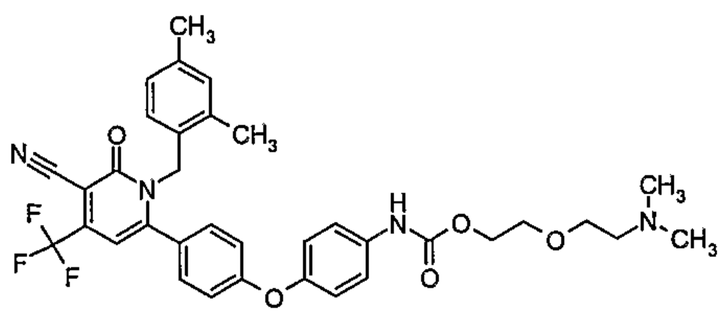
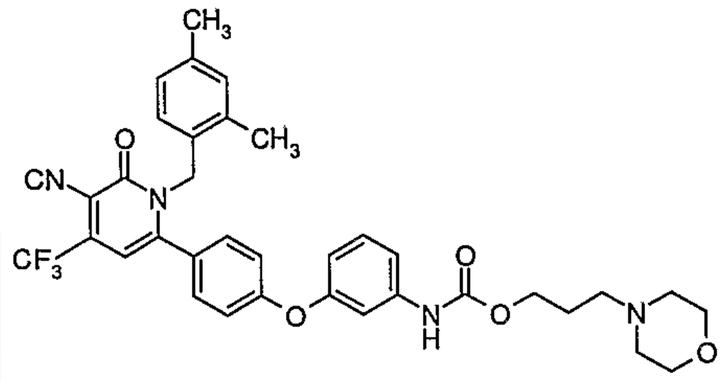
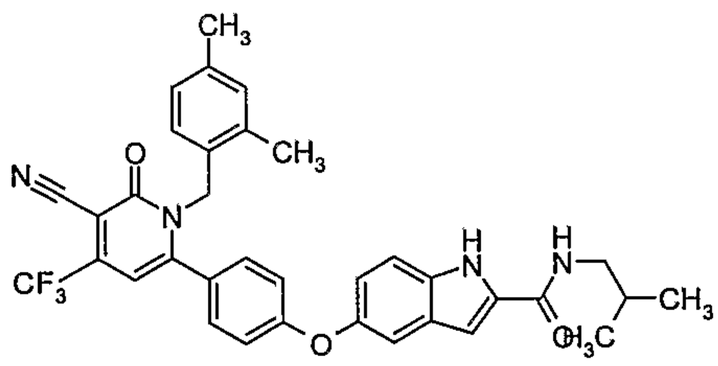
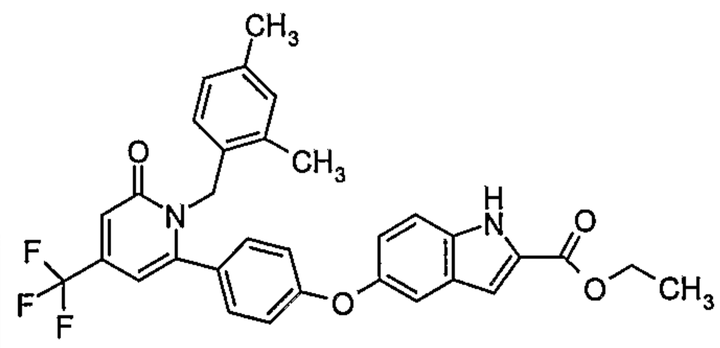
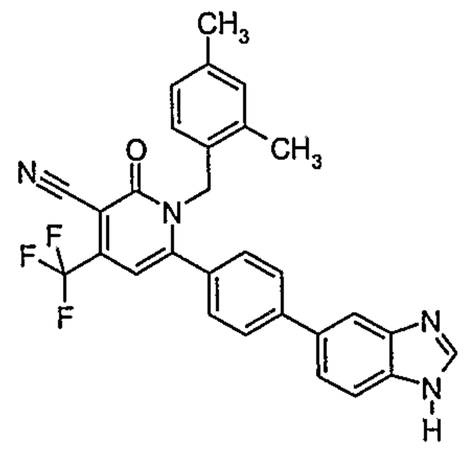
529		1-[(2,4-difluorophenyl)methyl]-6-(4-{3-ethyl-5-[(1-methylethyl)oxy]phenyl}-2-thienyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
530		1-[(2,4-difluorophenyl)methyl]-6-{5-[2-ethyl-6-(ethylsulfonyl)pyridin-4-yl]-2-thienyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
531		3-morpholin-4-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
532		3-piperazin-1-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
533		ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-4-methyl-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
534		4-(dimethylamino)butyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

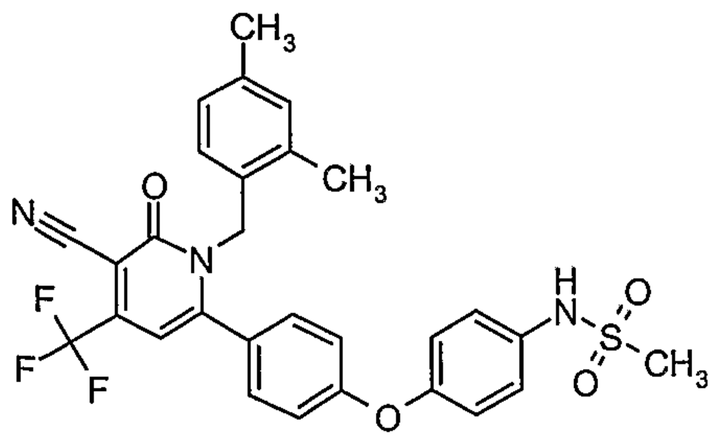
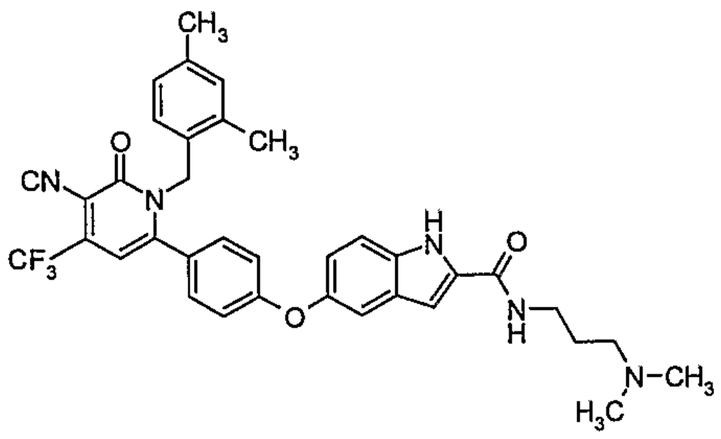
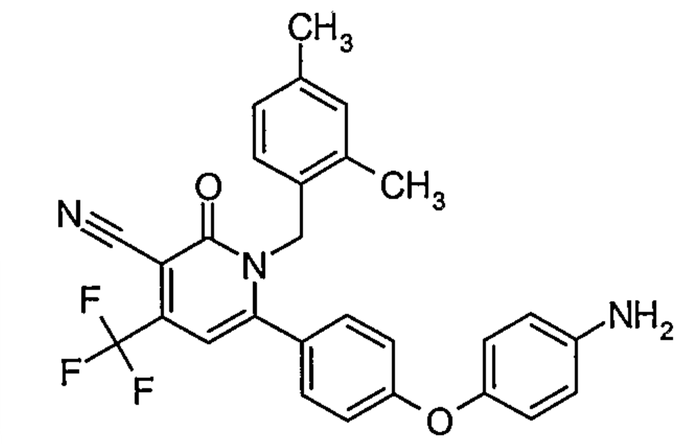
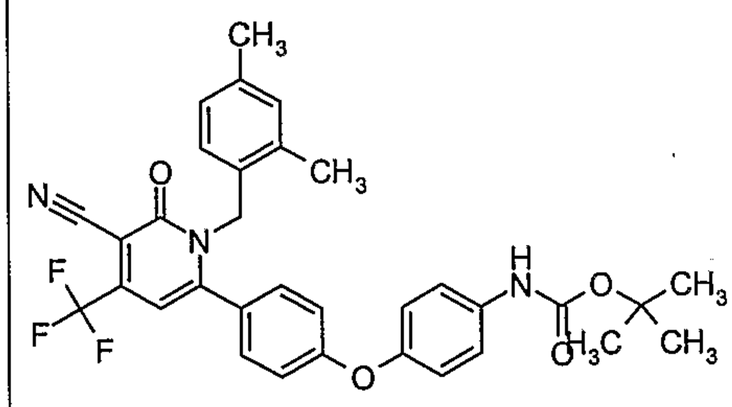
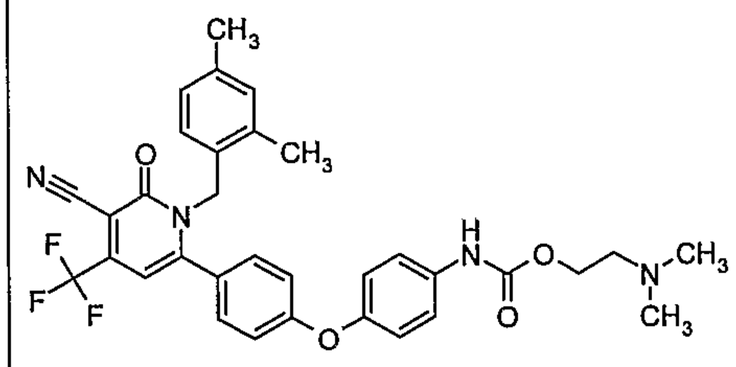
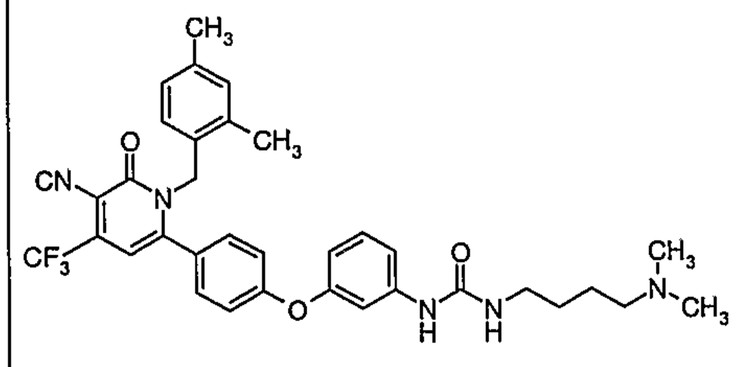
535		3-(dimethylamino)propyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
536		2-{[2-(dimethylamino)ethyl]oxy}ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
537		ethyl 6-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
538		ethyl 6-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
539		1-methylethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
540		ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

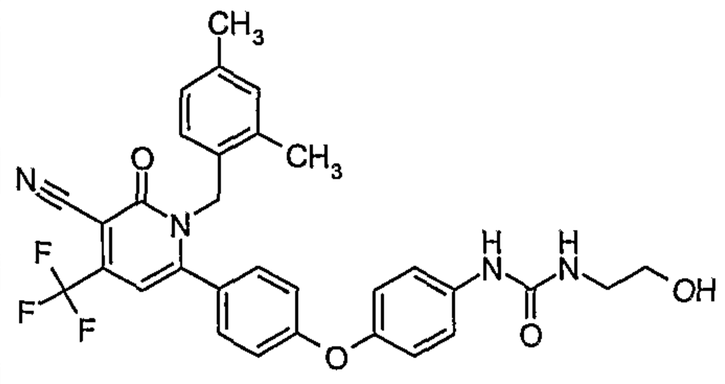
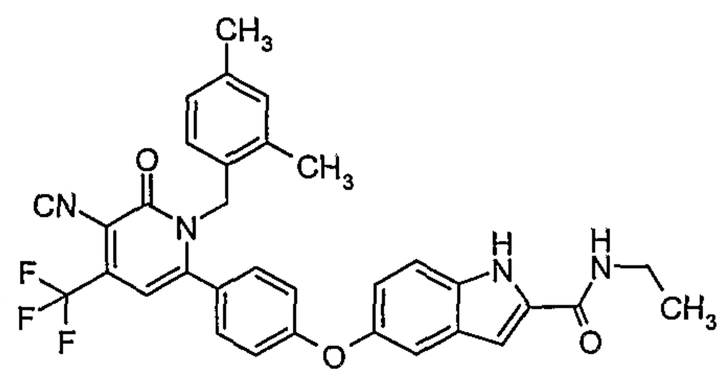
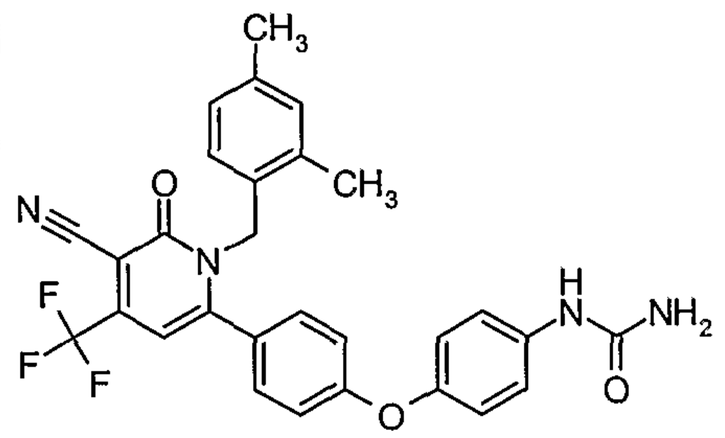
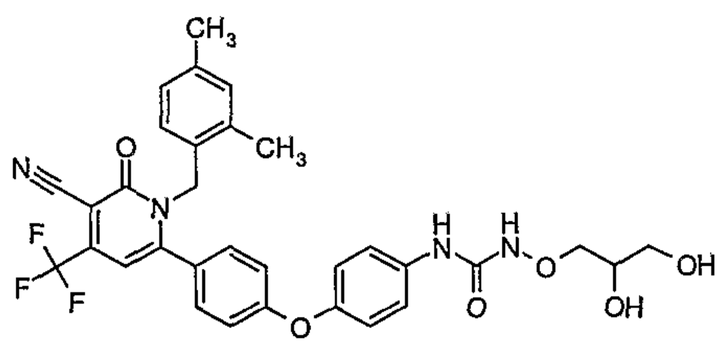
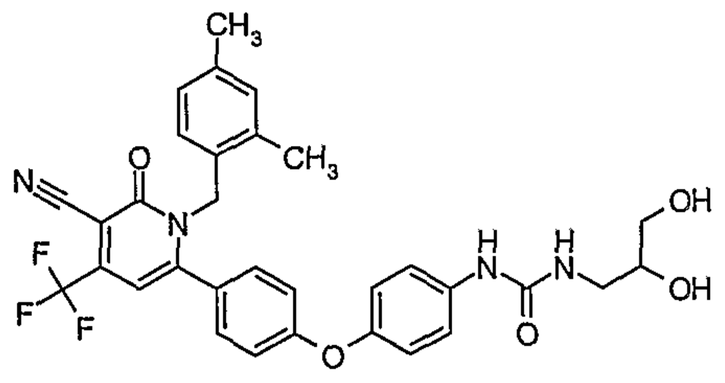
541		3-morpholin-4-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
542		3-(dimethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
543		1-methylpiperidin-4-yl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
544		3-piperazin-1-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
545		3-(diethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
546		ethyl 5-[(4-{5-cyano-1-[(2,4-dichlorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

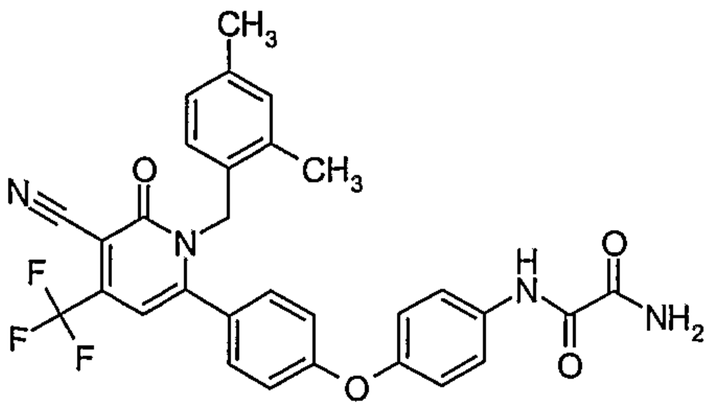
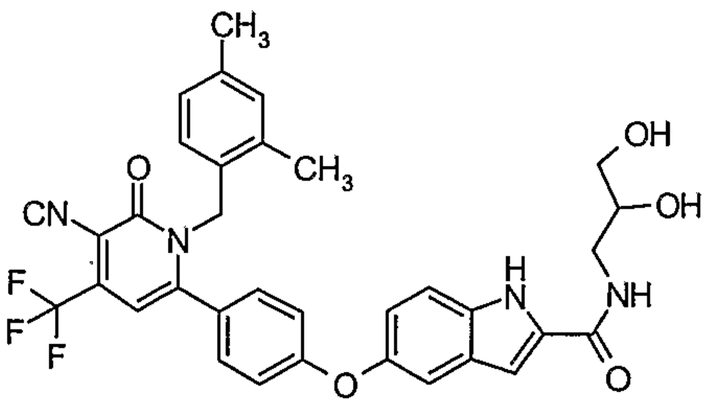
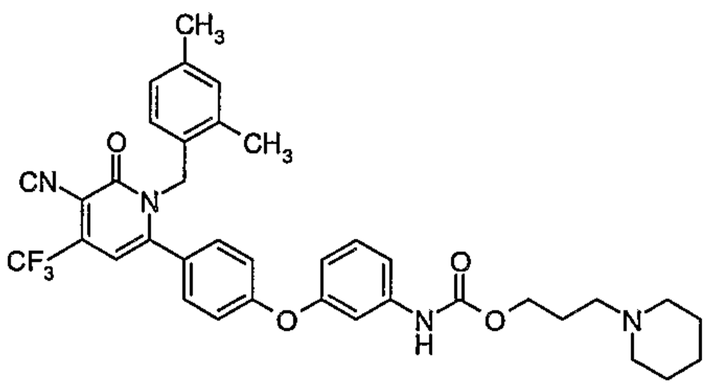
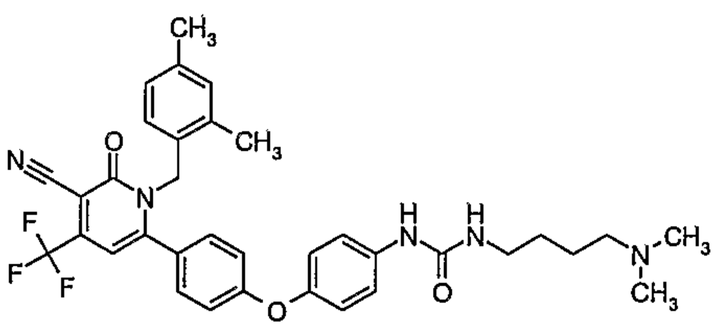
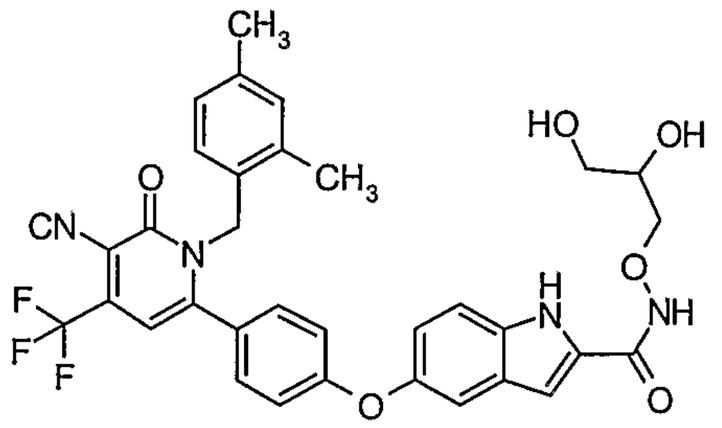
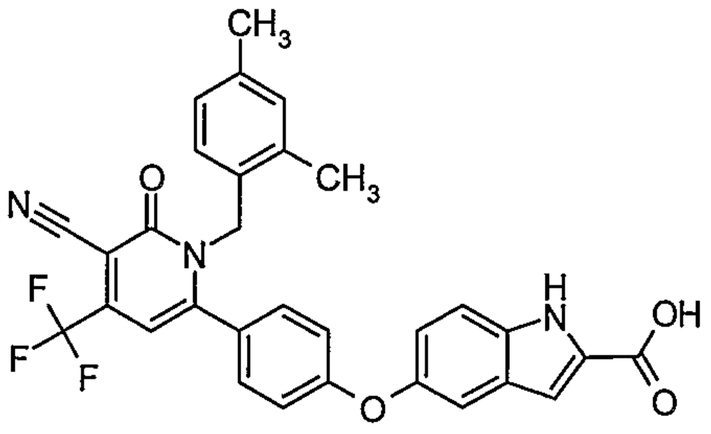
547		4-(dimethylamino)butyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
548		3-(dimethylamino)propyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
549		2-(dimethylamino)ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
550		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-propyl-1H-indole-2-carboxamide
551		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-*N,N-dimethyl-1H-indole-2-carboxamide*
552		2-[(2-hydroxyethyl)oxy]ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate

