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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 July 2005 (07.07.2005)

PCT

(10) International Publication Number
WO 2005/060963 A1

(51) International Patent Classification[7]: A61K 31/44, 31/4436, C07D 213/76, 409/12, 401/12, 417/12, C07C 311/37, 311/36, A61P 3/10, 3/04

(21) International Application Number:
PCT/IB2004/004056

(22) International Filing Date: 6 December 2004 (06.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/531,186 19 December 2003 (19.12.2003) US
60/556,921 26 March 2004 (26.03.2004) US

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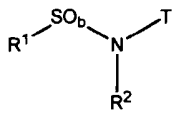
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, 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, 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*
— *with amended claims*

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: BENZENESULFONYLAMINO-PYRIDIN-2-YL DERIVATIVES AND RELATED COMPOUNDS AS INHIBITORS OF 11-BETA-HYDROXY STEROID DEHYDROGENASE TYPE 1 (11-BETA-HSD-1) FOR THE TREATMENT OF DIABETES AND OBESITY



(I)

(57) Abstract: The present invention relates to compounds with the formula (I), or a pharmaceutically acceptable satt thereof, formula (I), wherein: R' is selected from the group consisting of (C_1--C_6)alkyl, -(CR^3R^4),(C_3-C_12)cycloalkyl, -(*CR*^{3}R^4),(C_6-C_{12})aryl, and -(CR^3R^4)t(410)-membered heterocyclyl; b and k are each independently selected from 1 and 2; j is selected from the group consisting of 0, 1, and 2; t, u, p, q, and v are each independently selected from the group consisting of 0, 1, 2, 3, 4, and 5; T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom; R^2 is selected from the group consisting of H, (C_1-C_6)alkyl, -(CR^3R)t(C3-C12)cycloalkyl, -(CR^3R^4)$_t$(C6-C_{12})aryt, and -(CR^3R^4)$_t$(410)-membered heterocyclyl; each R^3 and R^4.is independently selected from H and (C1-C6)alkyl, the carbon atoms *of T, R', R*^{2}, R^3 and R^4 may each be optionally, substituted by I to 5 R^5 groups; $R^R$is defined in the claims; The compounds of the present invention are 11 ß-hsd-1 inhibitors, and are therefore believed to be useful in the treatment of diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression, hypertension, and metabolic diseases.

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BENZENESULFONYLAMINO-PYRIDIN-2-YL DERIVATIVES AND RELATED COMPOUNDS AS INHIBITORS OF 11-BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 1 (11-BETA-HSD-1) FOR THE TREATMENT OF DIABETES AND OBESITY

This application claims the benefit of US Application Serial Number 60/531,186 filed December 19, 2003 and US Application Serial Number 60/556,921 filed March 26, 2004.

Field Of The Invention

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, as well as to the use of the compounds in medicine and for the preparation of a medicament which acts on the human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11-β-hsd-1).

Background Of The Invention

It has been known for more than half a century that glucocorticoids have a central role in diabetes. For example, the removal of the pituitary or the adrenal gland from a diabetic animal alleviates the most severe symptoms of diabetes and lowers the concentration of glucose in the blood (Long, C. D. and F. D. W. Leukins (1936) *J. Exp. Med.* 63: 465-490; Houssay, B. A. (1942) *Endocrinology* 30: 884-892). Additionally, it is also well established that glucocorticoids enable the effect of glucagon on the liver.

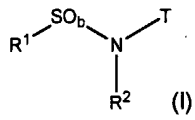
The role of 11-β-hsd-1 as an important regulator of local glucocorticoid effects and thus of hepatic glucose production is well substantiated (see e.g. Jamieson et al. (2000) *J. Endocrinol.* 165: p. 685-692). The hepatic insulin sensitivity was improved in healthy human volunteers treated with the non-specific 11-β-hsd-1 inhibitor carbenoxolone (Walker, B.R., et al. (1995) *J. Clin. Endocrinol. Metab.* 80: 3155-3159). Furthermore, the expected mechanism has been established by different experiments with mice and rats. These studies showed that the mRNA levels and activities of two key enzymes in hepatic glucose production were reduced, namely the rate-limiting enzyme in gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase) catalyzing the last common step of gluconeogenesis and glycogenolysis. Finally, the blood glucose level and hepatic glucose production was reduced in mice having the 11-β-hsd-1 gene knocked-out. Data from this model also confirms that inhibition of 11-β-hsd-1 will not cause hypoglycemia, as predicted, since the basal levels of PEPCK and G6Pase are regulated independently of glucocorticoids (Kotelevtsev, Y., et al., (1997) *Proc. Natl. Acad. Sci. USA* 94: 14924-14929).

Abdominal obesity is closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other factors of the so-called Metabolic Syndrome (e.g. raised blood pressure, decreased levels of HDL and increased levels of VLDL) (Montague & O'Rahilly, *Diabetes* 49: 883-888, 2000). Obesity is an important factor in Metabolic Syndrome as well as in the majority (>80%) of type 2 diabetic, and omental fat appears to be of central importance. Inhibition of the enzyme in pre-adipocytes (stromal cells) has been shown to decrease the rate of differentiation into adipocytes. This is predicted to result in diminished expansion (possibly reduction) of the omental fat depot, i.e. reduced central obesity (Bujalska, I.J., Kumar, S., and Stewart, P.M. (1997) *Lancet* 349: 1210-1213).

The compounds of the present invention are 11 β-hsd-1 inhibitors, and are therefore believed to be useful in the treatment of diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression, hypertension, and metabolic diseases.

Summary of The Invention

The present invention relates to a compound of formula (I):



(I)

wherein:

R^1 is selected from the group consisting of $(C_1–C_6)$alkyl, $-(CR^3R^4)_t(C_3-C_{12})$cycloalkyl, $-(CR^3R^4)_t(C_6-C_{12})$aryl, and $-(CR^3R^4)_t$(4-10)-membered heterocyclyl;

b and k are each independently selected from 1 and 2;

j is selected from the group consisting of 0, 1, and 2;

t, u, p, q, and v are each independently selected from the group consisting of 0, 1, 2, 3, 4, and 5;

T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom;

R^2 is selected from the group consisting of H, $(C_1–C_6)$alkyl, $-(CR^3R^4)_t(C_3-C_{12})$cycloalkyl, $-(CR^3R^4)_t(C_6-C_{12})$aryl, and $-(CR^3R^4)_t$(4-10)-membered heterocyclyl;

each R^3 and R^4 is independently selected from H and (C_1-C_6)alkyl;

the carbon atoms of T, R^1, R^2, R^3 and R^4 may each be optionally substituted by 1 to 5 R^5 groups;

each R^5 group is independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(C=O)-R^6$, $-(C=O)-O-R^6$, $-O-(C=O)-R^7$, $-O-(C=O)-NR^7$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, $-O-SO_2-R^9$, $-NR^8-S(O)_k-R^9$, $-(CR^{10}R^{11})_v(C_6-C_{12}$ aryl), $-(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v(C_6-C_{12})$aryl, and $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl of the foregoing R^6 groups are optionally substituted with an oxo (=O);

any carbon atom of any (C_1-C_6)alkyl, any (C_6-C_{12})aryl, and any (4-10)-membered heterocyclyl of the foregoing R^5 groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$, trifluoromethoxy, azido, $-OR^{12}$, $-(C=O)-R^{12}$, $-(C=O)-O-R^{13}$, $-O-(C=O)-R^{13}$, $-NR^{13}(C=O)-R^{14}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{17}R^{18}$, $-NR^{14}OR^{15}$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(CR^{16}R^{17})_u(C_6-C_{12})$aryl, and

$-(CR^{16}R^{17})_u$(4-10)-membered heterocyclyl;

each R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} group is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $-(C=O)N(C_1$–$C_6)$alkyl, $-(CR^{18}R^{19})_p(C_6$-$C_{12})$aryl, and $-(CR^{18}R^{19})_p$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of each said R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} group is optionally substituted with an oxo (=O);

any carbon atom of any $(C_1$-$C_6)$alkyl, any $(C_6$-$C_{12})$aryl, and any (4-10)-membered heterocyclyl of the foregoing R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-NR^{21}R^{22}$, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, and $(C_1$-$C_6)$ alkoxy;

each R^{18}, R^{19}, R^{20}, R^{21} and R^{22} group is independently selected from H and $(C_1$-$C_6)$alkyl;

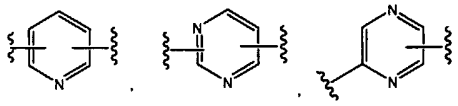
and wherein any of the above-mentioned substituents comprising a $-CH_3$ (methyl), $-CH_2$ (methylene), or -CH (methine) group which is not attached to a halo, -SO or $-SO_2$ group or to a N, O or S atom optionally bears on said group a substituent independently selected from the group consisting of hydroxy, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $-NH_2$, $-NH(C_1$-$C_6)$(alkyl) and $-N((C_1$-$C_6)$(alkyl))$_2$;

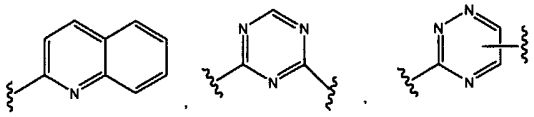
or a pharmaceutically acceptable salt or solvate thereof.