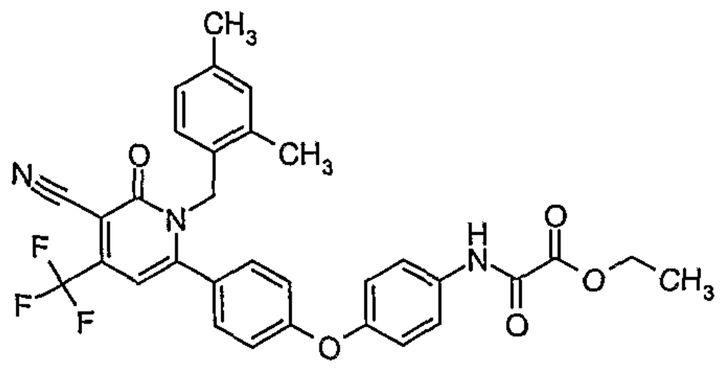
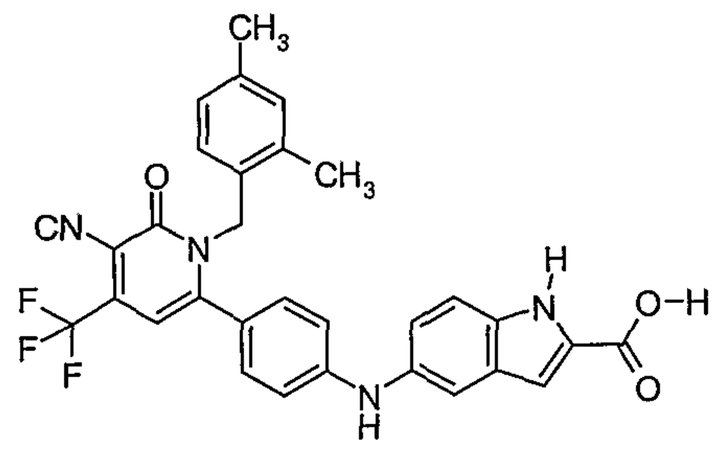
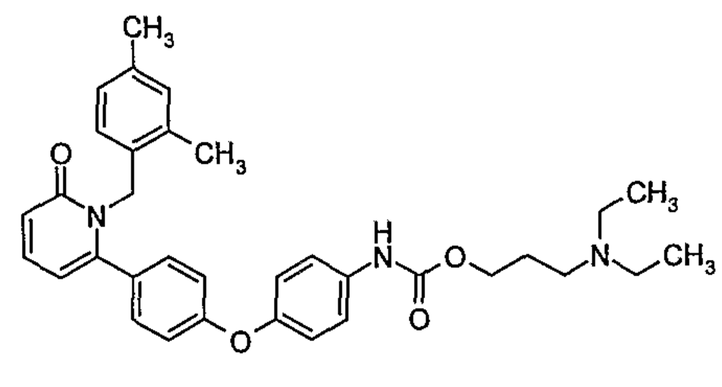
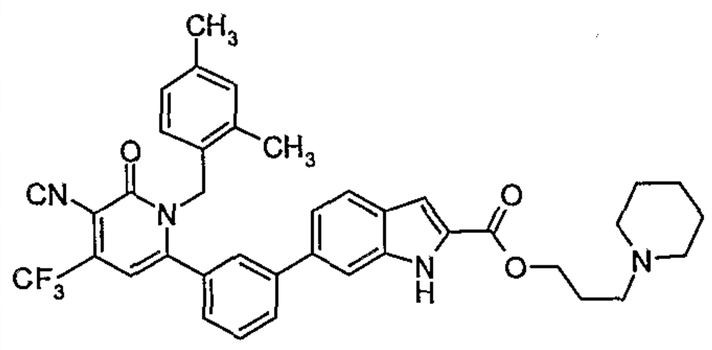
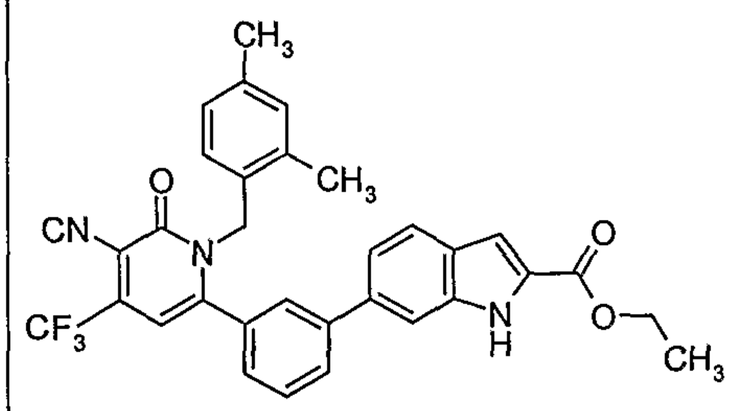
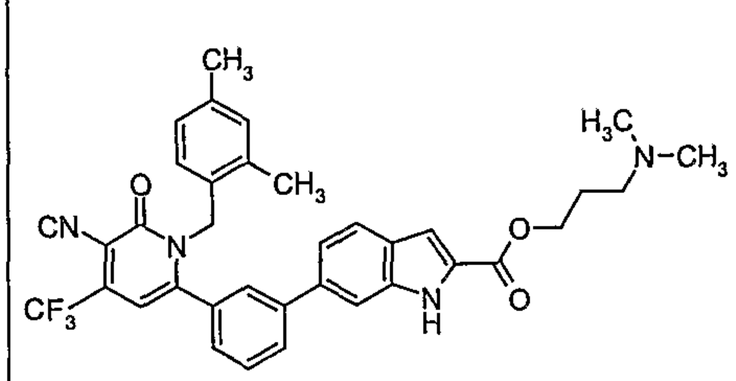
553		ethyl 5-({4-[5-cyano-1-{[2-methyl-4-(methyloxy)phenyl]methyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl]phenyl}oxy)-1H-indole-2-carboxylate
554		2,3-dihydroxypropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
555		methyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
556		ethyl 5-[(4-{5-cyano-1-[(2,6-dimethylpyridin-3-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
557		ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylate
558		3-(dimethylamino)propyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate

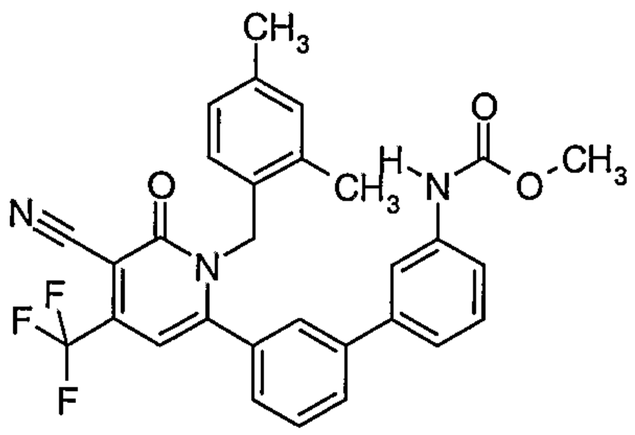
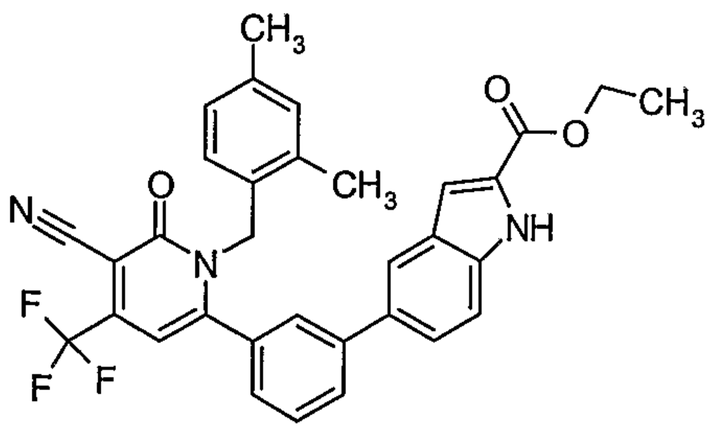
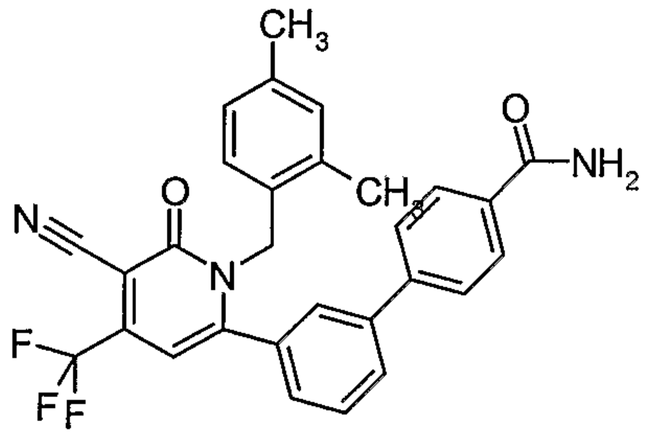
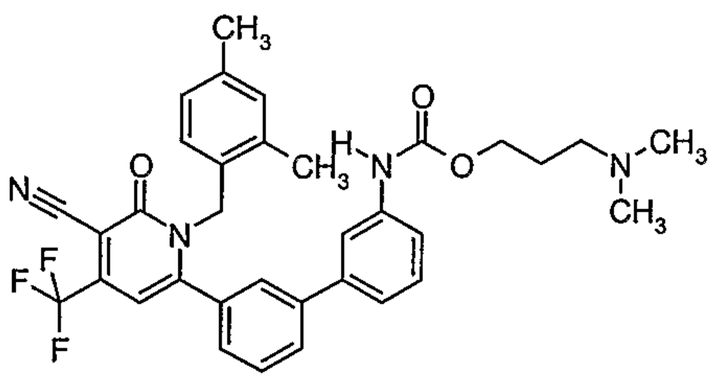
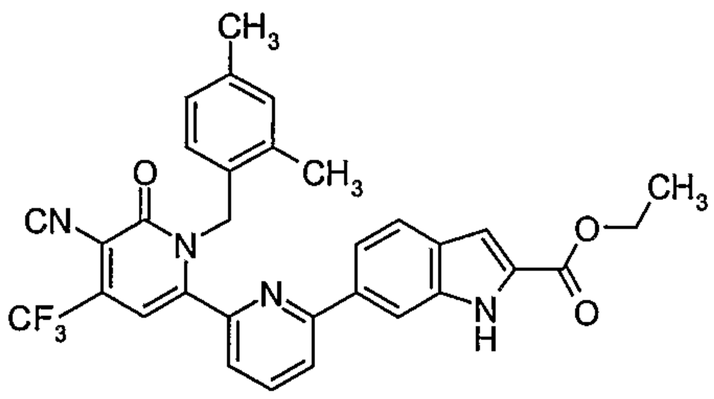
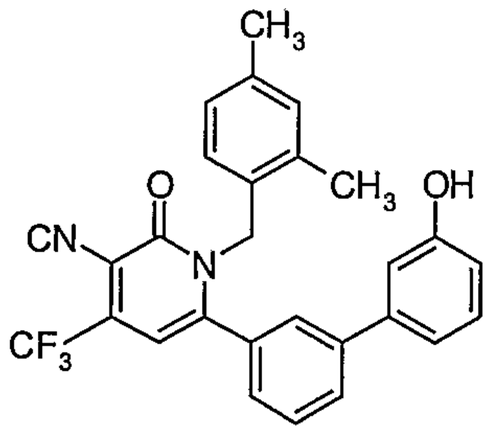
559		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(1-methylethyl)-1H-indole-2-carboxamide
560		2-{[2-(dimethylamino)ethyl]oxy}ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
561		3-morpholin-4-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
562		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-methylpropyl)-1H-indole-2-carboxamide
563		ethyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
564		6-[4-(1H-benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

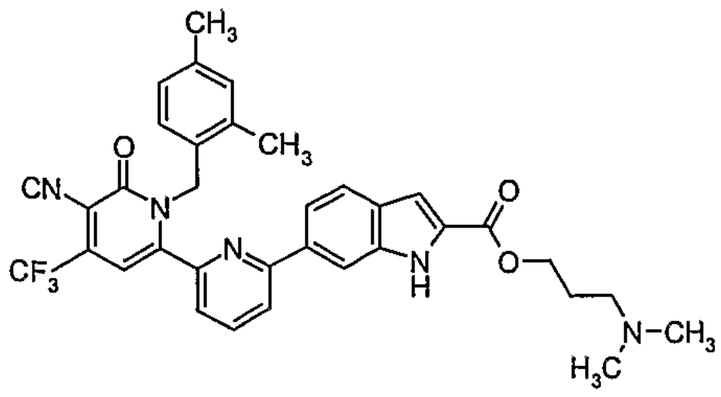
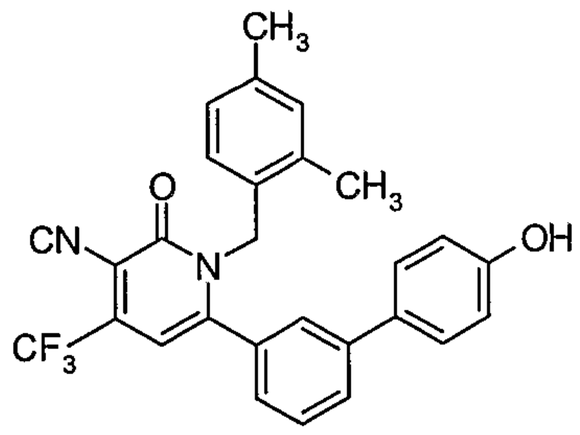
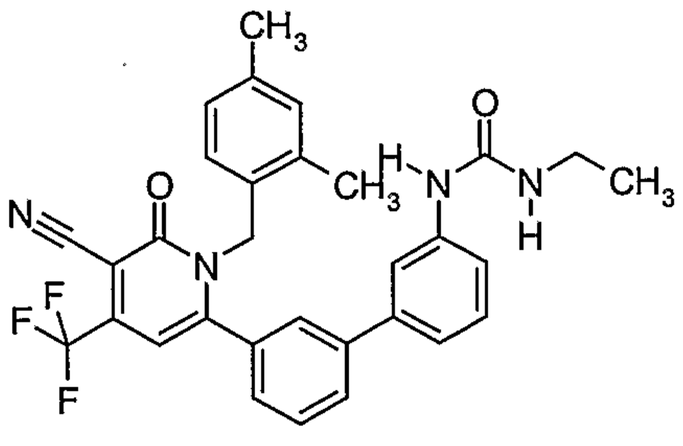
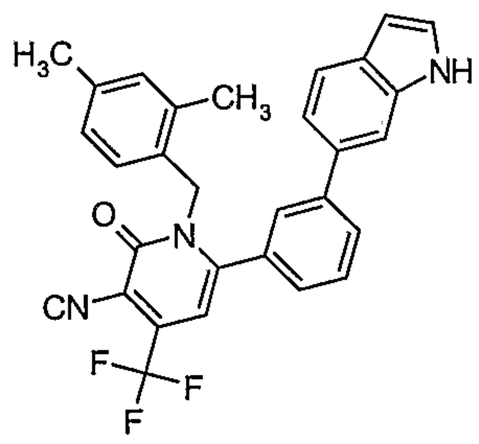
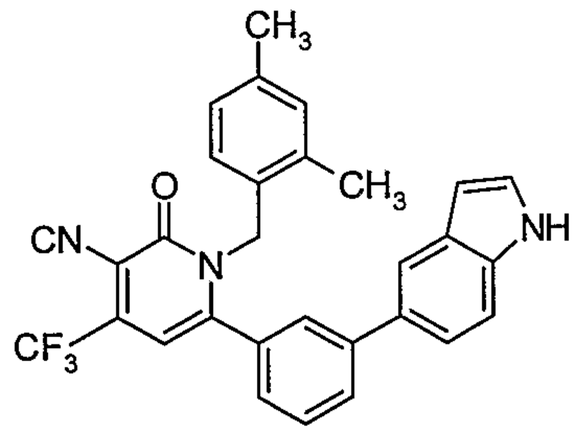
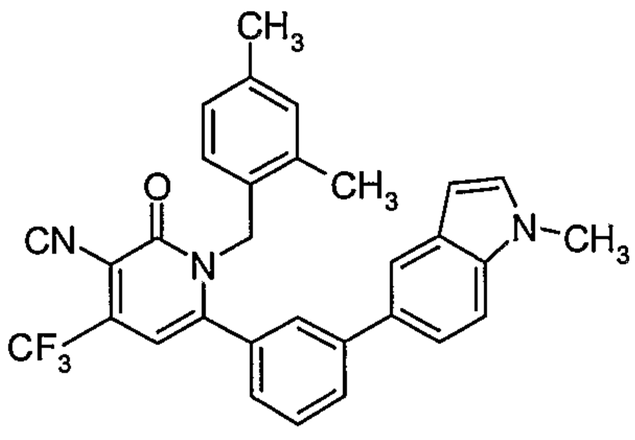
565		N-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}methanesulfonamide
566		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[3-(dimethylamino)propyl]-1H-indole-2-carboxamide
567		6-{4-[(4-aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
568		1,1-dimethylethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
569		2-(dimethylamino)ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
570		1-{3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea

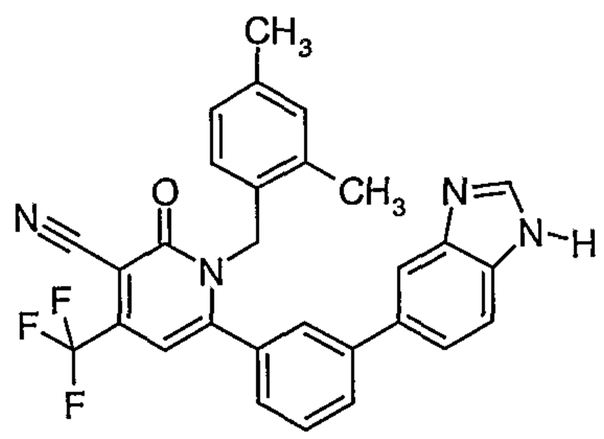
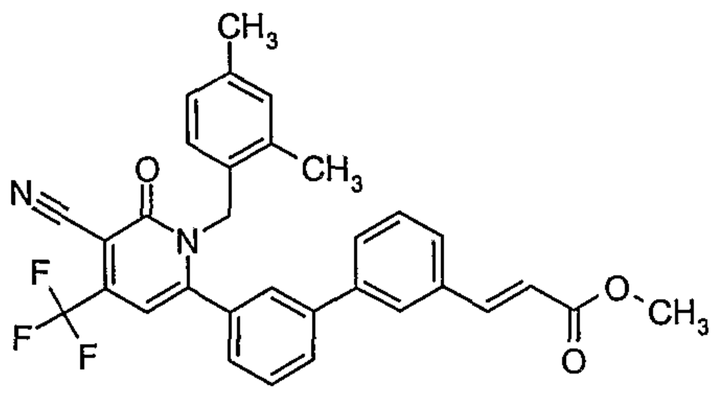
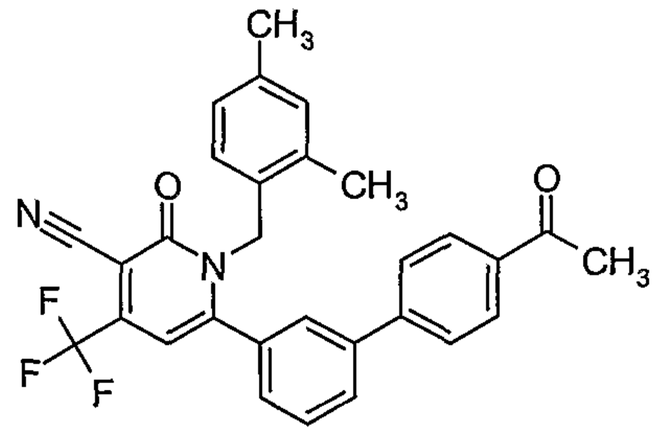
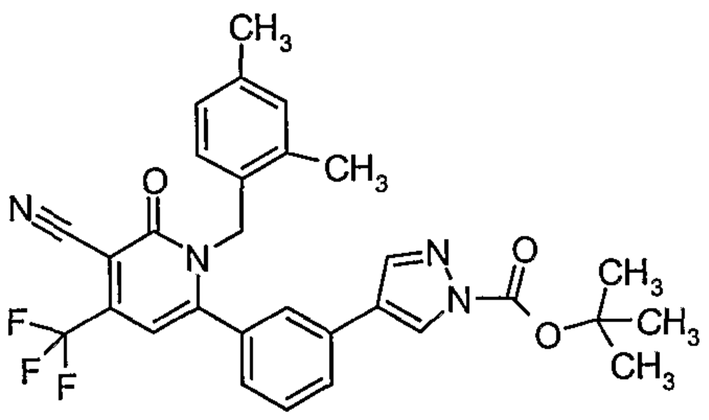
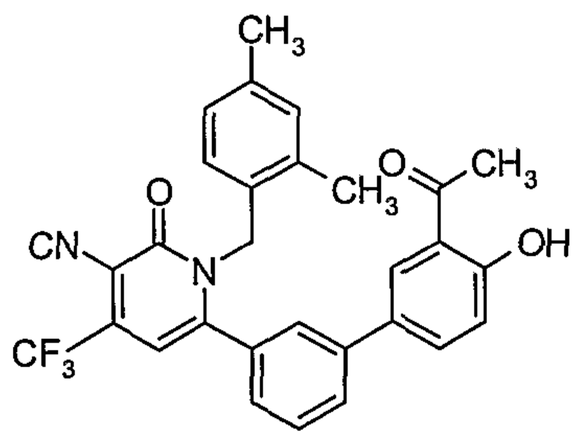
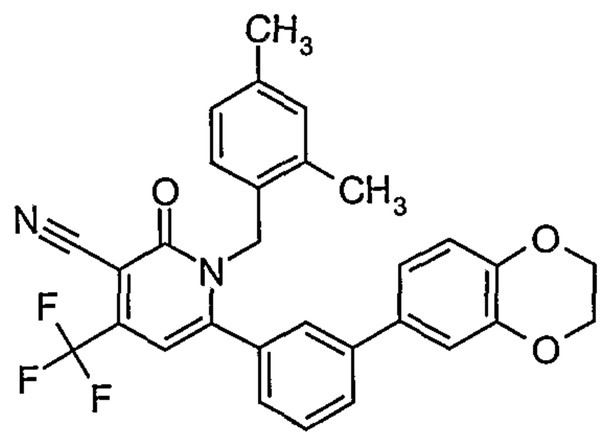
571		1-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2-hydroxyethyl)urea
572		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-ethyl-1H-indole-2-carboxamide
573		1-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}urea
574		1-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[(2,3-dihydroxypropyl)oxy]urea
575		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-hydroxyethyl)-1H-indole-2-carboxamide
576		1-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2,3-dihydroxypropyl)urea

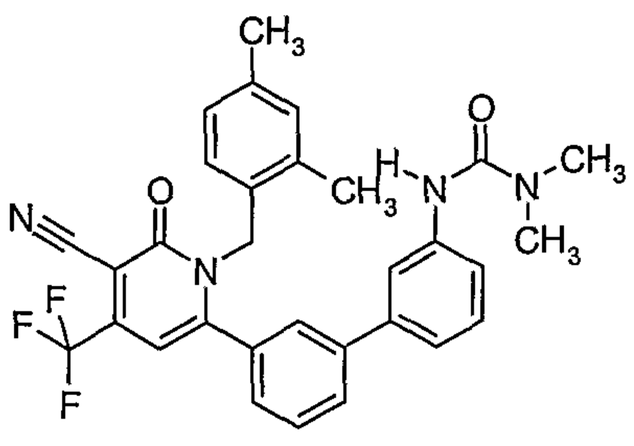
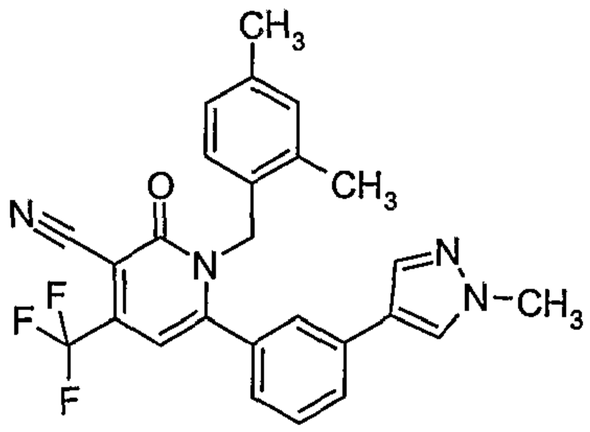
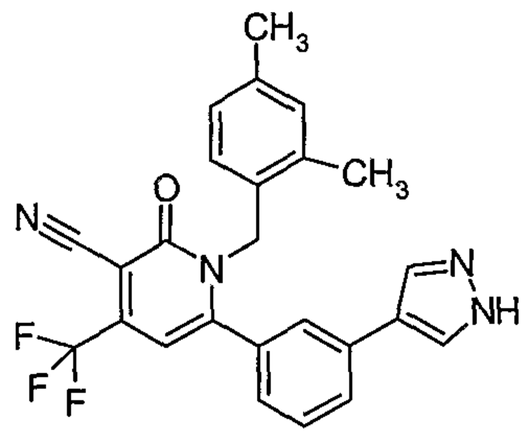
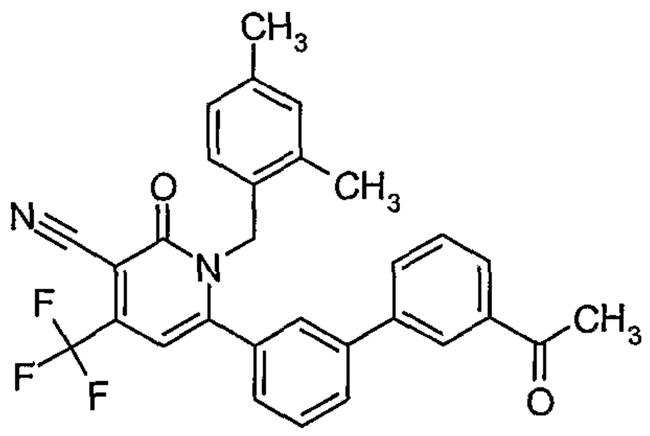
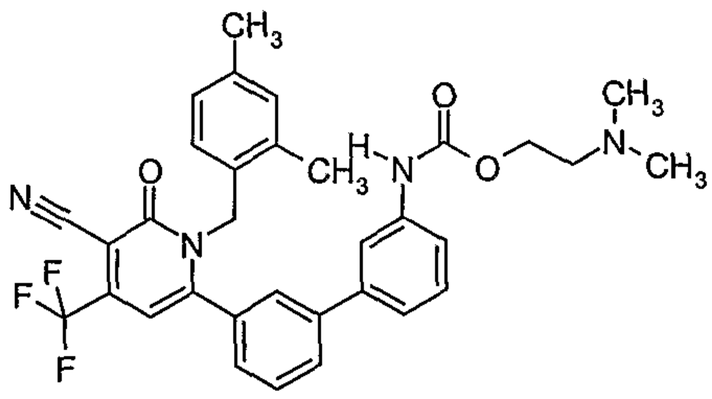
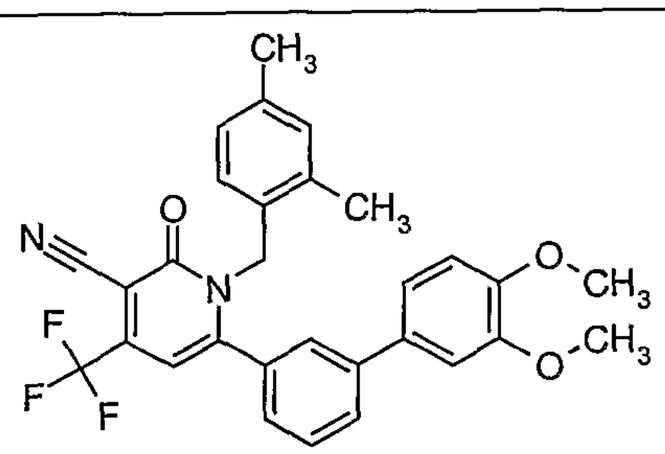
577		N-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}ethanediamide
578		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2,3-dihydroxypropyl)-1H-indole-2-carboxamide
579		3-piperidin-1-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
580		1-{4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea
581		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[(2,3-dihydroxypropyl)oxy]-1H-indole-2-carboxamide
582		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid

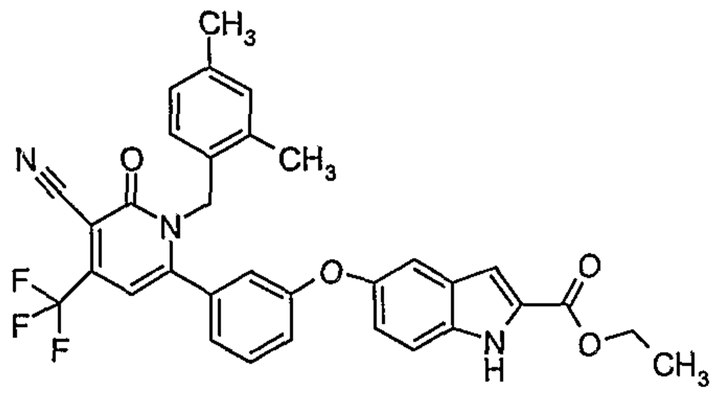
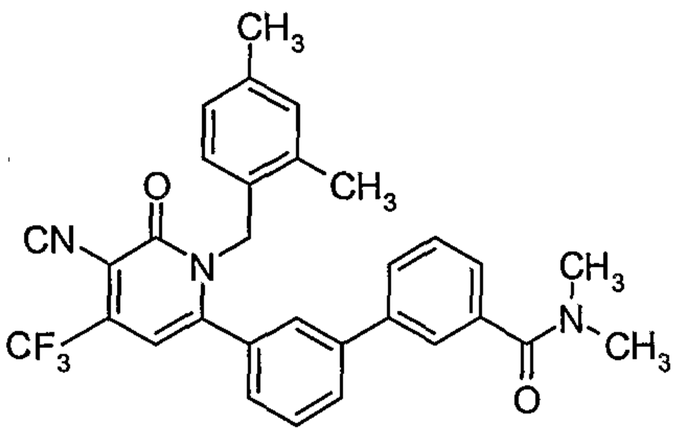
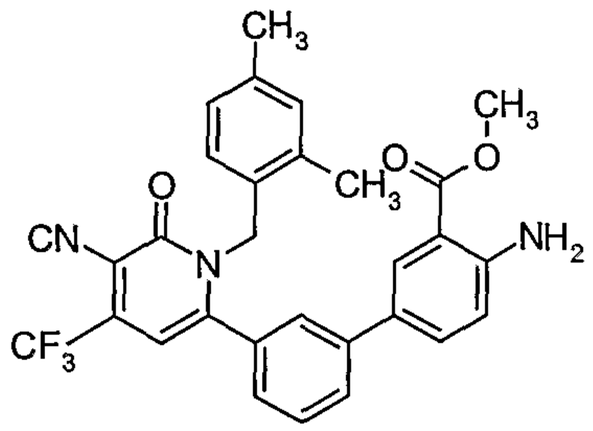
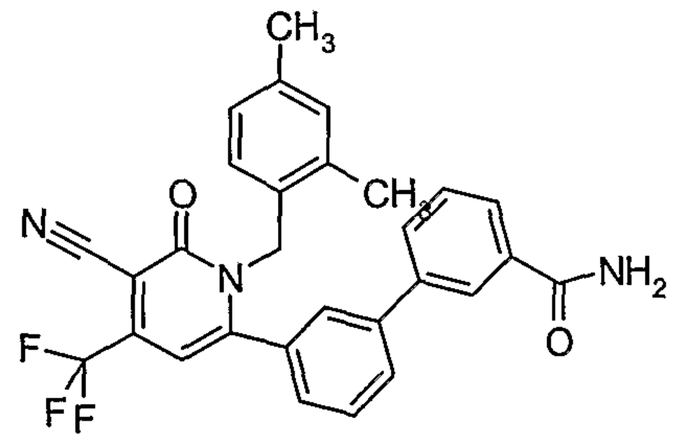
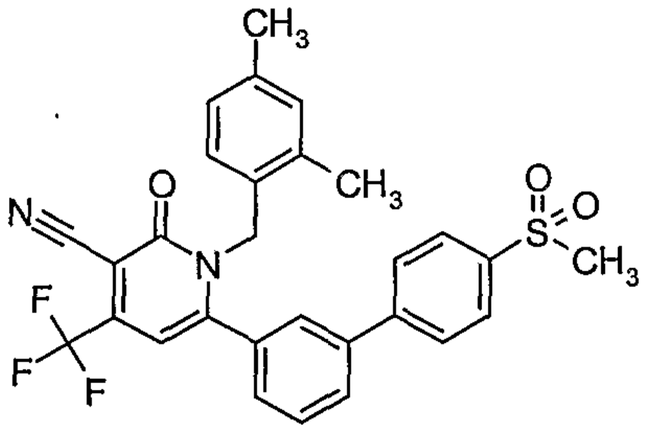
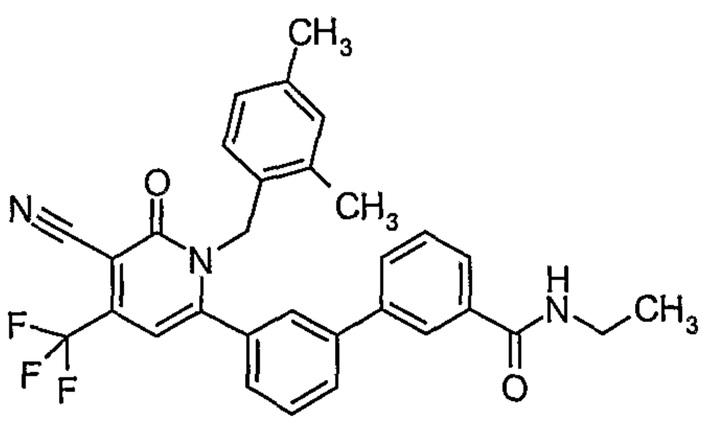
583		ethyl ({4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}amino)(oxo)acetate
584		5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylic acid
585		3-(diethylamino)propyl {4-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate
586		3-piperidin-1-ylpropyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate
587		ethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate
588		3-(dimethylamino)propyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate

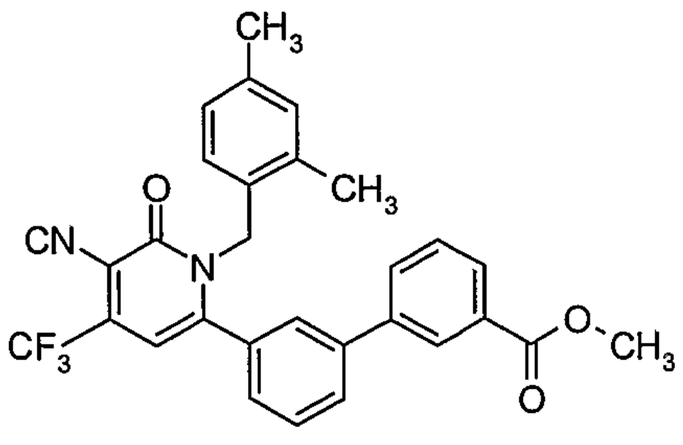
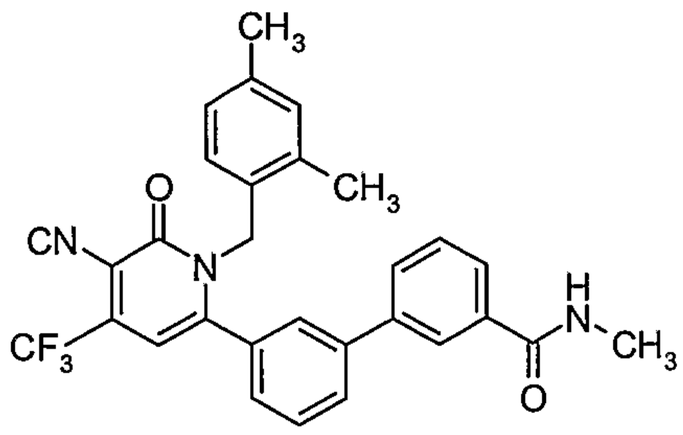
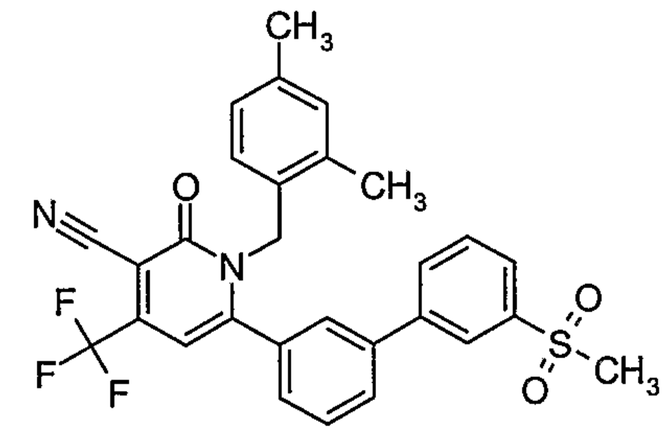
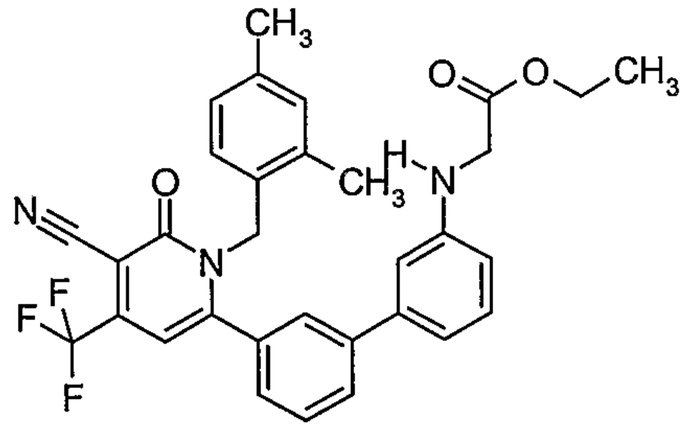
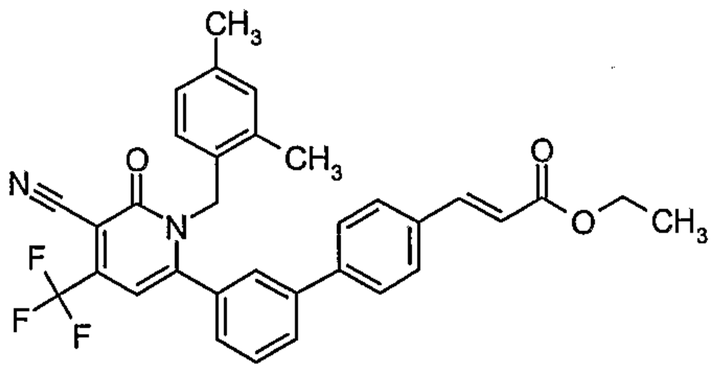
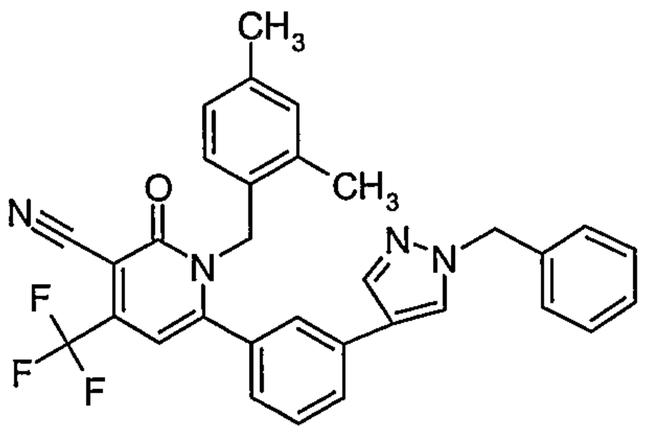
589		methyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate
590		ethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate
591		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-carboxamide
592		3-(dimethylamino)propyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate
593		ethyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate
594		1-[(2,4-dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