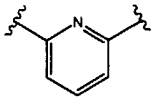
In another embodiment, the invention relates to a compound according to formula (I), wherein b is 2.

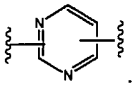
In yet another embodiment, the invention relates to a compound according to formula (I), wherein T is a 6-membered heterocyclyl containing at least one nitrogen atom.

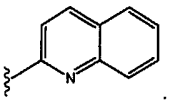
In an embodiment, the invention relates to a compound according to formula (I), wherein said T a (6-10)-membered heterocyclyl selected from the group consisting of





In yet another embodiment, the invention relates to a compound according to formula (I) wherein T is  .

In yet another embodiment, the invention relates to a compound according to formula (I), wherein T is  .

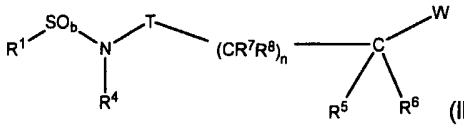
In an embodiment, the invention relates to a compound according to formula (I), wherein T is  .

In another embodiment, the invention relates to a compound according to formula (I), wherein each R^1 is selected from the group consisting of phenyl, biphenyl, benzothiophenyl, and napthyl and may optionally be substituted by 1 to 5 R^6 groups;

wherein:

each R^6 group is independently selected from the group consisting of halo, cyano, $-CF_3$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, $-(CR^{10}R^{11})_p$(4-10)-membered heterocyclyl, $-(C=O)-R^6$, $-(C=O)-O-R^6$, $-O-(C=O)-R^7$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-(CR^{10}R^{11})-O-(CR^{10}R^{11})_p(C_6-C_{12})$aryl, and $-(CR^{10}R^{11})_p-O-(CR^{10}R^{11})_p$(4-10)-membered heterocyclyl.

The invention relates to a compound according to formula (II):


(II)

wherein:

R^1 is (C_1-C_6)alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, or $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

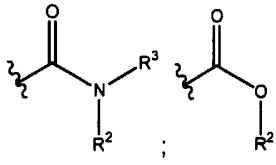
b and k are each independently selected from 1 and 2;

n and j are each independently selected from the group consisting of 0, 1, and 2;

t, u, p, q and v are each independently selected from the group consisting of 0, 1, 2, 3, 4, and 5;

T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom;

W is selected from the group consisting of:

 ; ; (C_1-C_6) alkyl; and a 5-membered heterocyclyl;

each R^2, R^3, and R^4 are independently selected from the group consisting of H, (C_1-C_6)alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, and $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

each R^2 and R^3 may optionally be taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl;

each R^5 and R^6 are independently selected from the group consisting of H, (C_1-C_6) alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, and $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

or R^5 and R^6 may optionally be taken together with the carbon to which they are attached to form a (C_3-C_6)cycloalkyl or a (3-7)-membered heterocyclyl;

each R^7 and R^8 are independently selected from H and $(C_1$-$C_6)$alkyl;

the carbon atoms of T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and said W 5-membered heterocyclyl are optionally substituted by 1 to 5 R^9 groups;

each R^9 group is independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(C=O)-R^{10}$, $-(C=O)-O-R^{11}$, $-O-(C=O)-R^{11}$, $-NR^{11}(C=O)-R^{12}$, $-(C=O)-NR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}OR^{12}$, $-S(O)_kNR^{11}R^{12}$, $-S(O)_j(C_1$-$C_6)$alkyl, $-O-SO_2-R^{10}$, $-NR^{11}-S(O)_k-R^{12}$, $-(CR^{13}R^{14})_v(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v(C_6$-$C_{10})$aryl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_vO(CR^{13}R^{14})_q(C_6$-$C_{10})$aryl, $-(CR^{13}R^{14})_vO(CR^{13}R^{14})_q$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_qS(O)_j(CR^{13}R^{14})_v(C_6$-$C_{10})$aryl, and $-(CR^{13}R^{14})_qS(O)_j(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with an oxo (=O);

any carbon atom of any $(C_1$-$C_6)$alkyl, any $(C_6$-$C_{10})$aryl and any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$, trifluoromethoxy, azido, $-OR^{15}$, $-(C=O)-R^{15}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $-(CR^{17}R^{18})_u(C_6$-$C_{10})$aryl, and $-(CR^{17}R^{18})_u$(4-10)-membered heterocyclyl;

each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $-(CR^{19}R^{20})_p(C_6$-$C_{10})$aryl, and $-(CR^{19}R^{20})_p$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of said each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is optionally substituted with an oxo (=O);

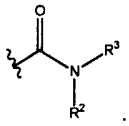
any carbon atom of any $(C_1$-$C_6)$alkyl, any $(C_6$-$C_{10})$aryl and any (4-10)-membered heterocyclyl of the foregoing R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-NR^{21}R^{22}$, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, and $(C_1$-$C_6)$ alkoxy;

each R^{19}, R^{20}, R^{21}, and R^{22} group is independently selected from H and $(C_1$-$C_6)$alkyl;

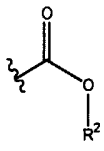
and wherein any of the above-mentioned substituents comprising a $-CH_3$ (methyl), $-CH_2$ (methylene), or -CH (methine) group which is not attached to a halo, -SO or $-SO_2$ group or to a N, O or S atom optionally bears on said group a substituent independently hydroxy, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, amino, $-NH(C_1$-$C_6)$(alkyl) or $-N(C_1$-$C_6)$(alkyl)$(C_1$-$C_6)$ alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

In an embodiment, the invention relates to a compound according to formula (II),

wherein W is  .

In another embodiment, the invention relates to a compound according to formula (II),

wherein W is  .

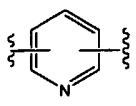
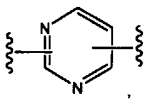
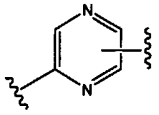
In yet another embodiment, the invention relates to a compound according to formula (II), wherein W is a 5-membered heterocyclyl.

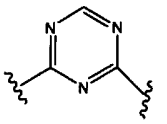
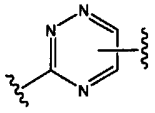
In yet another embodiment, the invention relates to a compound according to formula (II), wherein said 5-membered heterocyclyl is selected from the group consisting of oxazolyl, thiazolyl, pyrazolyl, triazolyl, and oxadiazolyl.

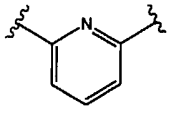
In another embodiment, the invention relates to a compound according to formula (II), wherein b is 2.

In another embodiment, the invention relates to a compound according to formula (II), wherein T is a 6-membered heterocyclyl containing at least one nitrogen atom.

In another embodiment, the invention relates to a compound according to formula (II), wherein said 6-membered heterocyclyl is selected from the group consisting of

 ,  ,  ,

 , and  .

In yet another embodiment, the invention relates to a compound according to formula (II), wherein T is  .

In yet another embodiment, the invention relates to a compound according to formula (II), wherein each R^1 is phenyl or napthyl substituted by 1 to 5 R^9 groups; wherein:

each R^9 is independently selected from the group consisting of halo, cyano, $-CF_3$, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{–}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $-(C{=}O)\text{-}R^{10}$, $-(C{=}O)\text{-}O\text{-}R^{11}$, $-O\text{-}(C{=}O)\text{-}R^{11}$, $-NR^{11}(C{=}O)\text{-}R^{12}$, $-(C{=}O)\text{-}NR^{11}R^{12}$, $-NR^{11}R^{12}$, and $-NR^{11}OR^{12}$.

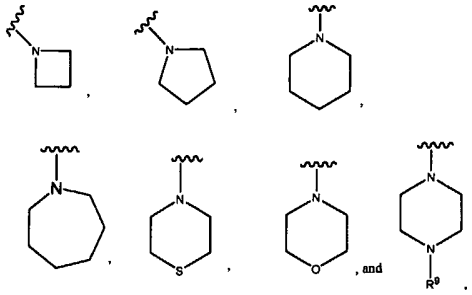
In an embodiment, the invention relates to a compound according to formula (II), wherein R^2 and R^3 are each independently selected from H and $(C_1\text{–}C_6)$alkyl;

wherein:

said (C_1-C_6) alkyl is optionally substituted by (C_2-C_6) alkenyl or $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl.

In another embodiment, the invention relates to a compound according to formula (II), wherein R^2 and R^3 are taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl.

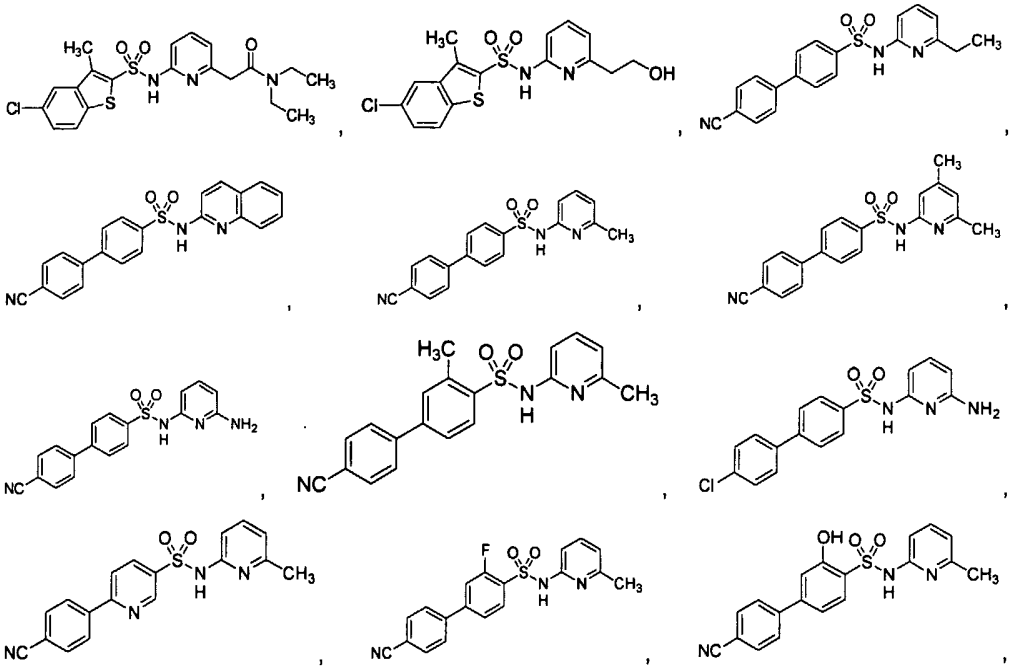
In yet another embodiment, the invention relates to a compound according to formula (II), wherein said (4-10)-membered heterocyclyl is selected from the group consisting of:

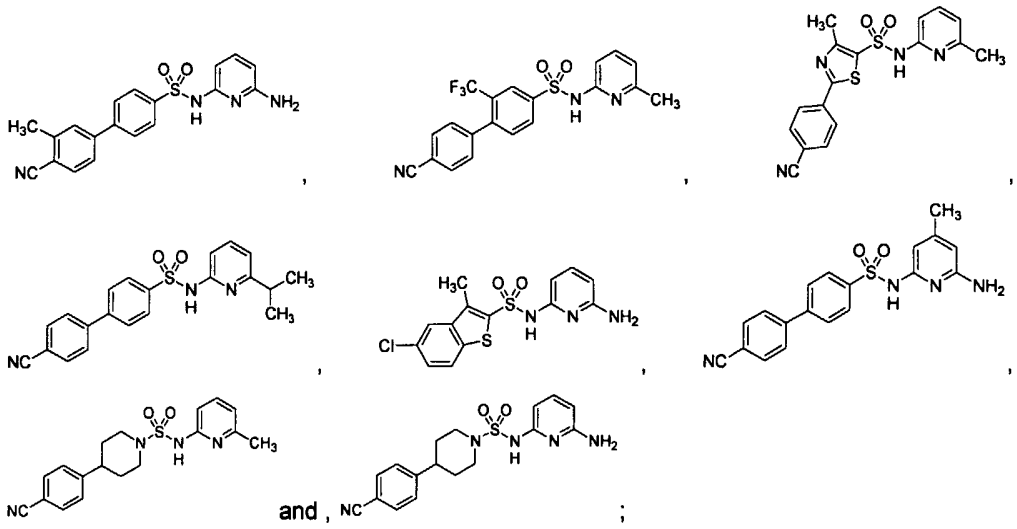


In another embodiment, the invention relates to a compound according to formula (II), wherein R^2 is (C_1-C_6)alkyl.

In an embodiment, the invention relates to a compound according to formula (II), wherein n is 0 and at least one of R^5 and R^6 is H.

In another embodiment, the invention relates to a compound selected from the group consisting of:





and ; or a pharmaceutically acceptable salt or solvate thereof.

An embodiment of the invention relates to a pharmaceutical composition comprising an effective amount of a compound according formula (I) or formula (II), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

In yet another embodiment, the invention relates to a method of treating a condition that is mediated by the modulation of 11-β-hsd-1, the method comprising administering to a mammal an effective amount of a compound according formula (I) or formula (II), or a pharmaceutically acceptable salt or solvate thereof.

In yet another embodiment, the invention relates to a method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, virus diseases, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound according to formula (I) or formula (II), or a pharmaceutically acceptable salt or solvate thereof.

Definitions

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "amino", as used herein, is intended to include the $-NH_2$ radical, and any substitutions of the N atom.

The terms "halogen" and "halo," as used herein represent chlorine, fluorine, bromine or iodine.

The term "trifluoromethyl," as used herein, is meant to represent a $-CF_3$ group.

The term "trifluoromethoxy," as used herein, is meant to represent a $-OCF_3$ group.

The term "cyano," as used herein, is meant to represent a –CN group.

The term, "OMs " as used herein, is intended to mean, unless otherwise indicated methanesulfonate.

The term "Me" as used herein, unless otherwise indicated, is intended to mean means methyl.

The term "MeOH" as used herein, unless otherwise indicated, is intended to mean means methanol.

The term "Et" as used herein, unless otherwise indicated, is intended to mean means ethyl.

The term "Et_2O " as used herein, unless otherwise indicated, is intended to mean means diethylether.

The term "EtOH " as used herein, unless otherwise indicated, is intended to mean means ethanol.

The term "Et_3N" as used herein, unless otherwise indicated, is intended to mean means triethylamine.

The term "EtOAc" as used herein, unless otherwise indicated, is ethyl acetate.

The term "$AlMe_2Cl$" as used herein, unless otherwise indicated, is intended to mean dimethyl aluminum chloride.

The term "Ac" as used herein, unless otherwise indicated, is intended to mean means acetyl.

The term "TFA" as used herein, unless otherwise indicated, is intended to mean trifluoroacetic acid.

The term "TEA", as used herein, unless otherwise indicated, is intended to mean triethanolamine.

The term "HATU", as used herein, unless otherwise indicated, is intended to mean *N,N,N',N'*-tetramethyluronium hexafluorophosphate.

The term "THF", as used herein, unless otherwise indicated, is intended to mean tetrahydrofuran.

The term "TlOH", as used herein, unless otherwise indicated, is intended to mean thallium(I) hydroxide.

The term "TlOEt", as used herein, unless otherwise indicated, is intended to mean thallium(I) ethoxide.

The term "PCy_3" as used herein, is intended to mean tricyclohexylphosphine.

The term "$Pd_2(dba)_3$", as used herein, unless otherwise indicated, is intended to mean tris(dibenzylideneacetone)dipalladium(0).

The term "$Pd(OAc)_2$", as used herein, unless otherwise indicated, is intended to mean palladium(II) acetate.

The term "$Pd(PPh_3)_2Cl_2$", as used herein, unless otherwise indicated, is intended to mean dichlorobis(triphenylphosphine)palladium(II).

The term "$Pd(PPh_3)_4$ ", as used herein, unless otherwise indicated, is intended to mean tetrakis(triphenylphophine)palladium(0).

The term "$Pd(dppf)Cl_2$"as used herein, is intended to mean (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II), complex with dichloromethane (1:1).

The term "G6P", as used herein, unless otherwise indicated, is intended to mean glucose-6-phosphate.

The term "NIDDM, as used herein, unless otherwise indicated, is intended to mean non insulin dependent diabetes mellitus

The term "NADPH", as used herein, unless otherwise indicated, is intended to mean nicotinamide adenine dinucleotide phosphate, reduced form.

The term "$CDCl_3$ or CHLORFORM-D" as used herein, is intended to mean deuterochloroform.

The term "CD_3OD" as used herein, is intended to mean deuteromethanol.

The term "CD_3CN" as used herein, is intended to mean deuteroacetonitrile.

The term "DEAD" as used herein, is intended to mean diethyl azodicarboxylate.

The term "$TsCH_2NC$" as used herein, is intended to mean tosylmethyl isocyanide.

The term "$ClSO_3H$" as used herein, is intended to mean chlorosulfonic acid.

The term "DMSO-d_6 or DMSO-D_6" as used herein, is intended to mean deuterodimethyl sulfoxide.

The term "DME" as used herein, is intended to mean 1,2-dimethoxyethane.

The term "DMF" as used herein, is intended to mean *N,N*-dimethylformamide.