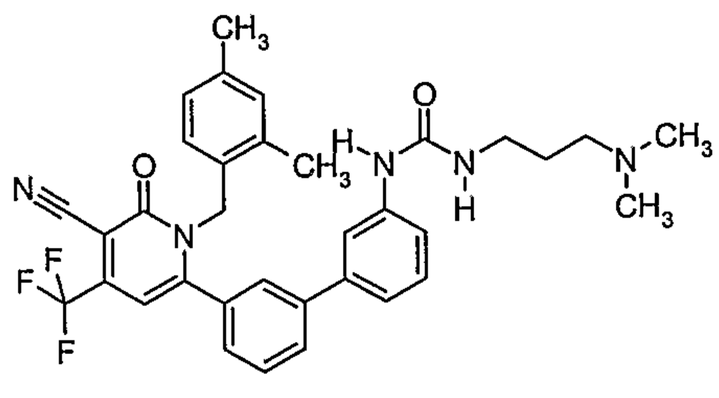
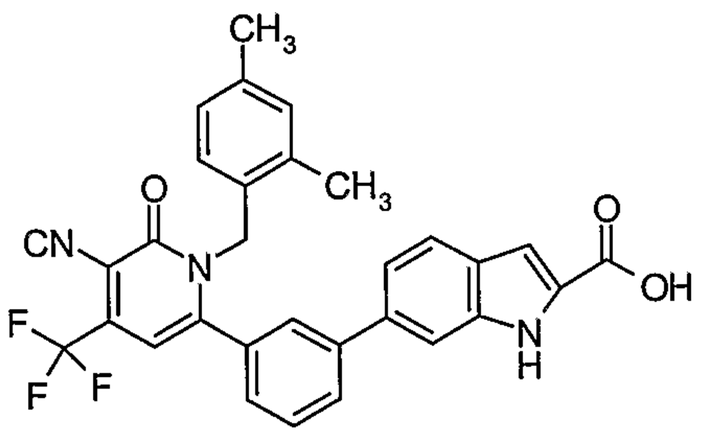
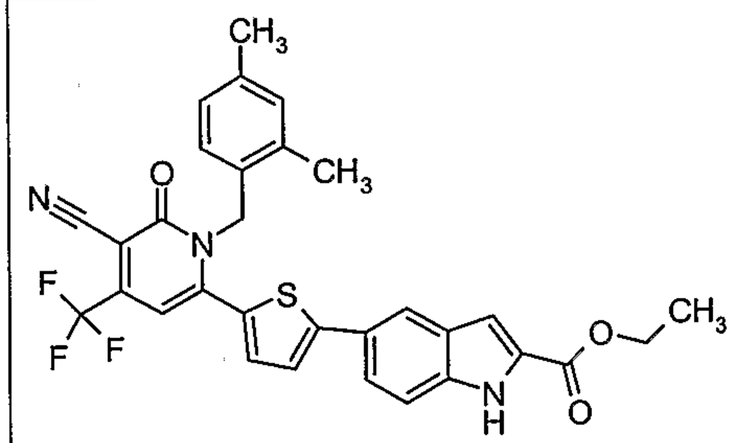
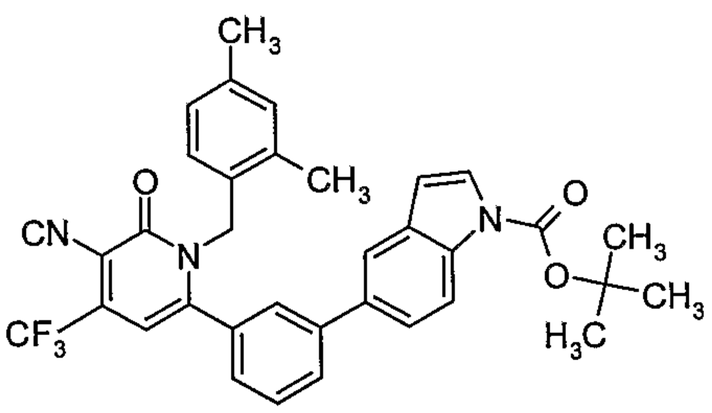
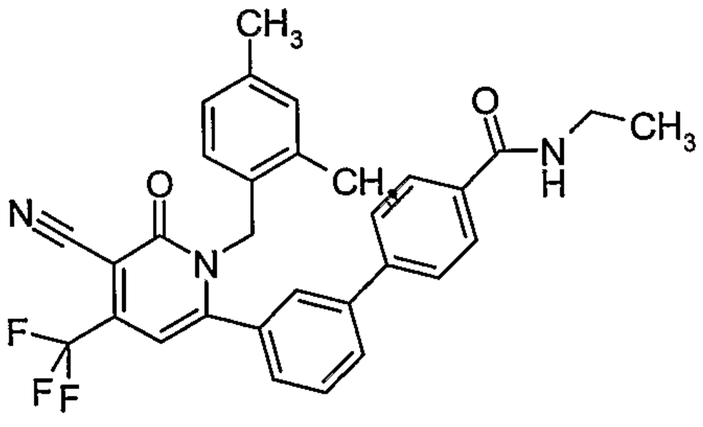
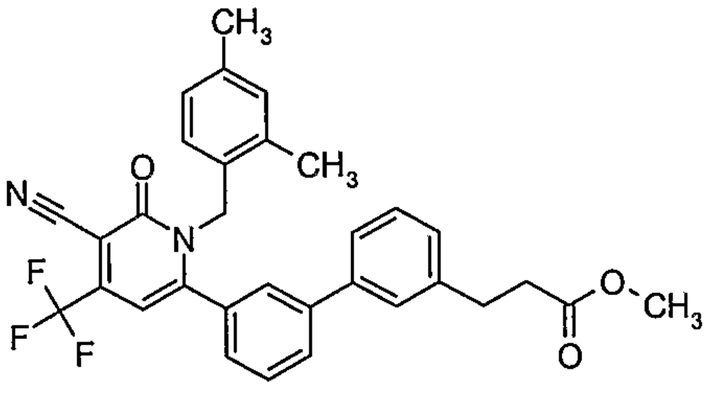
595		3-(dimethylamino)propyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate
596		1-[(2,4-dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
597		1-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-ethylurea
598		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
599		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
600		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methyl-1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

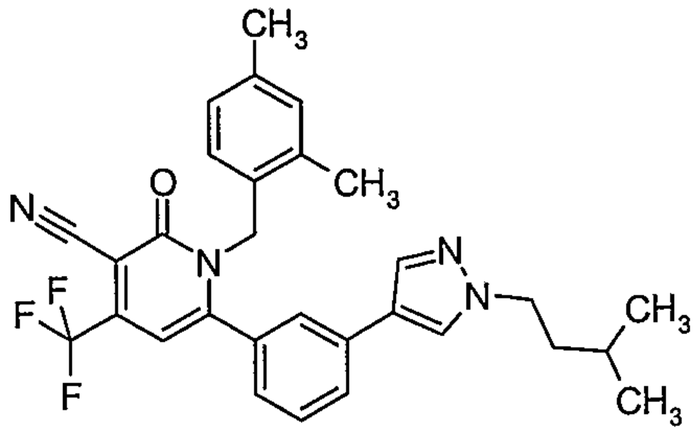
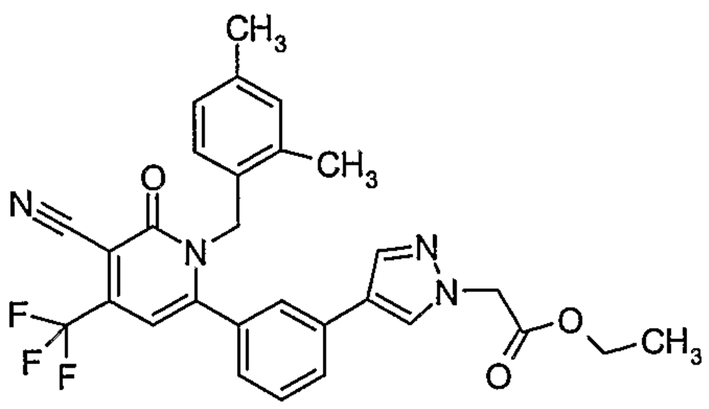
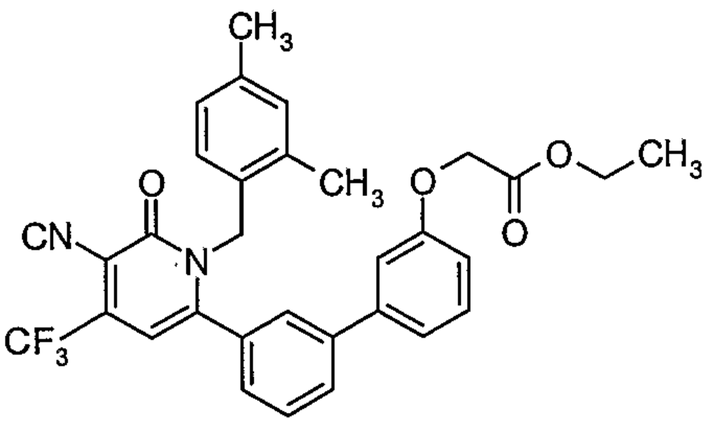
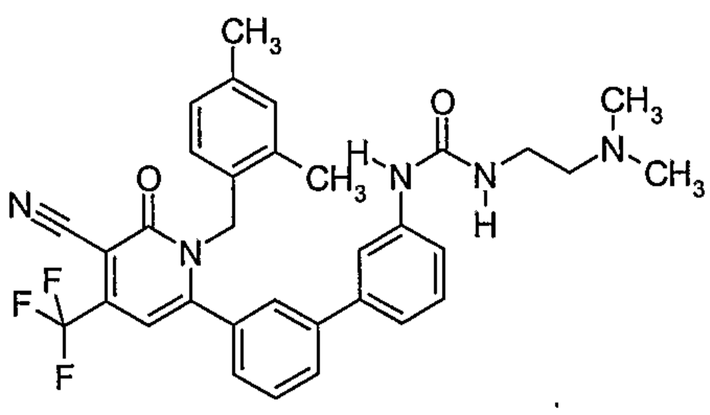
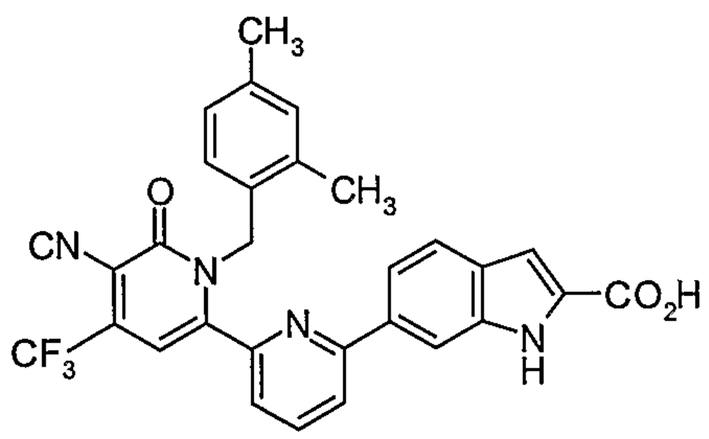
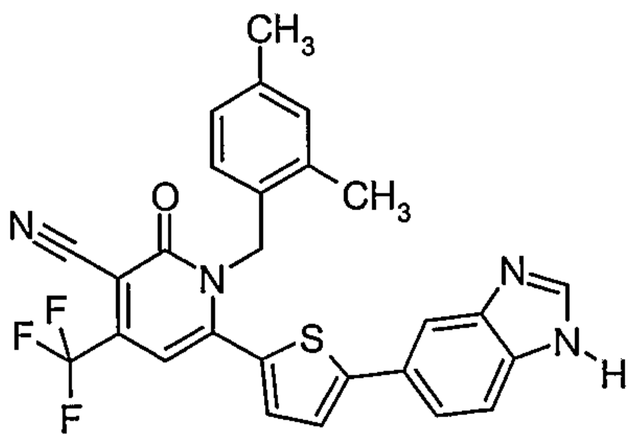
601		6-[3-(1H-benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
602		methyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate
603		6-(4'-acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
604		1,1-dimethylethyl 4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazole-1-carboxylate
605		6-(3'-acetyl-4'-hydroxybiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
606		6-[3-(2,3-dihydro-1,4-benzodioxin-6-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

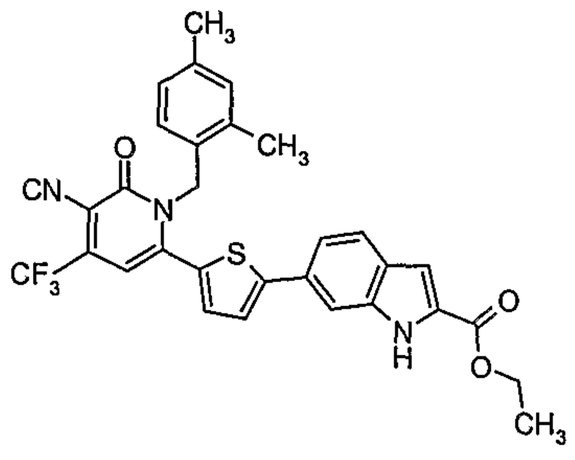
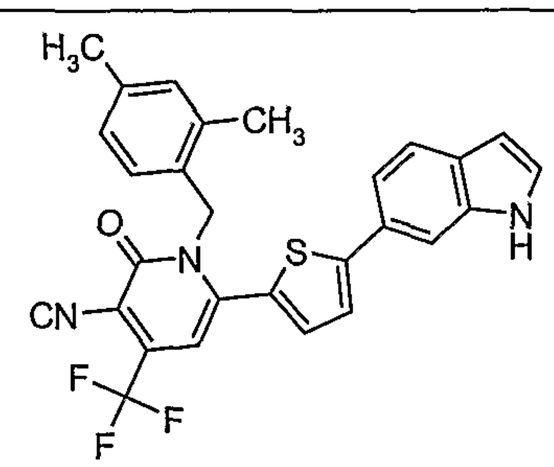
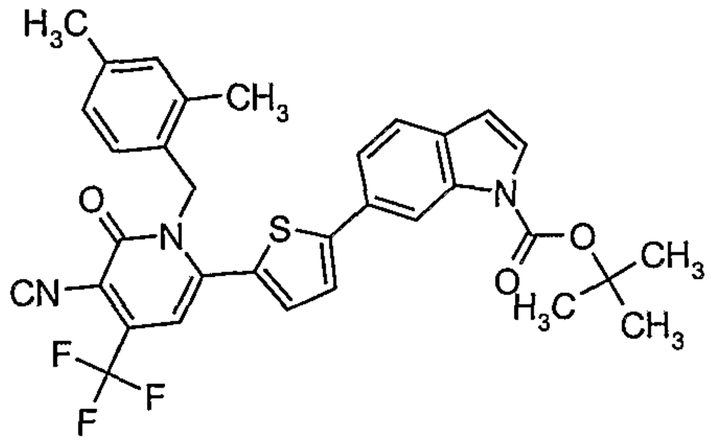
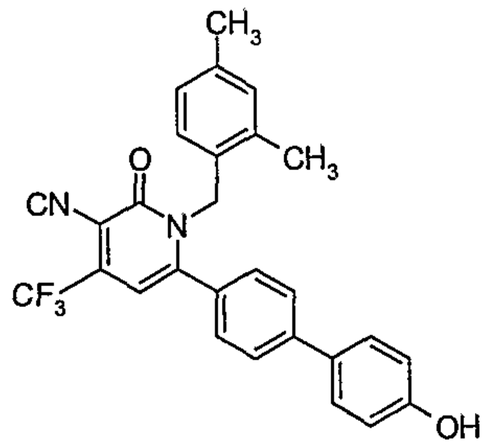
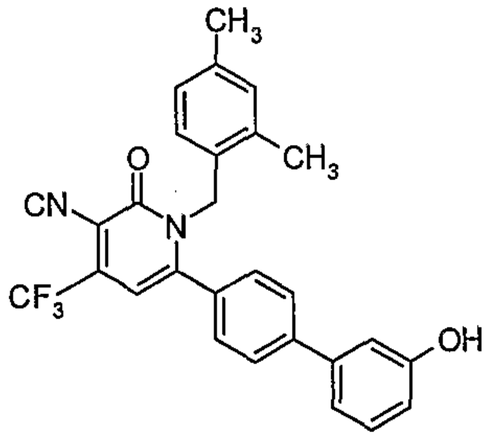
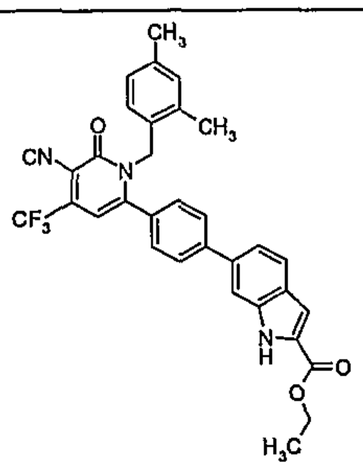
607		3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-1,1-dimethylurea
608		1-[(2,4-dimethylphenyl)methyl]-6-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
609		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-[3-(1H-pyrazol-4-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
610		6-(3'-acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
611		2-(dimethylamino)ethyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate
612		6-[3',4'-bis(methyloxy)biphenyl-3-yl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