The term "DMSO", as used herein, is intended to mean, unless otherwise indicated dimethylsulfoxide.

The term "DI", as used herein, is intended to mean deionized.

The term "KOAc" as used herein, is intended to mean potassium acetate.

The term "neat" as used herein, is meant to represent an absence of solvent.

The term "mmol" as used herein, is intended to mean millimole.

The term "equiv" as used herein, is intended to mean equivalent.

The term "mL" as used herein, is intended to mean milliliter.

The term "U" as used herein, is intended to mean units.

The term "mm" as used herein, is intended to mean millimeter.

The term "g" as used herein, is intended to mean gram.

The term "kg" as used herein, is intended to mean kilogram.

The term "h" as used herein, is intended to mean hour.

The term "min" as used herein, is intended to mean minute.

The term "µL" as used herein, is intended to mean microliter.

The term "µM" as used herein, is intended to mean micromolar.

The term "µm" as used herein, is intended to mean micrometer.

The term "M" as used herein, is intended to mean molar.

The term "N" as used herein, is intended to mean normal.

The term "nm" as used herein, is intended to mean nanometer.

The term "nM" as used herein, is intended to mean nanoMolar.

The term "amu" as used herein, is intended to mean atomic mass unit.

The term "°C" as used herein, is intended to mean Celsius.

The term "*m/z*", as used herein, is intended to mean, unless otherwise indicated, mass/charge ratio.

The term "wt/wt" as used herein, is intended to mean weight/weight.

The term "v/v" as used herein, is intended to mean volume/volume.

The term "mL/min" as used herein, is intended to mean milliliter/minute.

The term "UV" as used herein, is intended to mean ultraviolet.

The term "APCI-MS" as used herein, is intended to mean atmospheric pressure chemical ionization mass spectroscopy.

The term "HPLC" as used herein, is intended to mean high performance liquid chromatograph.

The term "LC" as used herein, is intended to mean liquid chromatograph.

The term "LCMS" as used herein, is intended to mean liquid chromatography mass spectroscopy.

The term "SFC" as used herein, is intended to mean supercritical fluid chromatography.

The term "sat" as used herein, is intended to mean saturated.

The term "aq" as used herein, is intended to mean aqueous.

The term "ELSD" as used herein, is intended to mean evaporative light scattering detection.

The term "MS" as used herein, is intended to mean mass spectroscopy.

The term "HRMS (ESI)" as used herein, is intended to mean high resolution mass spectrometry (electrospray ionization).

The term "Anal." as used herein, is intended to mean analytical.

The term "Calcd", as used herein, is intended to mean calculated.

The term "NT", as used herein, unless otherwise indicated, is intended to mean not tested.

The term "NA", as used herein, unless otherwise indicated, is intended to mean not tested.

The term "RT", as used herein, unless otherwise indicated, is intended to mean room temperature.

The term "Mth.", as used herein, unless otherwise indicated, is intended to mean Method.

The term "Celite®", as used herein, unless otherwise indicated, is intended to mean a white solid diatomite filter agent commercially available from World Minerals located in Los Angeles, California USA.

The term "Eg.", as used herein, unless otherwise indicated, is intended to mean example.

Terms such as $-(CR^3R^4)_t$ or $-(CR^{10}R^{11})_v$, for example, are used, R^3, R^4, R^{10} and R^{11} may vary with each iteration of t or v above 1. For instance, where t or v is 2 the terms $-(CR^3R^4)_v$ or $-(CR^{10}R^{11})_t$ may equal $-CH_2CH_2-$, or $-CH(CH_3)C(CH_2CH_3)(CH_2CH_2CH_3)-$, or any number of similar moieties falling within the scope of the definitions of R^3, R^4, R^{10} and R^{11}.

The term "K_i", as used herein, is intended to mean values of enzyme inhibition constant.

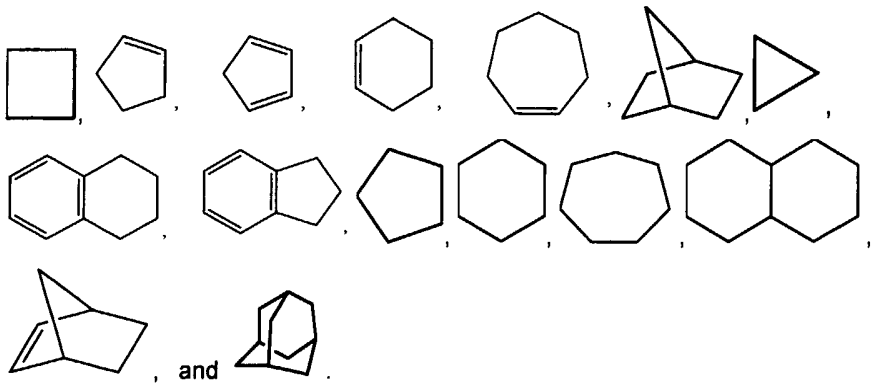
The term "K_i" app, as used herein, is intended to mean K_i apparent.

The term "IC_{50}", as used herein, is intended to mean concentrations required for at least 50% enzyme inhibition.

The term "substituted," means that the specified group or moiety bears one or more substituents. The term "unsubstituted," means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

In accordance with convention, in some structural formula herein, the carbon atoms and their bound hydrogen atoms are not explicitly depicted e.g.,  represents a methyl group,  represents an ethyl group,  represents a cyclopentyl group, etc.

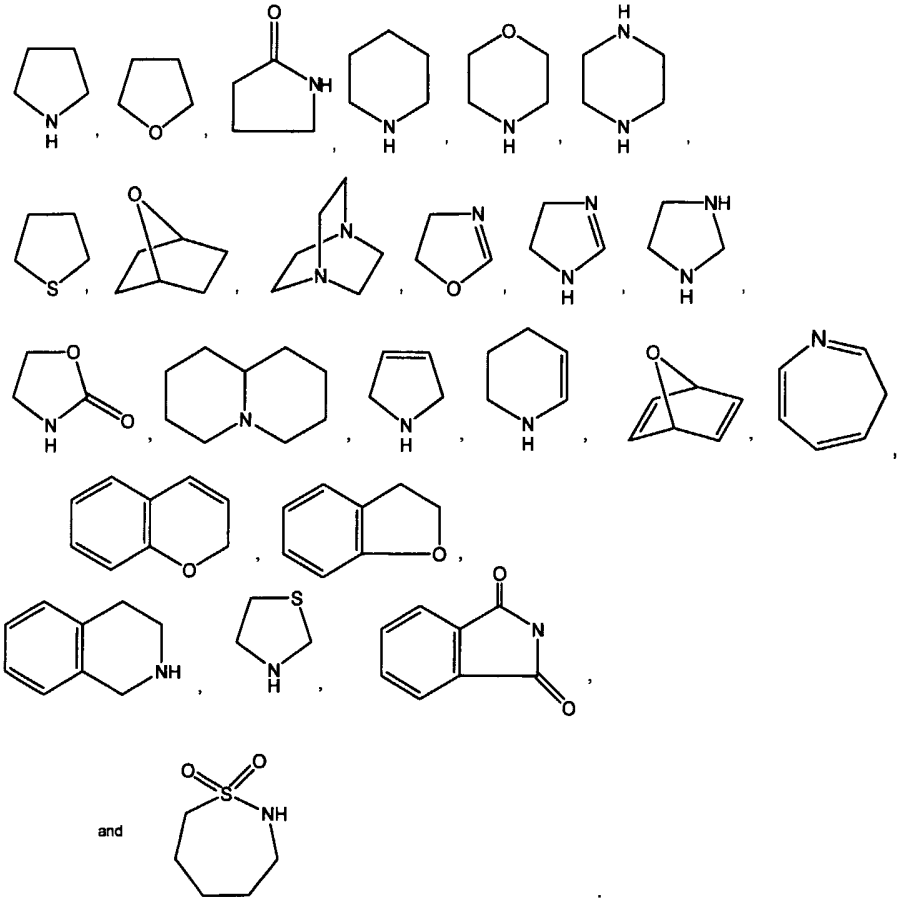
The term "cycloalkyl", as used herein, unless otherwise indicated, refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, suitably 5-8 ring carbon atoms. Exemplary cycloalkyls include rings having from 3-10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:



The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "(3-7)-membered heterocyclyl", "(6-10)-membered heterocyclyl", or "(4-10)-membered heterocyclyl", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 3-7, 6-10, or 4-10 atoms, respectively, in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3 membered heterocyclic group is aziridine, an example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl, an example of a 7 membered ring is azepinyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). The 4-10 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or

nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl. Other Illustrative examples of 4-10 membered heterocyclic are derived from, but not limited to, the following:



and

Unless otherwise indicated, the term "oxo" refers to =O.

A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO (dimethylsulfoxide), ethyl acetate, acetic acid, or ethanolamine.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula (I) or formula (II). The compounds of formula (I) or formula (II)that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula (I) or formula (II) are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edislyate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate,

hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phospate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The term "diseases in which the liver is a target organ", as used herein, unless otherwise indicated means diabetes, hepatitis, liver cancer, liver fibrosis, and malaria.

The term "Metabolic syndrome", as used herein, unless otherwise indicated means psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases, galactosemia, maple syrup urine disease, phenylketonuria, hypersarcosinemia, thymine uraciluria, sulfinuria, isovaleric acidemia, saccharopinuria, 4-hydroxybutyric aciduria, glucose-6-phosphate dehydrogenase deficiency, and pyruvate dehydrogenase deficiency.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "modulate" or "modulating", as used herein, refers to the ability of a modulator for a member of the steroid/thyroid superfamily to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control.

The term "obesity" or "obese", as used herein, refers generally to individuals who are at least about 20-30% over the average weight for his/her age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.8 kg/m^2, and for females, as individuals whose body mass index is greater than 27.3 kg/m^2. Those of skill in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the method of the invention can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example, by those who may be prone to obesity.

The term "inflammatory disorders", as used herein, refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

The phrase "therapeutically effective amount", as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

The phrase "amount . . . effective to lower blood glucose levels", as used herein, refers to levels of compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different compounds which fall within the definition of formula (I) or formula (II) as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

The phrase "insulin resistance", as used herein, refers to the reduced sensitivity to the actions of insulin in the whole body or individual tissues, such as skeletal muscle tissue, myocardial tissue, fat tissue or liver tissue. Insulin resistance occurs in many individuals with or without diabetes mellitus.

The phrase "insulin resistance syndrome", as used herein, refers to the cluster of manifestations that include insulin resistance, hyperinsulinemia, NIDDM, arterial hypertension, central (visceral) obesity, and dyslipidemia.

Certain compounds of formula (I) or formula (II) may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula (I) or formula (II), and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula (I) or formula (II), the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula (I) or formula (II) may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) or formula (II), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts or solvates of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate

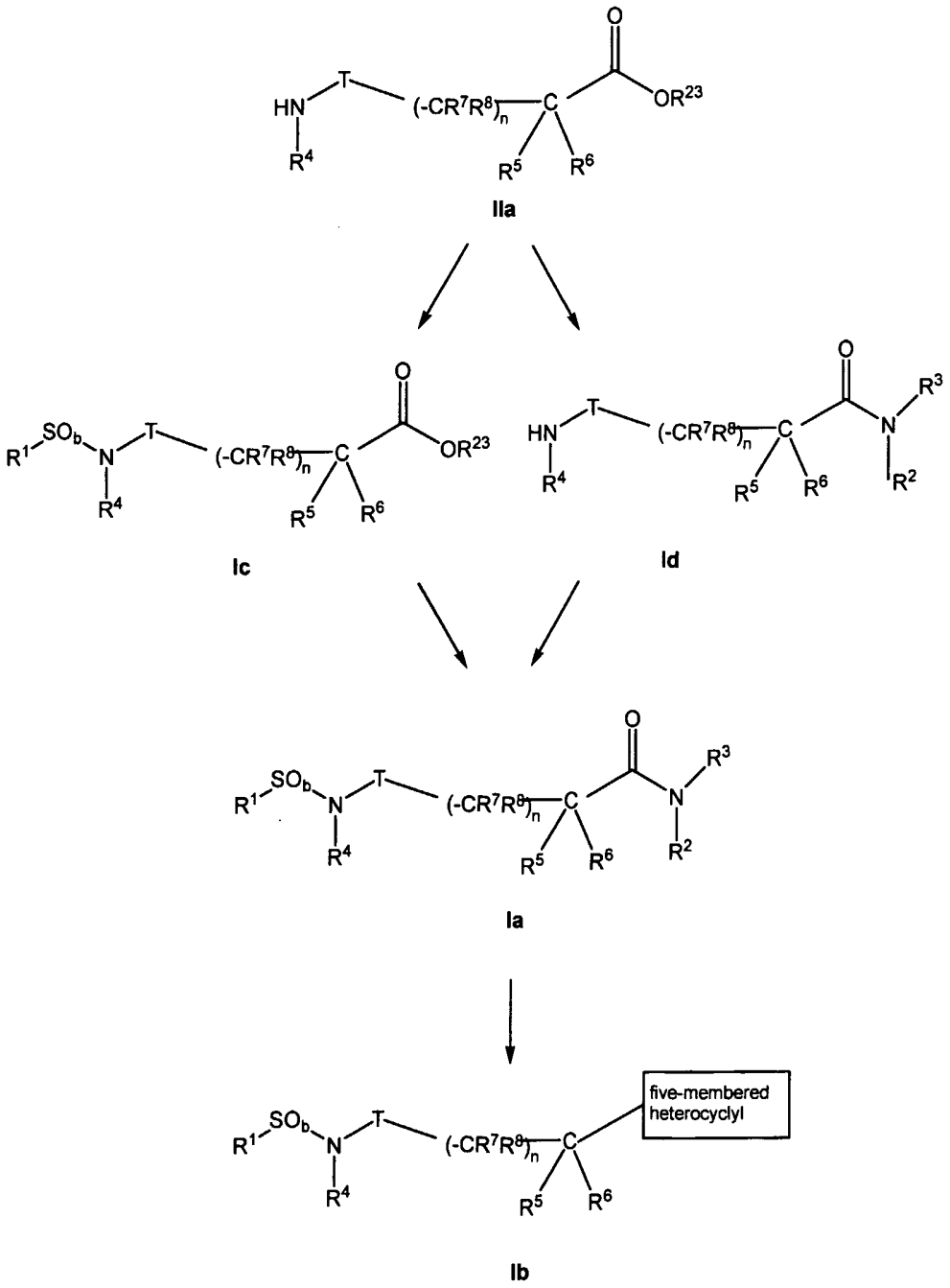
tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula (I) or formula (II) of this invention thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Other aspects, advantages, and features of the invention will become apparent from the detailed description below.

Detailed Description And Embodiments of The Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated, $R^{1} - R^{22}$, T, and W in the reaction schemes and the discussion that follows are as defined above.

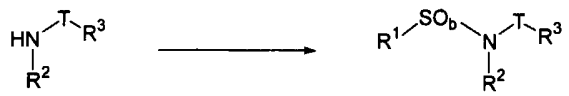
Scheme 1



Referring to Scheme 1 above, the compound of formula **Ia** may be prepared by reacting a compound of formula **Ic**, wherein the group CO_2R^{23} is an ester group such as methyl ester (CO_2-CH_3) or ethyl ester (CO_2-CH_2CH_3), with aluminum amides (Me_2Al-NR^2R^3) or (MeAl(Cl)-NR^2R^3) in a suitable solvent (e.g. dichloromethane or toluene) advantageously,

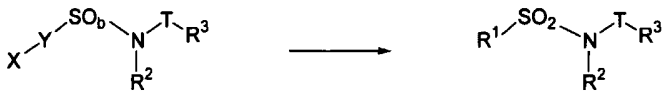
from room temperature to the boiling point of the solvent, typically from about 20 degrees Celsius to about 100 degrees Celsius. The compound of formula **Ia** may also be prepared by reacting a compound of formula **Ic**, wherein the group CO_2R^{23} is a carboxylic acid (CO_2H) with an amine of formula HNR^2R^3 using standard amide coupling chemistry. Compounds of formula **Ic** may be prepared by reacting a compound of formula **IIa**, wherein the group CO_2R^{23} is an ester group such as methyl ester (CO_2-CH_3) or ethyl ester (CO_2-CH_2CH_3), with a R^1-sulfonyl halide or R^1-sulfinyl halide. Alternatively, the compound of formula **Ia** may be prepared by reacting a compound of formula **Id** with a R^1-sulfonyl halide or R^1-sulfinyl halide. Compounds of formula **Id** may be prepared by reacting a compound of formula **IIa**, wherein the group CO_2R^{23} is an ester group such as methyl ester (CO_2-CH_3) or ethyl ester (CO_2-CH_2CH_3), with aluminum amides (Me_2Al-NR^2R^3) or (MeAl(Cl)-NR^2R^3) in a suitable solvent (e.g. dichloromethane or toluene) at a temperature from room temperature to the boiling point of the solvent, typically from about 20 degrees Celsius to about 100 degrees Celsius. The compound of formula **Ib** may be obtained by cyclodehydration of suitable amide **Ia**.

Scheme 2



B **A**

Scheme 3



A2 **A3**

Referring to Scheme 2 above, the compound of formula **A** may be prepared by reacting **B** with an R^1-sulfonyl halide, R^1-sulfinyl halide, or R^1 –sulfinate in the presence of a base such as an amine. Suitable bases include pyridine, triethylamine, and diisopropylethylamine. Suitable solvents include pyridine, dichloromethane, or THF. The aforementioned reaction can be conducted at room temperature or heated for an appropriate time period, such as 2 to 16 hours, depending on the solvent system used. After the reaction is substantially completed, the base may be removed *in vacuo* and the resulting residue may be purified using conventional purification techniques.