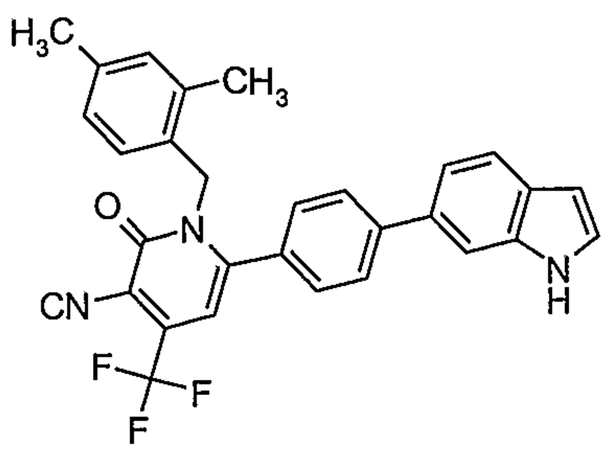
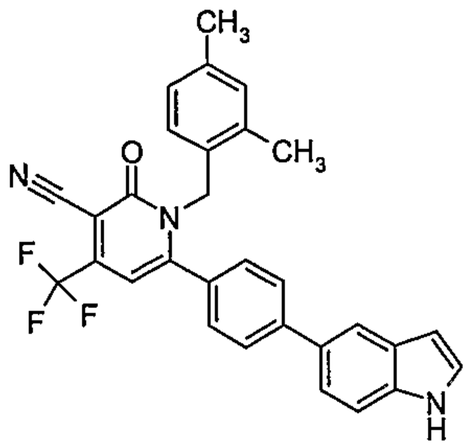
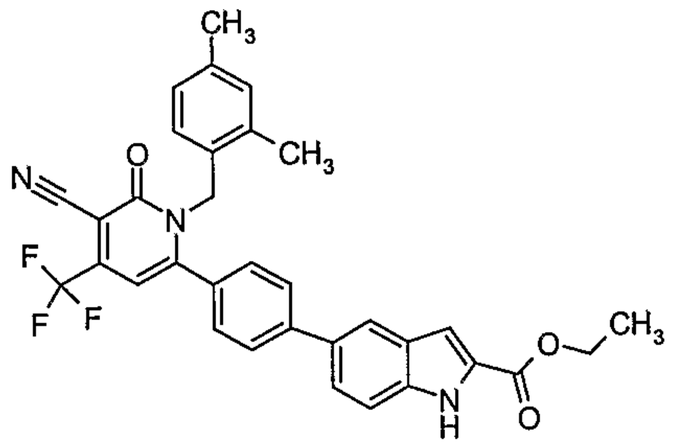
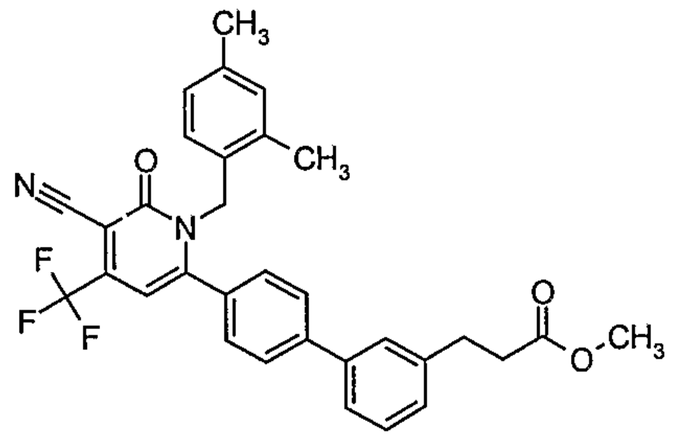
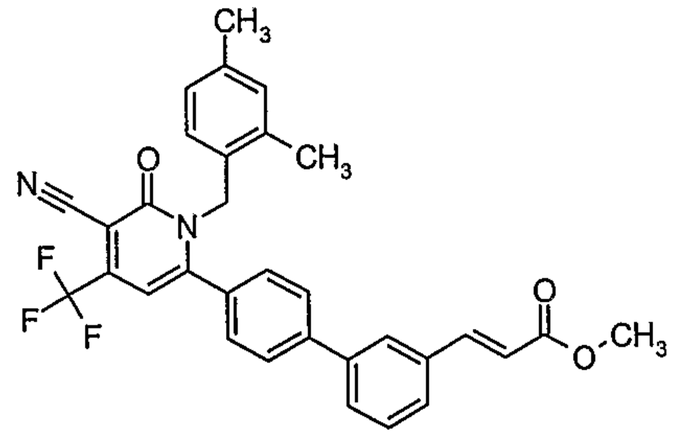
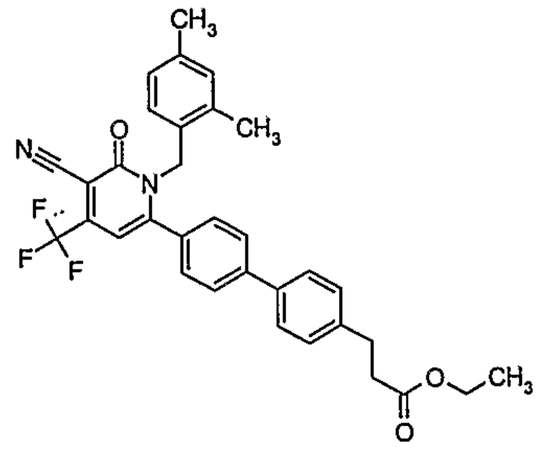
613		ethyl 5-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
614		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N,N-dimethylbiphenyl-3-carboxamide
615		methyl 4-amino-3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate
616		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxamide
617		1-[(2,4-dimethylphenyl)methyl]-6-[4'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
618		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-3-carboxamide

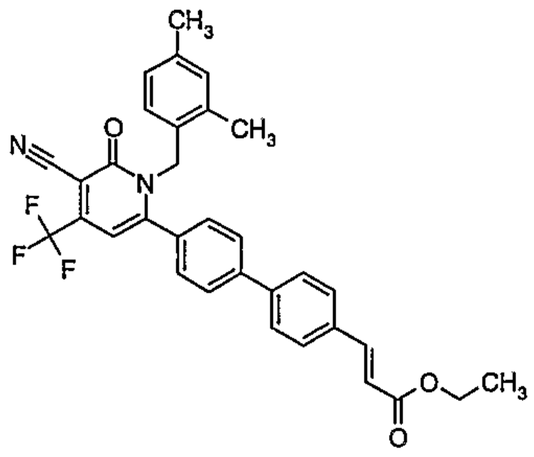
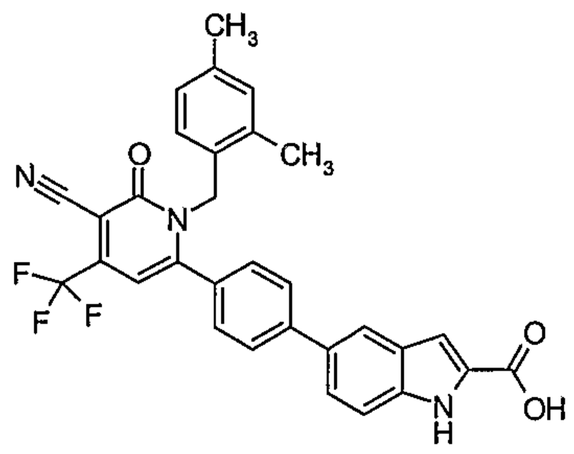
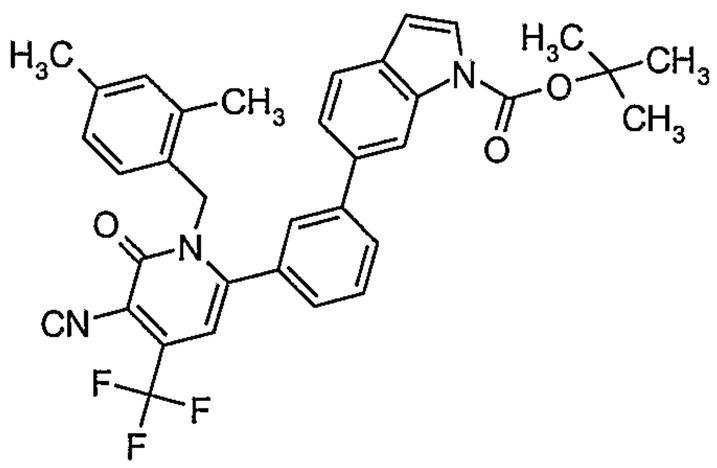
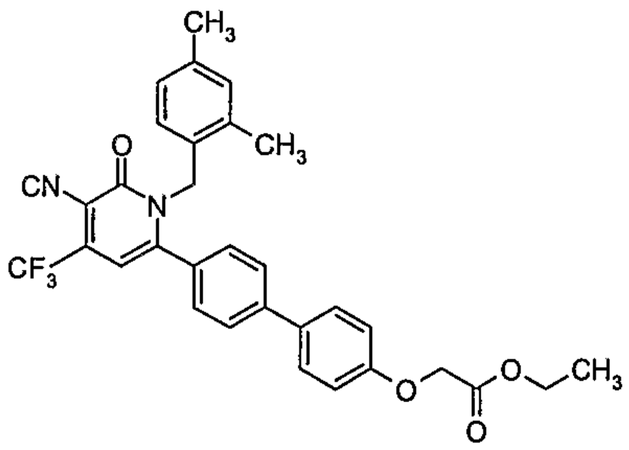
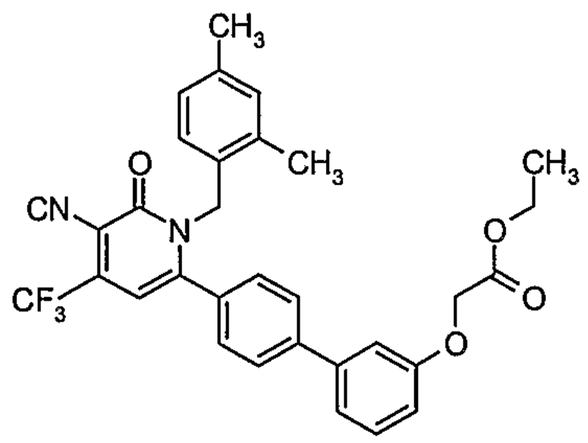
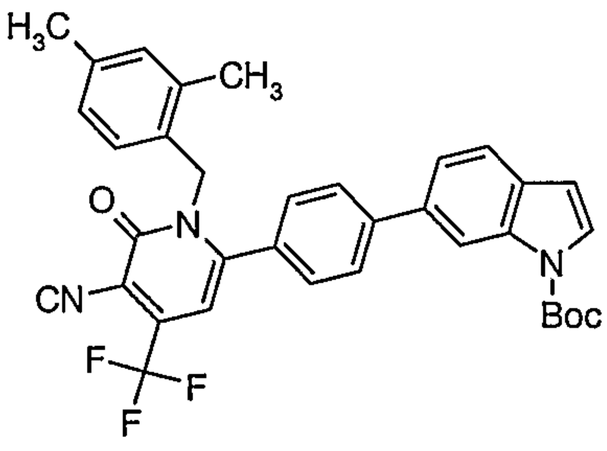
619		methyl 3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate
620		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-methylbiphenyl-3-carboxamide
621		1-[(2,4-dimethylphenyl)methyl]-6-[3'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
622		ethyl N-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)glycinate
623		ethyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate
624		1-[(2,4-dimethylphenyl)methyl]-2-oxo-6-{3-[1-(phenylmethyl)-1H-pyrazol-4-yl]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

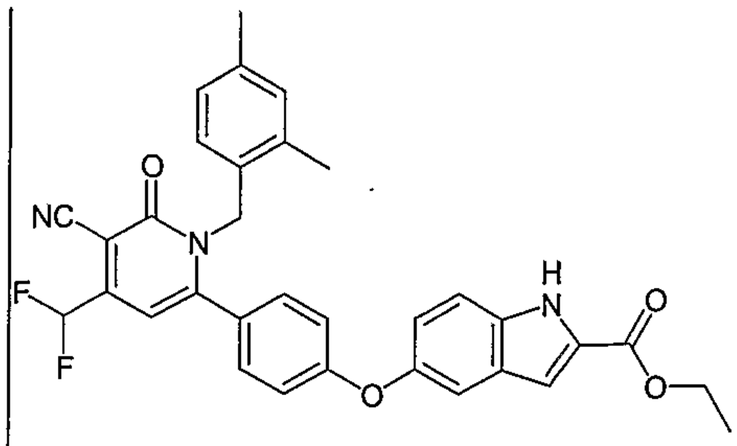
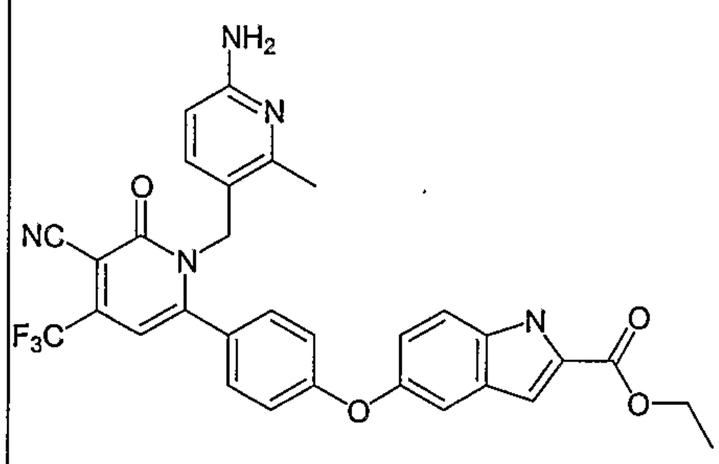
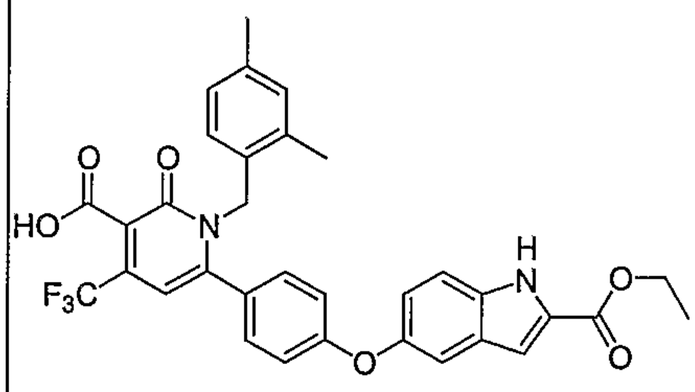
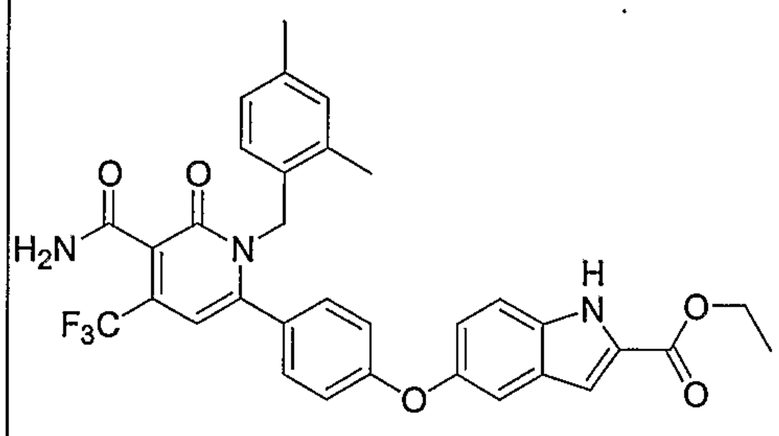
625		1-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[3-(dimethylamino)propyl]urea
626		6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid
627		ethyl 5-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate
628		1,1-dimethylethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate
629		3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-4-carboxamide
630		methyl 3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate

631		1-[(2,4-dimethylphenyl)methyl]-6-{3-[1-(3-methylbutyl)-1H-pyrazol-4-yl]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
632		ethyl [4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazol-1-yl]acetate
633		ethyl [(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate
634		1-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[2-(dimethylamino)ethyl]urea
635		6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid
636		6-[5-(1H-benzimidazol-5-yl)-2-thienyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

637		ethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate
638		1-[(2,4-dimethylphenyl)methyl]-6-[5-(1H-indol-6-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
639		1,1-dimethylethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-1-carboxylate
640		1-[(2,4-dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
641		1-[(2,4-dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
642		ethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate

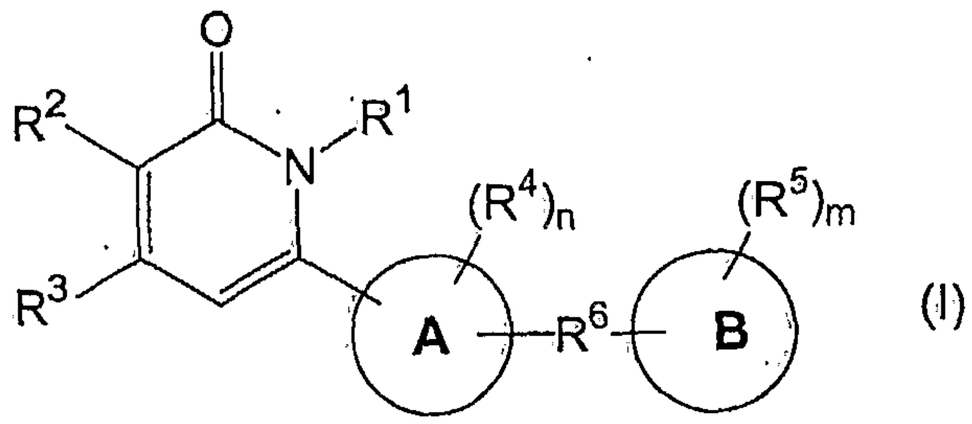
643		1-[(2,4-dimethylphenyl)methyl]-6-[4-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
644		1-[(2,4-dimethylphenyl)methyl]-6-[4-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile
645		ethyl 5-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate
646		methyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate
647		methyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate
648		ethyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)propanoate

649		ethyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate
650		5-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid
651		1,1-dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate
652		ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)oxy]acetate
653		ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate
654		1,1-dimethylethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate

655		Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(difluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate.
656		Ethyl 5-[(4-{5-cyano-1-[(2-amino-6-methylpyridin-5-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
657		Ethyl 5-[(4-{5-carboxy-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate
658		Ethyl 5-[(4-{5- carbamoyl-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate

WHAT IS CLAIMED IS:

1. A compound of formula (I):

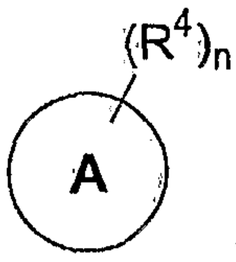


(I)

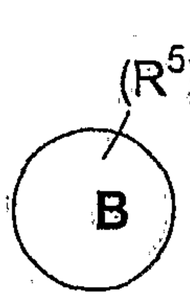
wherein:

n is 1 to 4;

m is 1 to 4;



is aryl or heteroaryl;



is aryl, heterocyclyl or heteroaryl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-C(O)OR^8$, $-R^7-N(R^8)_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^4 is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted

SUBSTITUTE SHEET (RULE 26)

heteroarylalkyl, -R^7-CN, -R^7-OR^8, -R^7-O-R^9-C(O)OR^8, -R^7-C(O)R^{11}, -R^7-C(O)OR^8, -R^7-C(O)OR^9-N(R^{11})$_2$, -R^7-C(O)N(R^8)OR^{11}, -R^7-C(O)OR^9-OR^9-N(R^{11})$_2$, -R^7-C(O)N(R^8)$_2$, -R^7-C(O)N(R^8)OR^8, -R^7-C(O)N(R^8)N(R^8)$_2$, -R^7-C(O)N(R^8)-R^9-C(O)OR^8, -R^7-C(O)N(R^8)-R^9-OR^{11}, -R^7-C(O)N(R^8)-R^9-N(R^{11})$_2$, -R^7-C(S)N(R^8)$_2$, -R^7-N(R^8)$_2$, -R^7-N(R^8)-R^9-C(O)OR^{10}, -R^7-N(R^8)C(O)R^8, -R^7-N(R^8)C(O)N(R^8)$_2$, -R^7-N(R^8)C(O)N(R^8)-OR^{11}, -R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}, -R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})$_2$, -R^7-N(R^8)C(O)OR^{10}, -R^7-N(R^8)C(O)OR^9-N(R^{11})$_2$, -R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})$_2$, -R^7-N(R^8)C(O)OR^9-OR^{11}, -R^7-N(R^8)C(O)C(O)N(R^{11})$_2$, -R^7-N(R^8)C(O)C(O)OR^{11}, -R^7-N(R^8)S(O)$_2$-R^8, -R^7-S(O)$_t$$R^8$ (where t is 0 to 2) and -R^7-S(O)$_2$N(R^8)$_2$;

R^6 is -OR^7-, -N(R^8)-, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted haloalkyl, optionally substituted haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

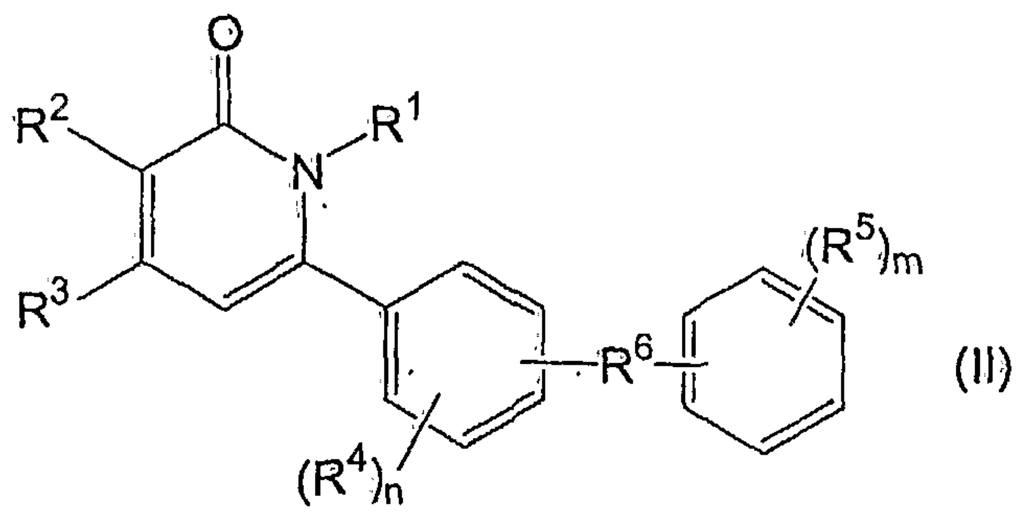
each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

2. The compound of Claim 1 having the following formula (II):



(II)

wherein:

n is 1 to 4;

m is 1 to 4;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano or $-R^7-N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl, haloalkyl, cyano, $-OR^8$, $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted haloalkyl, optionally substituted haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

3. The compound of Claim 2 wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl, or haloalkyl;

R^4 is hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, haloalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

SUBSTITUTE SHEET (RULE 26)

each R^8 is independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted haloalkyl, optionally substituted haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^9 is a straight or branched alkylene chain optionally substituted by aryl or heteroaryl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

4. The compound of Claim 3 wherein R^6 is $-OR^7-$.

5. The compound of Claim 4 wherein R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $NR^8C(O)OR^{10}$.

6. The compound of Claim 5 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl, ethyl, 1-hydroxy-1-methylethyl, fluoromethyl, difluoromethyl, pentafluoroethyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl or haloalkyl.