Referring to Scheme 3, an alternative method of synthesis is shown for compounds where R^1 is a non-fused ring system of more than one ring of either an aryl or heterocyclyl. The compound of formula **A3**, may be prepared by a palladium-catalyzed coupling reaction of

A2 where X is a halo or trifluoromethylsulfonyl with a reagent Y–N where Y is aryl or heterocyclyl, N is boronic acid, boronate ester, stannane, or zincate. Suitable palladium sources for this reaction include $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2$. Ligands such as diphenylphosphinoethane, diphenylphosphinoferrocene, or triphenylphosphine may also be added. Suitable solvents for the palladium-catalyzed coupling reaction include dimethylformamide, tetrahydrofuran, or toluene. The aforementioned reaction can be conducted at a temperature of about 50 °C to about 150 °C with or without microwave heating for a time period of about 15 min to about 16 hours. For couplings using boronic acids, base additives such as Na_2CO_3, Cs_2CO_3, TlOH, TlOEt may be added.

Any of the above compounds of formula **Ia, Ib, Ic, Id, IIa, A, B, A2**, and **A3** can be converted into another analogous compound by standard chemical manipulations. All starting materials, regents, and solvents are commercially available and are known to those of skill in the art unless otherwise stated. These chemical manipulations are known to those skilled in the art and include (a) removal of a protecting group by methods outlined in T. W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley and Sons, New York, 1991; (b) displacement of a leaving group (halide, mesylate, tosylate, etc) with a primary or secondary amine, thiol or alcohol to form a secondary or tertiary amine, thioether or ether, respectively; (c) treatment of primary and secondary amines with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding urea, amide, carbamate or sulfonamide; (d) reductive amination of a primary or secondary amine using an aldehyde.

The compounds of the present invention may have asymmetric carbon atoms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formula (I) or formula (II) that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula (I) or formula (II) from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be

precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of formula (I) or formula (II) that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula (I) or formula (II). Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the present invention may be modulators of 11-β-hsd-1. The compounds of the present invention may modulate processes mediated by 11-β-hsd-1, which refer to biological, physiological, endocrinological, and other bodily processes which are mediated by receptor or receptor combinations which are responsive to the 11-β-hsd-1 inhibitors described herein (e.g., diabetes, hyperlipidemia, obesity, impaired glucose tolerance, hypertension, fatty liver, diabetic complications (e.g. retinopathy, nephropathy, neurosis, cataracts and coronary artery diseases and the like), arteriosclerosis, pregnancy diabetes, polycystic ovary syndrome, cardiovascular diseases (e.g. ischemic heart disease and the like), cell injury (e.g.) brain injury induced by strokes and the like) induced by atherosclerosis or ischemic heart disease, gout, inflammatory diseases (e.g. arthrosteitis, pain, pyrexia, rheumatoid arthritis, inflammatory enteritis, acne, sunburn, psoriasis, eczema, allergosis, asthma, GI ulcer, cachexia, autoimmune diseases, pancreatitis and the like), cancer, osteoporosis and cataracts. Modulation of such processes can be accomplished in vitro or in vivo. In vivo modulation can be carried out in a wide range of subjects, such as, for example, humans, rodents, sheep, pigs, cows, and the like.

The compounds according to the present invention may be used in several indications which involve modulations of 11-β-hsd-1 enzyme. Thus, the compounds according to the present invention may be used against dementia (See WO97/07789), osteoporosis (See Canalis E 1996, "Mechanisms of Glucocorticoid Action in Bone: Implications to Glucocorticoid-Induced Osteoporosis", Journal of Clinical Endocrinology and Metabolism, 81, 3441-3447) and may also be used disorders in the immune system (see Franchimont, et. al, "Inhibition of Th1 Immune Response by Glucocorticoids: Dexamethasone Selectively Inhibits

IL-12-induced Stat 4 Phosphorylation in T Lymphocytes", *The Journal of Immunology 2000*, Feb 15, vol 164 (4), pages 1768-74) and also in the above listed indications.

Inhibition of 11-β-hsd-1 in isolated murine pancreatic β-cells improves the glucose-stimulated insulin secretion (Davani, B., et al. (2000) *J. Biol. Chem.* Nov. 10, 2000; 275(45): 34841-4). Glucocorticoids were previously known to reduce pancreatic insulin release *in vivo* (Billaudel, B. and B. C. J. Sutter (1979) *Horm. Metab. Res.* 11: 555-560). Thus, inhibition of 11-β-hsd-1 is predicted to yield other beneficial effects for diabetes treatment, besides effects on liver and fat.

Recent data suggests that the levels of the glucocorticoid target receptors and the 11-β-hsd-1 enzymes determine the susceptibility to glaucoma (Stokes, J., et al., (2000) *Invest.* Ophthalmol. 41:1629-1638). Further, inhibition of 11-β-hsd-1 was recently presented as a novel approach to lower the intraocular pressure (Walker E. A., et al, poster P3-698 at the Endocrine society meeting Jun. 12-15, 1999, San Diego). Ingestion of carbenoxolone, a non-specific inhibitor of 11-β-hsd-1, was shown to reduce the intraocular pressure by 20% in normal subjects. In the eye, expression of 11-β-hsd-1 is confined to basal cells of the corneal epithelium and the non-pigmented epithelialium of the cornea (the site of aqueous production), to ciliary muscle and to the sphincter and dilator muscles of the iris. In contrast, the distant isoenzyme 11 beta-hydroxysteroid dehydrogenase type 2 is highly expressed in the non-pigmented ciliary epithelium and corneal endothelium. None of the enzymes is found at the trabecular meshwork, the site of drainage. Thus, 11-β-hsd-1 is suggested to have a role in aqueous production, rather than drainage, but it is presently unknown if this is by interfering with activation of the glucocorticoid or the mineralocorticoid receptor, or both.

Bile acids inhibit 11-β-hydroxysteroid dehydrogenase type 2. This results in a shift in the overall body balance in favor of cortisol over cortisone, as shown by studying the ratio of the urinary metabolites (Quattropani C, Vogt B, Odermatt A, Dick B, Frey B M, Frey F J. 2001. *J Clin Invest.* Nov; 108(9): 1299-305. "Reduced Activity of 11-beta-hydroxysteroid dehydrogenase in Patients with Cholestasis"). Reducing the activity of 11-β-hsd-1 in the liver by a selective inhibitor is predicted to reverse this imbalance, and acutely counter the symptoms such as hypertension, while awaiting surgical treatment removing the biliary obstruction.

The compounds of the present invention may also be useful in the treatment of other metabolic disorders associated with impaired glucose utilization and insulin resistance include major late-stage complications of NIDDM, such as diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma, and many other conditions linked to NIDDM, including dyslipidemia glucocorticoid induced insulin resistance, dyslipidemia, polycystic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia, hypertriglyceridemia, hyperinsulinemia, and hypertension. Brief definitions of these conditions are available in any medical dictionary, for instance, Stedman's Medical Dictionary (10th Ed.).

Assay

The 11β-hsd-1 assay was performed in a 100mM Triethanolamine buffer pH 8.0, containing 200mM NaCl, 0.02% n-dodecyl β-D-maltoside, 5% glycerol, 5mM β-mercaptoethanol. A typical reaction for the determination of K_{iapp} values was carried at R.T. in a Corning® u-bottom 96-well plate and is described as follows: 11β-hsd-1 enzyme (5 nM, final concentration) was pre-incubated in the presence of the inhibitor and NADPH (500 μM, final concentration) for at least 30 minutes in the assay buffer. When pre-incubation was completed, the reaction was initiated by adding the regenerating system (2mM Glucose-6-Phosphate, 1U/mL Glucose-6-Phosphate dehydrogenase, and 6mM $MgCl_2$, all the concentration reported are final in the assay buffer), and 3H-cortisone (200 nM, final concentration). After 60 minutes, 60μL of the assay mixture was transferred to a second 96-well plate and mixed with an equal volume of dimethylsulfoxide to stop the reaction. A 15μL aliquot from the reaction mixture was loaded into a C-18 column (Polaris C18-A, 50 x 4.6mm, 5 μ, 180 Angstrom from Varian) connected to an automated High-throughput Liquid Chromatography instrument developed by Cohesive Technologies, commercially available from Franklin, Massachusetts USA, with a β-RAM model 3 Radio-HPLC detector from IN/US, commercially available from Tampa, Florida USA. The substrate and product peaks were separated by using an isocratic mixture of 43:57 methanol to water (v/v) at a flow rate of 1.0mL/min.

The initial reaction velocities were measured by stopping the reaction at 60 min and by measuring the area of product formation in the absence and the presence of various concentrations of inhibitors. The K_{iapp} values were determined using the equation for tight-binding inhibitor developed by Morrison, JF. (Morrison JF. *Biochim Biophys Acta.* 1969; 185: 269-86).

The radiolabeled [1,2-3H]-cortisone is commercially available from American Radiolabeled Chemicals Inc of St. Louis, Missouri USA. NADPH, Glucose-6-Phosphate, and Glucose-6-Phosphate dehydrogenase were purchased from Sigma®.

The K_{iapp} values of the compounds of the present invention for the 11-β-hsd-1 enzyme may lie typically between about 10 nM and about 10 μM. The compounds of the present invention that were tested all have K_{iapp}'s in at least one of the above SPA assays of less than 1 μM, preferably less than 100 nM. Certain preferred groups of compounds possess differential selectivity toward the various 11-β-hsd's. One group of preferred compounds possesses selective activity towards 11-β-hsd-1 over 11β-hsd-2. Another preferred group of compounds possesses selective activity towards 11β hsd-2 over 11-β-hsd-1. (Morrison JF. *Biochim Biophys Acta.* 1969; 185: 269-86).

Percentage of inhibition was determined in a 100mM Triethanolamine buffer, pH 8.0, 200mM NaCl, 0.02% n-dodecyl β-D-maltoside and 5mM β-ME. A typical reaction was carried on a Corning® u-bottom 96-well plate and is described as follows: 11β-hsd-1 enzyme (5 nM, final concentration) was pre-incubated in the presence of the inhibitor and NADPH (500 μM, final concentration) for at least 30 minutes in the assay buffer. When pre-incubation was

completed, the reaction was initiated by adding the regenerating system (2mM Glucose-6-Phosphate, 1U/mL Glucose-6-Phosphate dehydrogenase, and 6mM $MgCl_2$, all the concentration reported are final in the assay buffer), and 3H-cortisone (200 nM, final concentration). After 60 minutes, 60µL of the assay mixture was transferred to a second 96-well plate and mixed with an equal volume of dimethylsulfoxide to stop the reaction. A 15µL aliquot from the reaction mixture was loaded into a C-18 column (Polaris C18-A, 50 x 4.6mm, 5 µ, 180 Angstrom from Varian) connected to an automated High-throughput Liquid Chromatography instrument developed by Cohesive Technologies commercially available from Franklin, Massachusetts, with a β-RAM model 3 Radio-HPLC detector from IN/US commercially available from Tampa, Florida. The substrate and product peaks were separated by using an isocratic mixture of 43:57 methanol to water (v/v) at a flow rate of 1.0mL/min.

Percent Inhibition was calculated based on the following equation: (100 - (3H-Cortisol peak area with inhibitor/3Hcortisol peak area without inhibitor) x 100). Certain groups of compounds possess differential selectivity toward the various 11-β-hsd enzymes. One group of compounds possesses selective activity towards 11-β-hsd-1enzyme over 11β-hsd-2 enzyme. While another group of compounds possesses selective activity towards 11β hsd-2 enzymes over 11-β-hsd-1 enzymes.

[1,2-3H]-cortisone is commercially available from American Radiolabeled Chemicals Inc. of St. Louis, Missouri USA. NADPH while Glucose-6-Phosphate and Glucose-6-Phosphate dehydrogenase was purchased from Sigma®.

Pharmaceutical Compositions/Formulations, Dosaging and Modes of Administration

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. In addition, those of ordinary skill in the art are familiar with formulation and administration techniques. Such topics would be discussed, *e.g.* in Goodman and Gilman's The Pharmaceutical Basis of Therapeutics, current edition, Pergamon Press; and Remington's Pharmaceutical Sciences, current edition. Mack Publishing, Co., Easton, PA. These techniques can be employed in appropriate aspects and embodiments of the methods and compositions described herein. The following examples are provided for illustrative purposes only and are not meant to serve as limitations of the present invention.

The compounds of formula (I) or formula (II) may be provided in suitable topical, oral and parenteral pharmaceutical formulations for use in the treatment of 11-β-hsd-1 mediated diseases. The compounds of the present invention may be administered orally as tablets or capsules, as oily or aqueous suspensions, lozenges, troches, powders, granules, emulsions, syrups or elixirs. The compositions for oral use may include one or more agents for flavoring, sweetening, coloring and preserving in order to produce pharmaceutically elegant and palatable preparations. Tablets may contain pharmaceutically acceptable excipients as an aid in the manufacture of such tablets. As is conventional in the art these tablets may be coated

with a pharmaceutically acceptable enteric coating, such as glyceryl monostearate or glyceryl distearate, to delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over a longer period.

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

Aqueous suspensions normally contain active ingredients in admixture with excipients suitable for the manufacture of an aqueous suspension. Such excipients may be a suspending agent, such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; a dispersing or wetting agent that may be a naturally occurring phosphatide such as lecithin, a condensation product of ethylene oxide and a long chain fatty acid, for example polyoxyethylene stearate, a condensation product of ethylene oxide and a long chain aliphatic alcohol such as heptadecaethylenoxycetanol, a condensation product of ethylene oxide and a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate or a fatty acid hexitol anhydrides such as polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to know methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be formulated as a suspension in a non toxic perenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride solution. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) or formula (II) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at about 25 Celsius but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and other glycerides.

For topical use preparations, for example, creams, ointments, jellies solutions, or suspensions, containing the compounds of the present invention are employed.

The compounds of formula (I) or formula (II) may also be administered in the form of liposome delivery systems such as small unilamellar vesicles, large unilamellar vesicles and multimellar vesicles. Liposomes can be formed from a variety of phospholipides, such as cholesterol, stearylamine or phosphatidylcholines.

Dosage levels of the compounds of the present invention are of the order of about 0.5 mg/kg body weight to about 100 mg/kg body weight. A preferred dosage rate is between about 30 mg/kg body weight to about 100 mg/kg body weight. It will be understood, however,

that the specific dose level for any particular patient will depend upon a number of factors including the activity of the particular compound being administered, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. To enhance the therapeutic activity of the present compounds they may be administered concomitantly with other orally active antidiabetic compounds such as the sulfonylureas, for example, tolbutamide and the like.

EXAMPLES

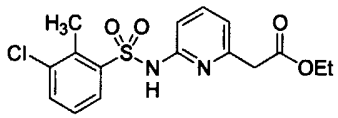
The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to the characteristic protons in the titled compound are presented where appropriate. ^{1}H NMR shift (δ_H) are given in parts per million (ppm) down filed from an internal reference standard.

The invention will now be described in reference to the following EXAMPLES. These EXAMPLES are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

Method A

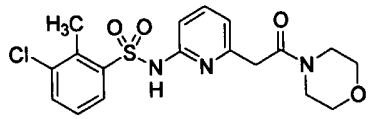
Example 1: **Ethyl [6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetate**



3-Chloro-2-methylbenzenesulfonyl chloride (3.4 g, 15 mmol, 1.5 equiv) was added in one portion to a solution of ethyl (6-amino-pyridin-2-yl)-acetate (Goto, J.; Sakane, K.; Nakai, Y.; Teraji, T.; Kamiya, T *J. Antibiot.* **1984**, *37*, 532) (1.8 g, 10 mmol, 1 equiv) in pyridine (75 mL) at 24 °C. After 16 hours, the pyridine was removed *in vacuo* (<1 mm Hg), and the resulting residue was dissolved in ethyl acetate (200 mL). The organic solution was washed sequentially with water (3 × 100 mL) and saturated aqueous sodium chloride (100 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→5% methanol in dichloromethane) yielded product (2.76g, 75%).

Method B

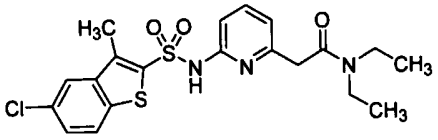
Example 8: **3-Chloro-2-methyl-*N*-[6-(2-morpholin-4-yl-2-oxo-ethyl)-pyridin-2-yl]-benzenesulfonamide**



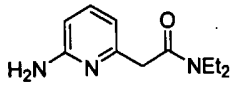
Dimethylaluminum chloride (1.36 mL, 1.36 mmol, 5.0 equiv, 1.0 M in hexanes) was added dropwise to an ice-cooled solution of morpholine (0.119 mL, 1.36 mmol, 5.0 equiv) in dichloromethane (3 mL). The resulting solution was warmed to 24 °C for 1 hour before the addition of a solution of ethyl [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetate (0.100 g, 0.271 mmol, 1 equiv) in dichloromethane (2 mL). After 1 hour, 20% sodium potassium tartrate aqueous solution (5 mL) was slowly added to the reaction mixture, and the resulting suspension was stirred vigorously for an additional hour. The resulting mixture was extracted with dichloromethane (2 × 25 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→10% methanol in dichloromethane) yielded a light orange solid (0.107 g, 96%).