7. The compound of Claim 6 wherein each R^5 is independently selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, ethenyl or trifluoromethyl.

8. The compound of Claim 7 selected from the group consisting of the following:

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Dimethyl-benzyl)-6-[4-(3-isopropyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-tert-Butyl-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-fluoro-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,5-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,6-dimethyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(2-Chloro-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(2-trifluoromethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(3-trifluoromethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Bromo-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Benzyloxy-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3,5-Bis-trifluoromethyl-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Benzyloxy-phenyl)-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2-Chloro-4-fluoro-benzyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Benzyloxy-phenyl)-1-(2-chloro-4-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-4-pentafluoroethyl-6-(4-phenoxy-phenyl)-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-phenoxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-o-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,5-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2,4-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3,4-dimethyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-m-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(3-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(4-isopropyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-(3-isopropyl-4-p-tolyloxy-phenyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-tert-Butyl-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(4-vinyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-2-methyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-ethyl-2-methyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-4-methyl-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Dimethyl-benzyl)-6-[4-(2-ethyl-4-methyl-phenoxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4-Benzyloxy-3-chloro-phenyl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[3-Chloro-4-(4-fluoro-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[4-(4-fluoro-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

9. The compound of Claim 5 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$ and $R^7-O-R^9-C(O)OR^8$

each R^7 is independently selected from a direct bond or methylene chain;

each R^8 is independently selected from hydrogen, alkyl, aryl and aralkyl; and

R^9 is a methylene chain.

10. The compound of Claim 9 selected from the group consisting of the following:

6-[4-(4-Dimethylamino-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methoxy-phenoxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Cyano-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Benzyloxy-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Benzyloxy-phenoxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-[4-(4-Cyano-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Dimethylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4-hexyloxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-{4-[4-(3-methyl-butoxy)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hexyloxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-{4-[3-(3-methyl-butoxy)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-phenoxy)-acetic acid benzyl ester;

(4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-phenoxy)-acetic acid benzyl ester;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(4-phenylamino-phenoxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Benzylamino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3-hydroxymethyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Benzyloxy-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Benzyloxy-phenoxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-hydroxy-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

6-[4-(3-Cyano-4-trifluoromethyl-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

SUBSTITUTE SHEET (RULE 26)

11. The compound of Claim 5 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of heteroaryl, $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl or heterocyclyl optionally substituted with hydroxy;

R^9 is a straight or branched alkylene chain (optionally substituted by phenyl or imidazolyl); and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

12. The compound of Claim 11 wherein:

m is 1 or 2;

each R^5 is independently selected from $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$ or $-R^7-C(O)N(R^8)N(R^8)_2$;

each R^7 is independently selected from a direct bond or methylene;

each R^8 is independently selected from hydrogen, methyl, ethyl, 1,1-dimethylethyl, benzyl, 2-phenylethyl, cyclohexyl or piperidinyl optionally substituted by hydroxy; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

13. The compound of Claim 12 selected from the group consisting of the following:

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-methyl-phenoxy}-benzoic acid methyl ester;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-methyl-phenoxy}-benzoic acid methyl ester;

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methyl-benzamide;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-{4-[3-(piperidine-1-carbonyl)-phenoxy]-phenyl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-{4-[3-(3-hydroxy-piperidine-1-carbonyl)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

N-Benzyl-3-{4-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzamide;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid N'-phenyl-hydrazide;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-cyclopentyl-benzamide;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methoxy-N-methyl-benzamide;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-((S)-1-phenyl-ethyl)-benzamide;

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide;

3-Benzyloxy-5-{4-[5-cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoic acid methyl ester;

3-Benzyloxy-5-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide;

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-5-hydroxy-N,N-dimethyl-benzamide;

2-Benzyloxy-5-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-benzamide;

5-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-2-hydroxy-N,N-dimethyl-benzamide;

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N-methyl-benzamide;

SUBSTITUTE SHEET (RULE 26)

N-tert-Butyl-3-{4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzamide; and

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(piperidine-1-carbonyl)-phenoxy]-phenyl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

14. The compound of Claim 5 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of heteroaryl, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen alkyl, haloalkyl, aryl, aralkyl, aralkenyl, cycloalkyl or heterocyclyl; and

R^9 is a straight or branched alkylene chain (optionally substituted by phenyl or imidazolyl).

15. The compound of Claim 14 wherein:

n is 1;

m is 1;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen or chloro;

R^5 is $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$;

R^7 is a direct bond;

each R^8 is independently hydrogen or alkyl; and

R^9 is a straight or branched alkylene chain optionally substituted by phenyl or imidazolyl.

16. The compound of Claim 15 selected from the group consisting of the following:

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-propionic acid methyl ester;

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-propionic acid methyl ester;

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-methyl-butyric acid methyl ester;

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-methyl-butyric acid methyl ester;

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-4-methyl-pentanoic acid methyl ester;

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-4-methyl-pentanoic acid methyl ester;

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-phenyl-propionic acid methyl ester;

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-phenyl-propionic acid methyl ester;

(*S*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester;

(*R*)-2-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-3-(1H-imidazol-4-yl)-propionic acid methyl ester;

(*S*)-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-phenyl-acetic acid methyl ester; and

(*R*)-(3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-benzoylamino)-phenyl-acetic acid methyl ester.

17. The compound of Claim 14 wherein:

n is 1;

m is 1;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of phthalimidyl, $-R^7-C(S)N(R^8)_2$ and $-R^7-S(O)_tR^8$ (where t is 0 or 2);

each R^7 is a direct bond; and

each R^8 is independently selected from hydrogen or alkyl.

SUBSTITUTE SHEET (RULE 26)

18. The compound of Claim 17 selected from the group consisting of the following:

1-(2,4-Dimethyl-benzyl)-6-[4-(4-methylsulfanyl-phenoxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-{4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenoxy]-phenyl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-thiobenzamide; and

6-[3-Chloro-4-(4-methanesulfonyl-phenoxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

19. The compound of Claim 4 wherein R^1 is optionally substituted heteroarylalkyl.

20. The compound of Claim 19 wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted thiazol-5-ylmethyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen, methyl, 1-methylethyl or chloro;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl or haloalkyl.

21. The compound of Claim 20, *i.e.*, namely 1-(2,5-Diethyl-thiazol-4-ylmethyl)-2-oxo-6-(4-phenoxy-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

22. The compound of Claim 3 wherein:

R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$ or $-N(R^8)_2$;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl or heterocyclyl;

each R^9 is a straight or branched alkylene chain optionally substituted by aryl or heteroaryl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

23. The compound of Claim 22 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of alkyl, trifluoromethyl, $-R^7-OR^8$ and $R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

R^7 is a direct bond;

R^8 is hydrogen or alkyl; and

R^9 is a straight or branched alkylene chain.

24. The compound of Claim 23 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-ethylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-(4'-ethanesulfonyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-methylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5'-methylsulfanyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-methylsulfanyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5'-methylsulfanyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-3'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-methanesulfonyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3'-methanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-ethoxy-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5'-(propane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5'-(Butane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-3-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5'-phenylmethanesulfinyl-3'-trifluoromethyl-biphenyl-3-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(5'-Cyclopropylmethanesulfinyl-3'-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5'-(propane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5'-(Butane-1-sulfinyl)-3'-trifluoromethyl-biphenyl-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5'-phenylmethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-(5'-Cyclopropylmethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5'-ethanesulfinyl-3'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfinyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[3'-(Butane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-3-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[3'-(Butane-1-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3'-phenylmethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3'-phenylmethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3'-Cyclopropylmethanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3'-Cyclopropylmethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-trifluoromethyl-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(propane-2-sulfonyl)-5'-trifluoromethyl-biphenyl-4-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5'-isopropyl-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5'-ethyl-3'-methanesulfonyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3'-ethanesulfonyl-5'-isopropyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-(3'-methanesulfonyl-5'-trifluoromethyl-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

25. The compound of Claim 22 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of alkyl, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ or $-R^7-C(O)N(R^8)_2$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently hydrogen, alkyl, aryl or aralkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, pyrrolidinyl or piperidinyl.

26. The compound of Claim 25 selected from the group consisting of the following:

6-(3'-Acetyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(4'-Acetyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid amide;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid amide;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid dimethylamide;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid dimethylamide;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3'-(pyrrolidine-1-carbonyl)-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4'-(piperidine-1-carbonyl)-biphenyl-3-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-carboxylic acid ethylamide;

SUBSTITUTE SHEET (RULE 26)

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid methylamide;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid phenylamide;

3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-carboxylic acid benzylamide;

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-yl}-acetic acid;

{4'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-3-yl}-acetic acid;

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid;

{4'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid;

{3-Chloro-3'-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid methyl ester; and

{3-Chloro-3'-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-biphenyl-4-yl}-acetic acid.

27. The compound of Claim 22 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, haloalkyl or $-R^7-OR^8$;

R^6 is a direct bond, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

R^7 is a direct bond; and

R^8 is hydrogen or alkyl.

28. The compound of Claim 27 selected from the group consisting of the following:

6-(3',5'-Bis-trifluoromethyl-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3',5'-Bis-trifluoromethyl-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3'-Chloro-4'-ethoxy-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3',4'-dimethoxy-biphenyl-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(3'-Chloro-4'-ethoxy-biphenyl-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-phenylethynyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenylethynyl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[3-((E)-styryl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-((E)-styryl)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

29. The compound of Claim 22 wherein:

n is 1;

m is 1 or 2;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of nitro, $-R^7-N(R^8)_2$, $-R^7-OR^8$ or $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen or alkyl; and

R^{10} is alkyl.

30. The compound of Claim 29 selected from the group consisting of the following:

6-(3'-Amino-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(4'-ethoxy-3'-nitro-biphenyl-3-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-(3'-Amino-4'-ethoxy-biphenyl-3-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

{3'-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-4-ethoxy-biphenyl-3-yl}-carbamic acid tert-butyl ester.

31. The compound of Claim 2 wherein:

n is 1 or 2;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted

SUBSTITUTE SHEET (RULE 26)

cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

32. The compound of Claim 31 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, or $R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl; and

R^9 is selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain.

33. The compound of Claim 32 selected from the group consisting of the following compounds:

1-[(2,4-Dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-3-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

6-(4'-Acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

6-(3'-Acetyl-4'-hydroxybiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-(3'-Acetylbiphenyl-3-yl)-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

6-[3',4'-Bis(methyloxy)biphenyl-3-yl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[4'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[3'-(methylsulfonyl)biphenyl-3-yl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

Ethyl [(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate;

1-[(2,4-Dimethylphenyl)methyl]-6-(4'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-(3'-hydroxybiphenyl-4-yl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

Ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)oxy]acetate; and

Ethyl [(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)oxy]acetate.

34. The compound of Claim 31 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo or haloalkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)_2$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$ and $-R^7-C(O)N(R^8)_2$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl,

SUBSTITUTE SHEET (RULE 26)

optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

R^9 is selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{11} is hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

35. The compound of Claim 34 selected from the group consisting of the following compounds:

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-carboxamide;

Methyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate;

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N,N-dimethylbiphenyl-3-carboxamide;

Methyl 4-amino-3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate;

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxamide;

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-3-carboxamide;

Methyl 3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-carboxylate;

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-methylbiphenyl-3-carboxamide;

Ethyl (2E)-3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate;

3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-N-ethylbiphenyl-4-carboxamide;

Methyl 3-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate;

Methyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)propanoate;

SUBSTITUTE SHEET (RULE 26)

Methyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)prop-2-enoate;

Ethyl 3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)propanoate; and

Ethyl (2E)-3-(4'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-4-yl)prop-2-enoate.

36. The compound of Claim 31 wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, and $-R^7-N(R^8)S(O)_2-R^8$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

37. The compound of Claim 36 selected from the group consisting of the followng compounds:

1,1-Dimethylethyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

6-{4-[(3-Aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

6-[4-(4-Amino-phenoxy)-phenyl]-1-(2,4-dimethyl-benzyl)-1H-pyridin-2-one;

6-(3'-Amino-biphenyl-3-yl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

3-Morpholin-4-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

3-Piperazin-1-ylpropyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

4-(Dimethylamino)butyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

2-[(2-Hydroxyethyl)oxy]ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

Methyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

3-(Dimethylamino)propyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

2-{[2-(Dimethylamino)ethyl]oxy}ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

3-Morpholin-4-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

N-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}methanesulfonamide;

6-{4-[(4-Aminophenyl)oxy]phenyl}-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1,1-Dimethylethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

2-(Dimethylamino)ethyl {4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

SUBSTITUTE SHEET (RULE 26)

N-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}ethanediamide;

3-Piperidin-1-ylpropyl {3-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

Ethyl ({4-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}amino)(oxo)acetate;

3-(Diethylamino)propyl {4-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}carbamate;

Methyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate;

3-(Dimethylamino)propyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate;

2-(Dimethylamino)ethyl (3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)carbamate; and

Ethyl N-(3'-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)glycinate.

38. The compound of Claim 31 wherein:

n is 1;

m is 1 or 2;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen or cyano;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, and $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$;

R^6 is a direct bond or -O-;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

SUBSTITUTE SHEET (RULE 26)

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

39. The compound of Claim 38 selected from the group consisting of the following compounds:

1-{3-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea;

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2-hydroxyethyl)urea;

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}urea;

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[(2,3-dihydroxypropyl)oxy]urea;

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-(2,3-dihydroxypropyl)urea;

1-{4-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]phenyl}-3-[4-(dimethylamino)butyl]urea;

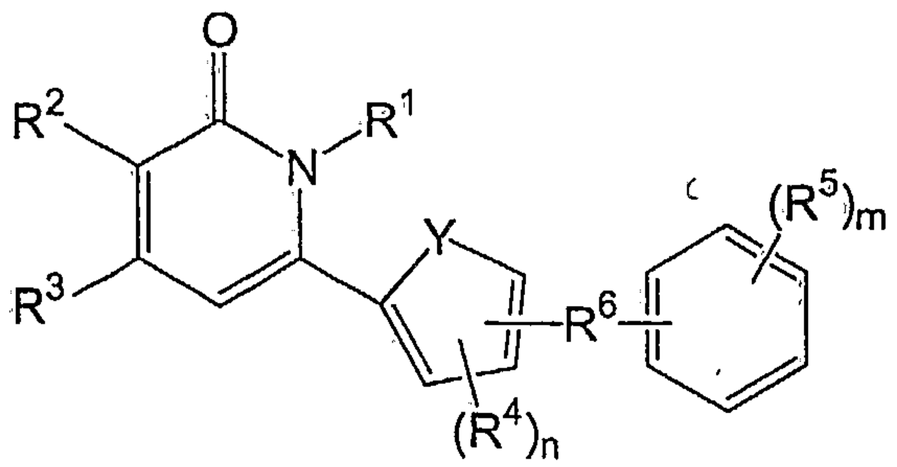
1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-ethylurea;

3-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-1,1-dimethylurea;

1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[3-(dimethylamino)propyl]urea; and

1-(3'-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}biphenyl-3-yl)-3-[2-(dimethylamino)ethyl]urea.

40. The compound of Claim 1 having the following formula (III):



(III)

wherein:

Y is oxygen or sulfur;

n is 1 or 2;

m is 1 to 4;

R^1 is optionally substituted aralkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, aryl, aralkyl, aralkenyl, haloalkyl, haloalkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^{10} is independently selected from alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

41. The compound of Claim 40 wherein:

Y is oxygen or sulfur;

n is 1 or 2;

m is 1 to 4;

R^1 is aralkyl or heteroarylalkyl each independently optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$ or $-N(R^8)_2$;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

each R^9 is a straight or branched alkylene chain;

each R^{10} is independently selected from alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

42. The compound of Claim 41 wherein Y is sulfur.

SUBSTITUTE SHEET (RULE 26)

43. The compound of Claim 42 wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

each R^{10} is independently selected from alkyl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

44. The compound of Claim 43 wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, halo, alkyl, haloalkyl, $-R^7-OR^8$ and $-R^7-O-R^9-OR^8$;

SUBSTITUTE SHEET (RULE 26)

R^6 is a direct bond, a straight or branched ethylene chain, a straight or branched ethenylene chain or a straight or branched ethynylene chain;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

each R^9 is a straight or branched ethylene chain.

45. The compound of Claim 44 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-(5-m-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[5-(4-methoxy-3-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-4-trifluoromethyl-6-[5-(2,4,5-trimethyl-phenyl)-thiophen-2-yl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[5-(4-methoxy-2-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3,5-Bis-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-dichloro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-(5-o-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[5-(3,5-dichloro-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3,5-Dichloro-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-o-tolyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-methyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(2-Bromo-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[5-(3-trifluoromethyl-phenyl)-thiophen-2-yl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3,5-dimethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxy-3,5-dimethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxymethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3,5-Bis-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3,4-dimethoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-phenylethynyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-phenylethynyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-((E)-styryl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-((E)-styryl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-phenethyl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-hydroxymethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-methyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-4-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-4-methyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-methoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{5-[3-Chloro-4-(2,2,2-trifluoro-ethoxy)-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-hydroxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{5-[3-Chloro-4-(2-hydroxy-ethoxy)-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-isopropoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropoxy-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethoxy-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-isopropoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-isopropoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

46. The compound of Claim 43 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

when m is 1, R^5 is hydrogen or $-R^7-S(O)_tR^8$ (where t is 0 to 2); or

when m is 2, one R^5 is $-R^7-S(O)_tR^8$ (where t is 0 to 2) or $-R^7-S(O)_2N(R^8)_2$ and the other R^5 is independently selected from the group consisting of alkyl, halo, haloalkyl and $-R^7-OR^8$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl.

SUBSTITUTE SHEET (RULE 26)

47. The compound of Claim 46 selected from the group consisting of the following:

1-(2,4-Dichloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-3-dimethylaminomethyl-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-pyridin-2-one;

1-(2,4-Dichloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

N-{1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl}-methanesulfonamide;

3-Diethylaminomethyl-1-(2,4-difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-pyridin-2-one;

N-{1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridin-3-ylmethyl}-guanidine;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3,5-Bis-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[5-(4-methyl-3-methylsulfanyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfinyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(5-methanesulfinyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{5-[3-(Butane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(3-phenylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Cyclopropylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{4-[3-(Butane-1-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(3-phenylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Cyclopropylmethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfinyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfinyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{5-[3-(Butane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(3-phenylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Cyclopropylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{4-[3-(Butane-1-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Cyclopropylmethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-thiophen-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Ethanesulfonyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid;

1-(2-Chloro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Ethanesulfonyl-phenyl)-thiophen-2-yl]-1-(4-ethyl-2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Ethanesulfonyl-5-trifluoromethyl-phenyl)-thiophen-2-yl]-1-(4-ethyl-2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(3-isopropyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

4-(1,1-Difluoro-propyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-tert-Butyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-tert-Butyl-5-methanesulfonyl-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{5-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{5-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-ethyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-5-isopropyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropyl-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropyl-phenyl)-acetic acid;

1-(4-Chloro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-[5-(4-methanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile; and

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzenesulfonamide.

48. The compound of Claim 43 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ and $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is -N(H)- or a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

49. The compound of Claim 48 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-6-[5-(3-formyl-4-methoxy-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

Carbonic acid tert-butyl ester 4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl ester;

6-[5-(3-Chloro-4-cyano-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Cyano-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-[4-(3-Cyano-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-ethoxy-3-nitro-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Amino-4-ethoxy-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenoxy)-acetic acid ethyl ester;

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenoxy)-acetic acid;

6-[5-(4-Amino-3-chloro-phenyl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester;

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid methyl ester;

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid methyl ester;

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid;

4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-benzoic acid;

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropyl-benzoic acid methyl ester;

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropyl-benzoic acid methyl ester;

3-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-N,N-dimethyl-thiobenzamide;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid;

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid;

SUBSTITUTE SHEET (RULE 26)

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester;

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester;

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-5-isopropoxy-phenyl)-acetic acid;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methoxy-phenyl)-acetic acid methyl ester;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methoxy-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropoxy-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-fluoro-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-methoxy-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-5-isopropoxy-phenyl)-acetic acid;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methoxy-phenyl)-acetic acid;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methoxy-phenyl)-acetic acid;

2-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-2-methyl-propionic acid methyl ester;

2-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-2-methyl-propionic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-4-fluoro-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-4-methoxy-phenyl)-acetic acid;

SUBSTITUTE SHEET (RULE 26)

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-heptyl)-6-oxo-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester;

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid methyl ester;

(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-acetic acid tert-butyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-4-(1,1-difluoro-3-methyl-butyl)-6-oxo-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-acetic acid methyl ester;

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-propionic acid methyl ester;

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-propionic acid methyl ester;

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-phenyl)-propionic acid methyl ester; and

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-phenyl)-propionic acid methyl ester.

50. The compound of Claim 41 wherein Y is oxygen.

51. The compound of Claim 50 wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, haloalkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-O-R^9-OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-N(R^8)C(O)OR^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

each R^7 is independently selected from a direct bond or a straight or branched alkylene chain;

SUBSTITUTE SHEET (RULE 26)

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

52. The compound of Claim 51 wherein:

n is 1;

m is 1 to 3;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is methyl or trifluoromethyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-OR^8$ and $-R^7-O-R^9-OR^8$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

each R^9 is a straight or branched ethylene chain.

53. The compound of Claim 52 selected from the group consisting of the following:

6-[5-(3,5-Bis-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(2-Chloro-5-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3,4-dimethoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-hydroxy-3-methoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3,5-Bis-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-[4-(3-Chloro-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-4-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-fluoro-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-4-methyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-4-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-trifluoromethyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-fluoro-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-fluoro-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(3-Chloro-4-methyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-4-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropoxy-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethoxy-5-ethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-isopropoxy-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

54. The compound of Claim 51 wherein:

SUBSTITUTE SHEET (RULE 26)

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

when m is 1, R^5 is hydrogen or $-R^7-S(O)_tR^8$ (where t is 0 to 2); or

when m is 2, one R^5 is $-R^7-S(O)_tR^8$ (where t is 0 to 2) and the other R^5 is independently selected from the group consisting of halo, haloalkyl and $-R^7-OR^8$;

R^6 is a direct bond;

each R^7 is a direct bond;

each R^8 is independently selected from hydrogen, alkyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl; and

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl.

55. The compound of Claim 54 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-methylsulfanyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[5-(4-methyl-3-methylsulfanyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-trifluoromethyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{4-[3-(propane-2-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-{5-[3-(propane-1-sulfonyl)-5-trifluoromethyl-phenyl]-furan-2-yl}-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-isopropyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(3-ethyl-5-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-6-[4-(4-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(3-ethanesulfonyl-5-isopropyl-phenyl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-tert-Butyl-5-methanesulfonyl-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2-Fluoro-benzyl)-6-[4-(3-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Ethanesulfonyl-phenyl)-furan-2-yl]-1-(2-fluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-1-sulfonyl)-phenyl]-furan-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{4-[3-ethyl-5-(propane-2-sulfonyl)-phenyl]-furan-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[5-(3-methanesulfonyl-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

56. The compound of Claim 51 wherein:

n is 1;

m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^2 is cyano;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of halo, nitro, alkyl, $-R^7-CN$, $-R^7-N(R^8)_2$, $-R^7-OR^8$, $-R^7-OC(O)OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$ and $-R^7-N(R^8)C(O)OR^{10}$;

R^6 is a direct bond;

each R^7 is independently a direct bond or a straight or branched alkylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl or cycloalkylalkyl;

each R^9 is a straight or branched alkylene chain;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl; and

R^{11} is hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heterarylalkyl.

57. The compound of Claim 56 selected from the group consisting of the following:

6-[4-(3-Chloro-4-cyano-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-[4-(3-Cyano-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(4-ethoxy-3-nitro-phenyl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(4-Amino-3-chloro-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-2-yl}-2-ethoxy-phenyl)-carbamic acid tert-butyl ester;

3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropyl-benzoic acid methyl ester;

6-[4-(3-Amino-4-ethoxy-phenyl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid;

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropyl-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester;

(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methoxy-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-5-isopropoxy-phenyl)-acetic acid;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-4-methoxy-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-4-fluoro-phenyl)-acetic acid methyl ester;

2-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-2-methyl-propionic acid methyl ester;

(5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methoxy-phenyl)-acetic acid;

SUBSTITUTE SHEET (RULE 26)

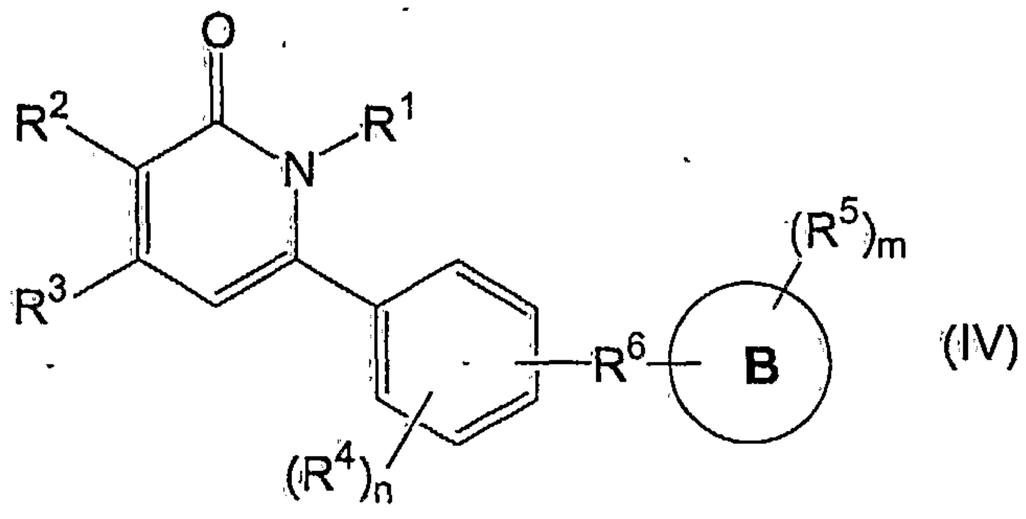
(2-Chloro-4-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-acetic acid methyl ester;

(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-benzyl)-carbamic acid tert-butyl ester;

3-(3-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-propionic acid methyl ester; and

3-(4-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-phenyl)-propionic acid methyl ester.

58. The compound of Claim 1 having the following formula (IV):



(IV)

wherein:

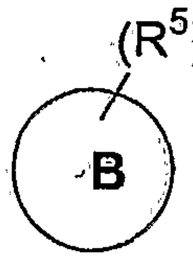
n is 1 to 4;

m is 1 to 4;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or $-R^7-N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl or heteroaryl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$,

$-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is $-OR^7-$, $-N(R^8)-$, a direct bond, a straight or branched alkylene chain, a straight or branched alkenylene chain or a straight or branched alkynylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

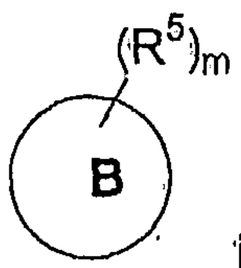
each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

59. The compound of Claim 58 wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



is a *N*-heteroaryl selected from the group consisting of indolyl and thiazolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-CN$ and $-R^7-C(O)OR^8$; and

R^6 is a direct bond.

SUBSTITUTE SHEET (RULE 26)

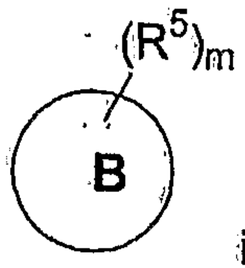
60. The compound of Claim 59 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-thiazol-2-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

5-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid ethyl ester.

61. The compound of Claim 58 wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



is a *N*-heteroaryl selected from the group consisting of indolyl, pyrimidyl, pyrazinyl, pyridinyl and thiazolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-CN$ and $-R^7-C(O)OR^8$; and

R^6 is -O-.

62. The compound of Claim 61 selected from the group selected from the following:

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(pyrimidin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(4,6-dimethyl-pyrimidin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(pyrazin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(6-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile;

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-6-methyl-nicotinonitrile;

1-(2,4-Dimethyl-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-4-fluoro-benzyl)-6-[4-(1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-methyl-4-(pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-pyrazin-2-yloxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(6-Chloro-pyrazin-2-yloxy)-3-methyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[3-isopropyl-4-(pyrazin-2-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(3-Chloro-pyrazin-2-yloxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(6-Chloro-pyrazin-2-yloxy)-3-isopropyl-phenyl]-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(3,6-dimethyl-pyrazin-2-yloxy)-3-isopropyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-2-isopropyl-phenoxy}-6-methyl-nicotinonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(pyrimidin-2-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

3-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-pyrazine-2-carbonitrile;

2-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-6-methyl-nicotinonitrile;

2-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile;

6-[4-(6-Chloro-pyrazin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[3-Chloro-4-(pyrimidin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[3-Chloro-4-(pyrazin-2-yloxy)-phenyl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

2-{2-Chloro-4-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-nicotinonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-3,5-dimethyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yl)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[3-(1H-indol-5-yl)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-pyridin-3-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-pyridin-4-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dimethyl-benzyl)-6-[4-(1H-indol-5-yloxy)-3-methyl-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(3-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[4-(6-trifluoromethyl-pyridin-2-yloxy)-phenyl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-6-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-4-trifluoromethyl-nicotinic acid methyl ester;

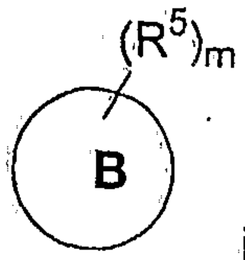
SUBSTITUTE SHEET (RULE 26)

1-(2,4-Dichloro-benzyl)-6-[4-(1-methyl-1H-indol-5-yloxy)-phenyl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

5-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid ethyl ester.

63. The compound of Claim 58 wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;



is *N*-heterocyclyl selected from the group consisting of piperidinyl and piperazinyl; and

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-CN$ and $-R^7-C(O)OR^8$.

64. The compound of Claim 63 selected from the group consisting of the following:

1-(2,4-Dimethyl-benzyl)-2-oxo-6-[4-(piperidin-4-yloxy)-phenyl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(3-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

4-{3-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-piperidin-1-yl-phenyl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

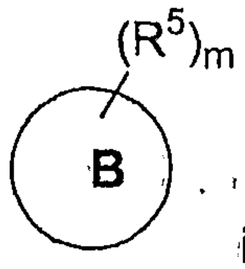
4-{4-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester; and

4-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester.

65. The compound of Claim 58 wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

SUBSTITUTE SHEET (RULE 26)



is benzodioxolyl;

each R^5 is independently selected from the group consisting of halo, alkyl, haloalkyl, $-R^7-CN$ and $-R^7-C(O)OR^8$; and

R^6 is a direct bond.

66. The compound of Claim 65 selected from the group consisting of the following:

6-(3-Benzo[1,3]dioxol-5-yl-phenyl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

6-(4-Benzo[1,3]dioxol-5-yl-phenyl)-1-(2,4-dimethyl-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

67. The compound of Claim 58 wherein:

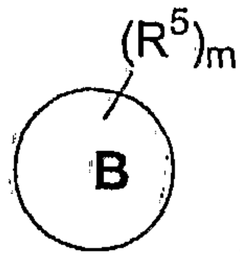
n is 1 to 4;

m is 1 to 4;

R^1 is optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or $-R^7-N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl or heteroaryl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, optionally substituted aralkyl, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, and $-R^7-N(R^8)C(O)OR^9-OR^{11}$;

R^6 is $-OR^7-$, $-N(R^8)-$ or a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl,

SUBSTITUTE SHEET (RULE 26)

optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

68. The compound of Claim 67 wherein:

n is 1;

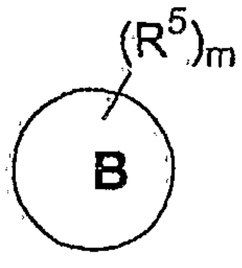
m is 1 or 2;

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo,haloalkyl, $-OR^8$, $-N(R^8)_2$, or $-N(R^8)C(O)OR^{10}$;

or R^1 is pyridinylalkyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $-N(R^8)C(O)OR^{10}$;

R^2 is hydrogen, $-C(O)OR^8$, $-C(O)N(R^8)_2$ or cyano;

R^3 is hydrogen, methyl, difluoromethyl or trifluoromethyl;



is indolyl, benzimidazolyl, pyrazolyl, or benzodioxinyl;

R^4 is hydrogen;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, optionally substituted aralkyl, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, and $-R^7-N(R^8)C(O)OR^9-OR^{11}$;

R^6 is -O-, -N(H)- or a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

SUBSTITUTE SHEET (RULE 26)

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

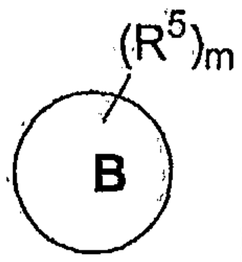
each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

69. The compound of Claim 68 wherein:

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $-N(R^8)C(O)OR^{10}$;



is indolyl, benzimidazolyl, pyrazolyl or benzodioxinyl; and

each R^5 is independently selected from the group consisting of hydrogen, alkyl, and optionally substituted aralkyl.

70. The compound of Claim 69 selected from the group consisting of the following compounds:

6-[4-(1H-Benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1-methyl-1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-[(2,4-Dimethylphenyl)methyl]-6-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

6-[3-(1H-Benzimidazol-5-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-2-oxo-6-[3-(1H-pyrazol-4-yl)phenyl]-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-2-oxo-6-{3-[1-(phenylmethyl)-1H-pyrazol-4-yl]phenyl}-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-{3-[1-(3-methylbutyl)-1H-pyrazol-4-yl]phenyl}-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

1-[(2,4-Dimethylphenyl)methyl]-6-[4-(1H-indol-6-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

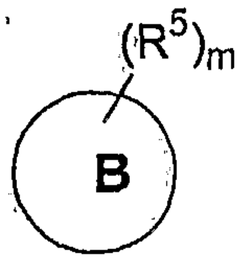
1-[(2,4-Dimethylphenyl)methyl]-6-[4-(1H-indol-5-yl)phenyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile; and

6-[3-(2,3-Dihydro-1,4-benzodioxin-6-yl)phenyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile.

71. The compound of Claim 68 wherein:

R^1 is benzyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$, or $-N(R^8)C(O)OR^{10}$;

or R^1 is pyridinylalkyl optionally substituted with one or more substituents independently selected from alkyl, halo, haloalkyl, $-OR^8$, $-N(R^8)_2$ or $-N(R^8)C(O)OR^{10}$;



is indolyl, benzimidazolyl or pyrazolyl;

each R^5 is independently selected from the group consisting of hydrogen, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, and $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

SUBSTITUTE SHEET (RULE 26)

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

72. The compound of Claim 71 selected from the group consisting of the following compounds:

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(difluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5- carbamoyl-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-carboxy-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2-amino-6-methylpyridin-5-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

5-{4-[1-(2,4-Dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenoxy}-1H-indole-2-carboxylic acid;

3-Morpholin-4-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

3-Piperazin-1-ylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-4-methyl-6-oxo-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

4-(Dimethylamino)butyl 5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

3-(Dimethylamino)propyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

2-{[2-(dimethylamino)ethyl]oxy}ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

SUBSTITUTE SHEET (RULE 26)

Ethyl 6-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 6-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

1-Methylethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

3-(Dimethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

1-Methylpiperidin-4-yl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

3-(Diethylamino)-2,2-dimethylpropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2,4-dichlorophenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

3-(Dimethylamino)propyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

2-(dimethylamino)ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-propyl-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N,N-dimethyl-1H-indole-2-carboxamide;

Ethyl 5-({4-[5-cyano-1-{[2-methyl-4-(methyloxy)phenyl]methyl}-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl]phenyl}oxy)-1H-indole-2-carboxylate;

2,3-Dihydroxypropyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2,6-dimethylpyridin-3-yl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

Ethyl 5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylate;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(1-methylethyl)-1H-indole-2-carboxamide;

SUBSTITUTE SHEET (RULE 26)

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-methylpropyl)-1H-indole-2-carboxamide;

Ethyl 5-[(4-{1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[3-(dimethylamino)propyl]-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-ethyl-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2-hydroxyethyl)-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-(2,3-dihydroxypropyl)-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-N-[(2,3-dihydroxypropyl)oxy]-1H-indole-2-carboxamide;

5-[(4-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylic acid;

5-[(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)amino]-1H-indole-2-carboxylic acid;

3-Piperidin-1-ylpropyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

Ethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

3-(Dimethylamino)propyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

Ethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

1,1-Dimethylethyl 4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazole-1-carboxylate;

Ethyl 5-[(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)oxy]-1H-indole-2-carboxylate;

6-(3-{5-Cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylic acid;

1,1-Dimethylethyl 5-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate;

SUBSTITUTE SHEET (RULE 26)

Ethyl [4-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-pyrazol-1-yl]acetate;

Ethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

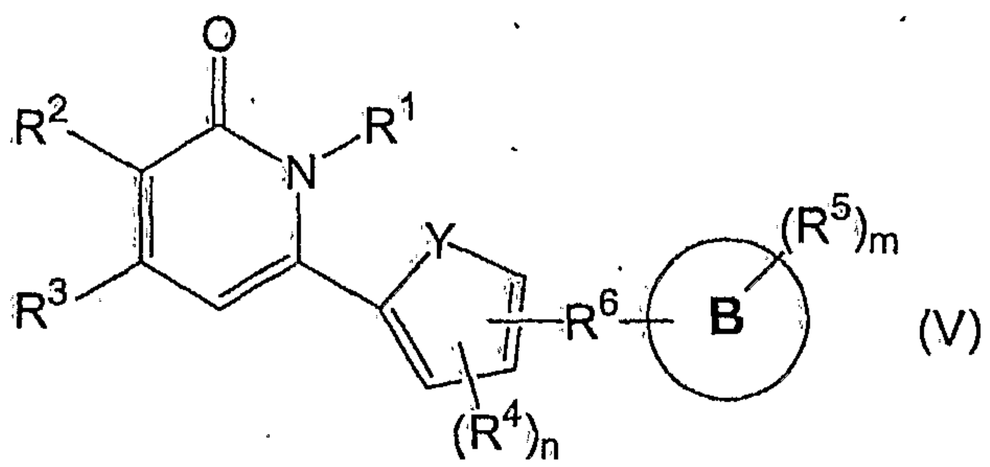
Ethyl 5-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-2-carboxylate;

5-{4-[5-Cyano-1-(2,4-dimethyl-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-phenyl}-1H-indole-2-carboxylic acid;

1,1-Dimethylethyl 6-(3-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate; and

1,1-Dimethylethyl 6-(4-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}phenyl)-1H-indole-1-carboxylate.

73. The compound of Claim 1 having the following formula (V):



(V)

wherein:

n is 1 or 2;

m is 1 to 4;

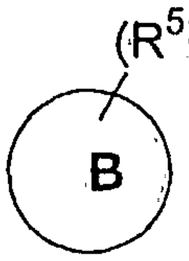
Y is oxygen or sulfur;

R^1 is optionally substituted aralkyl;

R^2 is cyano or $-R^7-N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;



is naphthyl, heterocyclyl or heteroaryl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, heterocyclyl, $-R^7-OR^8$, $-R^7-CN$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond;

SUBSTITUTE SHEET (RULE 26)

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

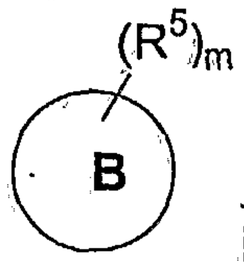
or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

74. The compound of Claim 73 wherein:

Y is -O-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is a *N*-heteroraryl selected from the group consisting of pyrimidinyl and pyridinyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, morpholinyl, piperazinyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl or cycloalkylalkyl.

75. The compound of Claim 74 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-6-[5-(6-methoxy-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2,4-dimethoxy-pyrimidin-5-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-4-yl-furan-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-nicotinonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-isopropoxy-5-trifluoromethyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-ethoxy-nicotinic acid ethyl ester;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-2-yl}-2-ethoxy-nicotinic acid ethyl ester;

1-(2,4-Difluoro-benzyl)-6-[4-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-furan-3-yl}-2-methanesulfonyl-nicotinic acid methyl ester;

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropenyl-6-methylsulfanyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropenyl-6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-4-(1,1-difluoro-propyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-6-[4-(5-isopropyl-6-methanesulfonyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[4-(2-Chloro-pyridin-4-yl)-furan-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;and

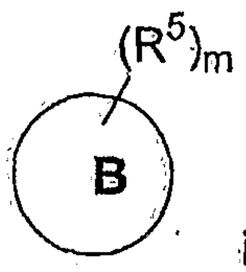
1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(6-piperazin-1-yl-pyridin-3-yl)-furan-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

76. The compound of Claim 73 wherein:

Y is -O-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is heterocyclyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl or cycloalkylalkyl.

77. The compound of Claim 76 selected from the group consisting of the following:

6-(5-Benzo[1,3]dioxol-5-yl-furan-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-furan-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

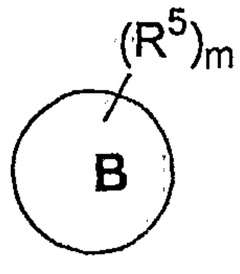
78. The compound of Claim 73 wherein:

Y is -S-;

SUBSTITUTE SHEET (RULE 26)

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is a *N*-heteroaryl selected from the group consisting of pyridinyl, indolyl and pyrimidinyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, morpholinyl, piperazinyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl or cycloalkylalkyl.

79. The compound of Claim 78 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-3-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-4-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-3-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(4-pyridin-4-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(1H-indol-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyridin-2-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-methoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2,4-dimethoxy-pyrimidin-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(5-pyrimidin-5-yl-thiophen-2-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

6-[5-(2,6-Bis-trifluoromethyl-pyridin-4-yl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-nicotinonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-ethoxy-nicotinonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-isopropoxy-5-trifluoromethyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(1-oxy-pyridin-4-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-ethoxy-nicotinic acid ethyl ester;

1-(2,4-Difluoro-benzyl)-6-[4-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(5-methyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methylsulfanyl-nicotinic acid methyl ester;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methylsulfanyl-nicotinic acid methyl ester;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methanesulfonyl-nicotinic acid methyl ester;

5-{5-[5-Cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-3-yl}-2-methanesulfonyl-nicotinic acid methyl ester;

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropenyl-6-methylsulfanyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropenyl-6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Ethyl-2-fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2-Chloro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropenyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-5-isopropyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethoxy-5-isopropyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(5-isopropyl-6-methanesulfonyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-ethoxy-2-methanesulfonyl-pyrimidin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

4-(1,1-Difluoro-propyl)-1-(2-fluoro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[4-(6-ethylsulfanyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2-methanesulfonyl-6-trifluoromethyl-pyridin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

Acetic acid 1-(5-{5-[5-cyano-1-(2,4-difluoro-benzyl)-6-oxo-4-trifluoromethyl-1,6-dihydro-pyridin-2-yl]-thiophen-2-yl}-2-methanesulfonyl-pyridin-3-yl)-ethyl ester;

1-(2,4-Difluoro-benzyl)-6-[5-(2-ethanesulfonyl-6-ethyl-pyridin-4-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-6-[5-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-{5-[5-(1-hydroxy-ethyl)-6-methanesulfonyl-pyridin-3-yl]-thiophen-2-yl}-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(6-morpholin-4-yl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[5-(2-Chloro-pyridin-4-yl)-thiophen-2-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(4-Chloro-benzyl)-6-[5-(3-ethanesulfonyl-phenyl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[5-(6-piperazin-1-yl-pyridin-3-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-[4-(6-piperazin-1-yl-pyridin-3-yl)-thiophen-2-yl]-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-[4-(6-morpholin-4-yl-pyridin-3-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

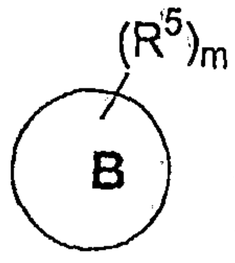
80. The compound of Claim 73 wherein:

Y is -S-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

SUBSTITUTE SHEET (RULE 26)



is heterocyclyl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is independently a direct bond or a methylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl or cycloalkylalkyl.

81. The compound of Claim 80 selected from the group consisting of the following:

6-(4-Benzo[1,3]dioxol-5-yl-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-(5-Benzo[1,3]dioxol-5-yl-thiophen-2-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[5-(2,3-dihydro-benzofuran-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

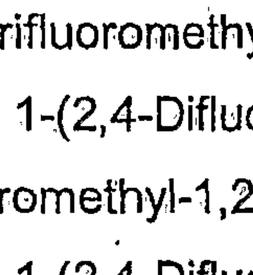
1-(2,4-Difluoro-benzyl)-6-[4-(2,3-dihydro-benzofuran-5-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

82. The compound of Claim 73 wherein:

Y is -S-;

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl;

R^3 is alkyl, hydroxyalkyl or haloalkyl;



is naphthyl; and

each R^5 is independently selected from hydrogen, alkyl, halo or haloalkyl.

SUBSTITUTE SHEET (RULE 26)

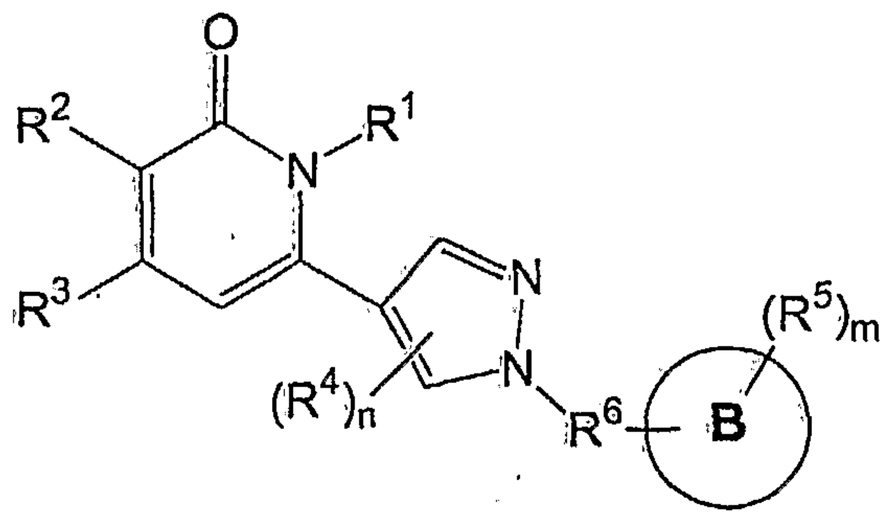
83. The compound of Claim 82 selected from the group consisting of the following:

1-(2,4-Dichloro-benzyl)-6-[5-(4-methyl-naphthalen-1-yl)-thiophen-2-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5-naphthalen-2-yl-thiophen-2-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

1-(2,4-Difluoro-benzyl)-6-(5-naphthalen-1-yl-thiophen-2-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

84. The compound of Claim 1 having the following formula (VI):



(VI)

wherein:

n is 1 or 2;

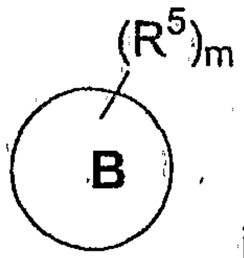
m is 1 to 4;

R^1 is optinally substituted aralkyl;

R^2 is cyano or $-R^7-N(R^8)_2$;

R^3 is alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;



is aryl or heteroaryl;

each R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$, $-R^7-C(O)OR^8$, $-R^7-OC(O)R^{10}$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

R^6 is a direct bond or a straight or branched alkylene chain;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, haloalkyl, haloalkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and

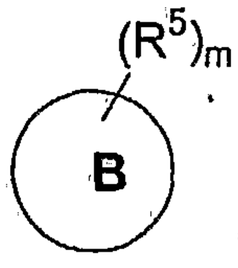
R^{10} is alkyl, aryl, aralkyl or cycloalkylalkyl;

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer;

or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

85. The compound of Claim 84 wherein:

R^1 is benzyl optionally substituted by one or more substituents selected from the group consisting of chloro, bromo, fluoro, methyl or ethyl; and



is phenyl or pyridinyl;

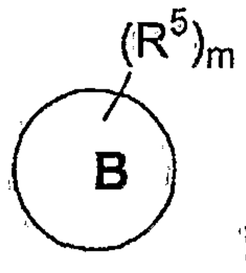
each R^5 is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2);

each R^7 is a direct bond or a straight or branched alkylene chain;

each R^8 is hydrogen or alkyl; and

R^{10} is alkyl.

86. The compound of Claim 85 wherein



is phenyl; and

each R^5 is independently selected from the group consisting of alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2).

87. The compound of Claim 86 selected from the group consisting of the following:

6-(1-Benzyl-1H-pyrazol-4-yl)-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-6-(1-phenyl-1H-pyrazol-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-2-oxo-6-(1-phenyl-5-trifluoromethyl-1H-pyrazol-4-yl)-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Dichloro-benzyl)-6-[1-benzyl-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[1-(4-methoxy-benzyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[1-(3-Cyano-4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[1-(3-Chloro-4-cyano-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

6-[1-(3-Chloro-4-ethoxy-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

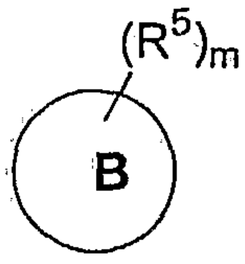
1-(2,4-Difluoro-benzyl)-6-[1-(4-methanesulfonyl-phenyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-6-[1-(3,4-dimethoxy-phenyl)-1H-pyrazol-4-yl]-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile; and

6-[1-(4-Cyano-3-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-(2,4-difluoro-benzyl)-2-oxo-4-trifluoromethyl-1,2-dihydro-pyridine-3-carbonitrile.

88. The compound of Claim 85 wherein

m is 1 or 2;



is pyridinyl; and

each R^5 is independently selected from the group consisting of hydrogen, alkyl, halo, haloalkyl, $-R^7-OR^8$, $-R^7-CN$ and $-R^7-S(O)_tR^8$ (where t is 0 to 2).

89. The compound of Claim 88 selected from the group consisting of the following:

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(3-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile;

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(6-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile; and

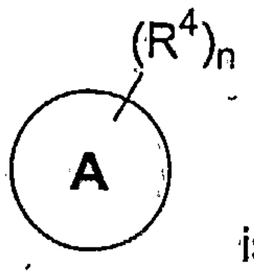
SUBSTITUTE SHEET (RULE 26)

1-(2,4-Difluoro-benzyl)-2-oxo-4-trifluoromethyl-6-[1-(5-trifluoromethyl-pyridin-2-yl)-1H-pyrazol-4-yl]-1,2-dihydro-pyridine-3-carbonitrile.

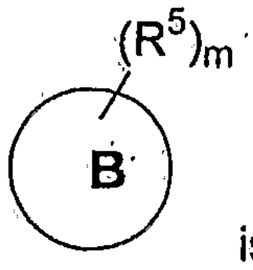
90. The compound of Claim 1 wherein:

n is 1 or 2;

m is 1 or 2;



is thienyl or pyridinyl;



is indolyl or benzimidazolyl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

each R^5 is independently selected from the group consisting of hydrogen, halo, nitro, alkyl, alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, haloalkyl, haloalkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^7-CN$, $-R^7-OR^8$, $-R^7-O-R^9-C(O)OR^8$, $-R^7-C(O)R^{11}$, $-R^7-C(O)OR^8$, $-R^7-C(O)OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)OR^{11}$, $-R^7-C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-C(O)N(R^8)_2$, $-R^7-C(O)N(R^8)OR^8$, $-R^7-C(O)N(R^8)N(R^8)_2$, $-R^7-C(O)N(R^8)-R^9-C(O)OR^8$, $-R^7-C(O)N(R^8)-R^9-OR^{11}$, $-R^7-C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-C(S)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)-R^9-C(O)OR^{10}$, $-R^7-N(R^8)C(O)R^8$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-OR^{11}$, $-R^7-N(R^8)C(O)N(R^8)-R^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)C(O)OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^9-N(R^{11})_2$, $-R^7-N(R^8)C(O)OR^9-OR^{11}$, $-R^7-N(R^8)C(O)C(O)N(R^{11})_2$, $-R^7-N(R^8)C(O)C(O)OR^{11}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond;

SUBSTITUTE SHEET (RULE 26)

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl;

each R^9 is independently selected from a straight or branched optionally substituted alkylene chain or a straight or branched optionally substituted alkenylene chain;

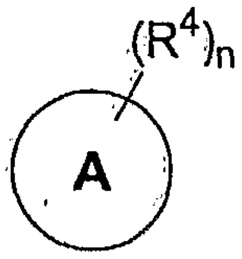
each R^{10} is independently selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl; and

each R^{11} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or optionally substituted heterarylalkyl.

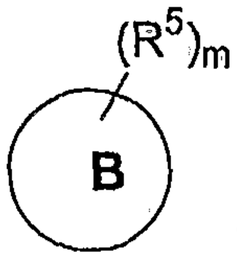
91. The compound of Claim 90 wherein:

n is 1 or 2;

m is 1 or 2;



is thienyl or pyridinyl;



is indolyl or benzimidazolyl;

R^1 is hydrogen, optionally substituted aralkyl or optionally substituted heteroarylalkyl;

R^2 is hydrogen, cyano, $-R^7-N(R^8)_2$, $-R^7-N(R^8)S(O)_2R^{10}$ or $-R^7-N(R^8)C(NR^8)N(R^8)_2$;

R^3 is hydrogen, alkyl, hydroxyalkyl or haloalkyl;

each R^4 is independently hydrogen, halo, alkyl or haloalkyl;

SUBSTITUTE SHEET (RULE 26)

each R^5 is independently selected from the group consisting of hydrogen, $-R^7-C(O)OR^8$, $-R^7-C(O)N(R^8)_2$, $-R^7-N(R^8)_2$, $-R^7-N(R^8)C(O)N(R^8)_2$, $-R^7-N(R^8)C(O)OR^{10}$, $-R^7-N(R^8)S(O)_2-R^8$, $-R^7-S(O)_tR^8$ (where t is 0 to 2) and $-R^7-S(O)_2N(R^8)_2$;

R^6 is a direct bond;

each R^7 is independently selected from a direct bond, a straight or branched alkylene chain or a straight or branched alkenylene chain;

each R^8 is independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, hydroxyalkenyl, haloalkyl, haloalkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl or heteroarylalkyl; and

R^{10} is selected from alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl or optionally substituted cycloalkylalkyl.

92. The compound of Claim 91 selected from the group consisting of the following compounds:

Ethyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate;

6-{5'-Cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylic acid;

3-(Dimethylamino)propyl 6-{5'-cyano-1'-[(2,4-dimethylphenyl)methyl]-6'-oxo-4'-(trifluoromethyl)-1',6'-dihydro-2,2'-bipyridin-6-yl}-1H-indole-2-carboxylate;

Ethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate;

1-[(2,4-Dimethylphenyl)methyl]-6-[5-(1H-indol-6-yl)-2-thienyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile;

Ethyl 5-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-2-carboxylate;

1,1-Dimethylethyl 6-(5-{5-cyano-1-[(2,4-dimethylphenyl)methyl]-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-yl}-2-thienyl)-1H-indole-1-carboxylate; and

6-[5-(1H-Benzimidazol-5-yl)-2-thienyl]-1-[(2,4-dimethylphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile.

93. A method of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity

SUBSTITUTE SHEET (RULE 26)

or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

94. The method of Claim 93, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

95. A method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

96. A method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

97. A method of modulating nuclear receptor activity, comprising contacting one or more nuclear receptors with a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

98. The method of claim 97, wherein at least one nuclear receptor is liver X receptor (LXRα or LXRβ).

99. The method of Claim 97, wherein at least one nuclear receptor is farnesoid X receptor (FXR) and another nuclear receptor is liver X receptor (LXRα and/or LXRβ).

SUBSTITUTE SHEET (RULE 26)

100. A method of modulating cholesterol metabolism, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

101. A method of treating, preventing or ameiliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

102. A method of increasing cholesterol efflux from cells of a subject, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

103. A method of increasing the expression of ATP-Binding Cassette transport protein (ABC1) in the cells of a subject, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

104. A method of increasing the expression of ATP-Binding Cassette transport protein (ABCG1) in the cells of a subject, comprising administering an effective amount of a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

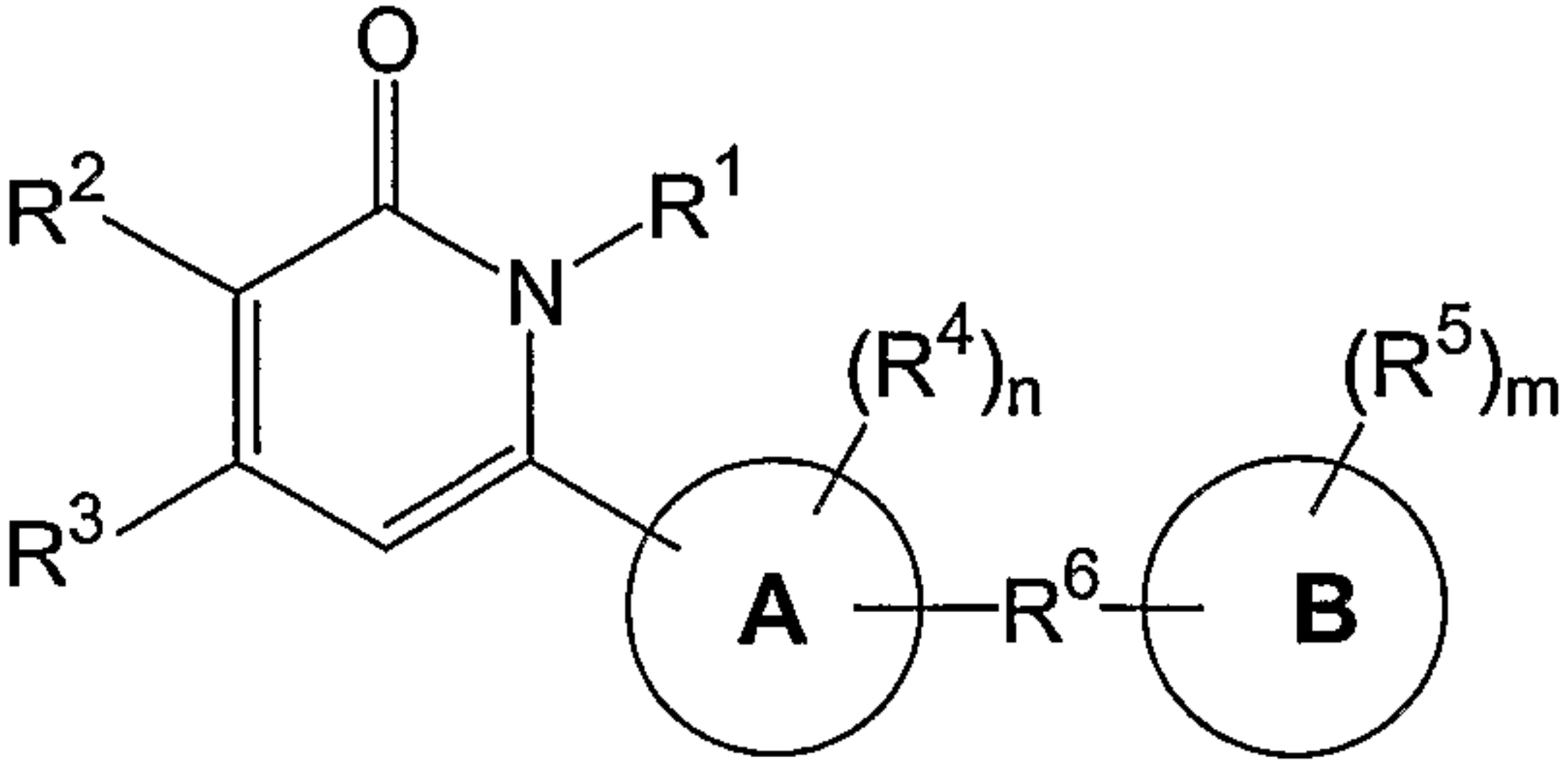
105. An *in vitro* method for altering nuclear receptor activity, comprising contacting the nuclear receptor with a compound of Claim 1, or a pharmaceutically acceptable derivative thereof.

106. The method of Claim 96, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

107. A method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective amount of a compound of Claim 1.

SUBSTITUTE SHEET (RULE 26)

108. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Claim 1.



(I)