Method C

Example 19: **2-[6-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-pyridin-2-yl]-N,N-diethyl-acetamide**



Preparation of (2-(6-Amino-pyridin-2-yl)-N,N-diethyl-acetamide



Dimethylaluminum chloride (4.3 mL, 4.3 mmol, 5.0 equiv, 1.0 M solution in hexanes) was added to an ice-cooled solution of diethylamine (445 µL, 4.30 mmol, 5.0 equiv) in dichloromethane (4 mL). After 10 min, the solution was warmed to 24 °C for 1 h. Ethyl (6-amino-pyridin-2-yl)-acetate (Goto, J.; Sakane, K.; Nakai, Y.; Teraji, T.; Kamiya, T. *J. Antibiot.* **1984**, *37*, 532) (155 mg, 0.860 mmol, 1 equiv) in dichloromethane (4 mL) was added at 24 °C. After 21.5 h, potassium sodium tartrate aqueous solution (20% wt/wt, 10 mL) and hexanes (20 mL) were added sequentially, and the resulting mixture was stirred vigorously overnight. Saturated aqueous sodium chloride (30 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→4.5% methanol in dichloromethane + 0.1% ammonium hydroxide) provided product (120 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.37 (m, 1 H), 6.66 (d, J = 7.6

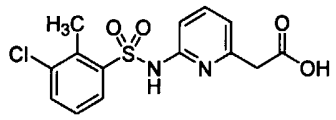
Hz, 1 H), 6.35 (d, *J* = 8.1 Hz, 1 H), 4.34 (br s, 2 H), 3.69 (s, 2 H), 3.30–3.44 (m, 4 H), 1.06–1.16 (m, 6 H).

2-[6-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-pyridin-2-yl]-N,N-diethyl-acetamide

5-chloro-3-methylbenzo[B]thiophene-2-sulfonyl chloride (163 mg, 0.580 mmol, 1.1 equiv) was added to a solution of 2-(6-amino-pyridin-2-yl)-*N,N*-diethyl-acetamide (100 mg, 0.483 mmol, 1 equiv) in pyridine (4 mL) at 24 °C. After 18 h, the reaction mixture was diluted with ethyl acetate (30 mL). The resulting solution was washed with water (60 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→5% methanol in dichloromethane) provided the title compound (93 mg, 43%).

Method D

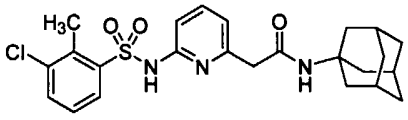
Example 26: [6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid



Potassium hydroxide (0.843 g, 15.0 mmol, 6.00 equiv) was added to a solution of [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid ethyl ester (0.922 g, 2.50 mmol, 1 equiv) in 20:1 ethanol / water (21 mL) at 24 °C. After 1 h, the reaction mixture was concentrated *in vacuo* (~25 mm Hg), and the resulting residue was dissolved in water (50 mL). The aqueous solution was acidified by the addition of 10% hydrochloric acid aqueous solution until pH = 2. The heterogeneous solution was then filtered, and the solid was rinsed sequentially with water (50 mL) and diethyl ether (2 × 50 mL). The solid was dried *in vacuo* (<1 mm Hg, 50 °C) to provide product as a tan solid (0.810 g, 71%).

Method E

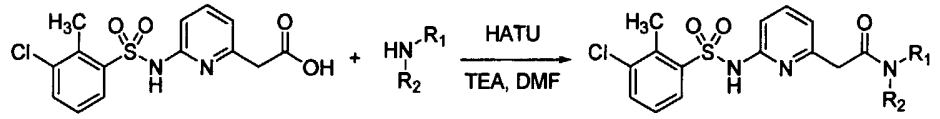
Example 27: *N*-Adamantan-1-yl-2-[6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetamide



O-(7-Azabenzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.11 g, 0.29 mmol, 0.98 equiv) was added in one portion to an ice-cooled solution of [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid (0.100 g, 0.293 mmol, 1 equiv), 1-adamantanamine (0.200 g, 1.32 mmol, 4.51 equiv), and *N,N*-diisopropylethylamine (0.462 mL, 2.65 mmol, 9.04 equiv) in dimethylformamide (5 mL). The solution was warmed to 24 °C and stirred overnight. Dimethylformamide was removed *in vacuo* (~ 1 mm Hg), and the resulting residue was dissolved in dichloromethane (20 mL). The organic was washed sequentially with deionized water (2 × 20 mL) and saturated aqueous sodium chloride (20

mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification of the resulting residue by high performance flash chromatography (0→2% methanol in dichloromethane) yielded desired amide (82 mg, 65%).

Alternative General Method for amide coupling



Reactant A
1 equiv

Reactant B
1 equiv

A stir bar, the amine (***Reactant B***, 400μL, 80 μmol, 1.00 equiv 0.2 M in anhydrous DMF), [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid (***Reactant A*** 200μL, 80 μmol, 1.00 equiv 0.2 M in anhydrous DMF), TEA (160μL, 80 μmol, 1.00 equiv 0.5 M in anhydrous DMF), HATU (160μL, 80 μmol, 1.00 equiv 0.5 M in anhydrous DMF) were placed into a 10 x 75 mm test tube. The tube was sealed with cellophane and the reaction stirred for 16 h at ambient temperature. The solvent was evaporated and the residue dissolved in DMSO containing 0.01 % BHT to yield a 0.05 M solution. The solution was injected into an automated HPLC system for purification. The solvent of the product containing fraction was evaporated, the residue dissolved in DMSO, analyzed, and submitted for screening.

General Analysis and Purification Procedures

The crude reaction mixtures were analyzed by HPLC using Method 1. Prior to purification, all samples were filtered through Whatman® GF/F Unifilter (#7700-7210), commercially available from Whatman® of Clifton, New Jersey USA. Purification of samples was performed by reverse phase HPLC using the method 3. Fractions were collected in 23 mL pre-tared tubes and centrifugal evaporated to dryness. Dried product was weighed and dissolved in DMSO. Products were then analyzed using Method 5 and submitted for screening.

Analytical LCMS Method 1 (Pre-purification)

Column: Peeke Scientific® HI-Q C-18, 50 x 4.6 mm, commercially available from Peeke Scientific® of Redwood City, CA, 5μm, Eluent A: Water with 0.05% TFA, Eluent B: Acetonitrile with 0.05% TFA, Gradient: linear gradient of 0-100% B in 3.0 min, then 100% B for 0.5 min, then 100-0% B in 0.25 min, hold 100% A for 0.75 min, Flow: 2.25 mL/min, Column Temperature: 25°C, Injection Amount: 15 μl of a 286 μM crude solution in methanol/DMSO/water 90/5/5, UV Detection: 260 and 210 nm, Mass Spectrometry: APCI, positive mode, mass scan range 111.6-1000 amu.

Preparative LC Method 3 (Gilson)

Column: Peeke Scientific® HI-Q C18, 50mm X 20mm, 5μm, Eluent A: 0.05% TFA in Water, Eluent B: 0.05% TFA in Acetonitrile, Pre-inject Equilibration: 0.50 min, Post-inject Hold: 0.16 min, Gradient: 0-100% B in 2.55 minutes, then ramp 100% back to 0% in 0.09min,

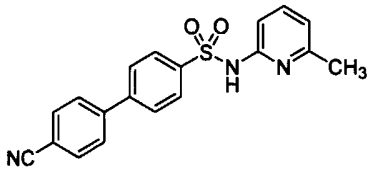
Flow: 50.0 mL/min, Column Temp: Ambient, Injection Amount: 1200 µL of filtered crude reaction mixture in DMSO, Detection: UV at 210 nm or 260 nm.

Analytical LCMS Method 5 (Post-purification)

Column: Peeke Scientific® HI-Q C-18, 50 x 4.6mm, 5 µm, Eluent A: Water with 0.05% TFA, Eluent B: Acetonitrile with 0.05% TFA, Gradient: linear gradient of 0-100% B in 1.75 min, then 100% B for 0.35 min, then 100-50% B for 0.5 min, Flow: 3.00 mL/min, Column Temperature: 25°C, Injection Amount: 15 µl of a 300 µM solution in methanol/DMSO 99/1, UV Detection: 260 nm, Mass Spectrometry: APCI, positive mode, mass scan range 100-1000 amu, ELSD: gain=9, temp 40°C, nitrogen pressure 3.5 bar.

Method F

Example 33: 4'-Cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



A solution of 4'-cyano-biphenyl-4-sulfonyl chloride (32.00 g, 115 mmol) and 2-amino-6-picoline (13.70 g, 127 mmol) in pyridine was stirred at room temperature for 18 h. The solvent was removed and the residue was poured into water (500 mL). The product was extracted with ethyl acetate (4 × 200 mL). The combine organic extracts were washed with brine and concentrated. Purification by flash silica chromatography on silica gel (40% ethyl acetate in hexanes → ethyl acetate) gave the title compound (28.80 g, 72%).

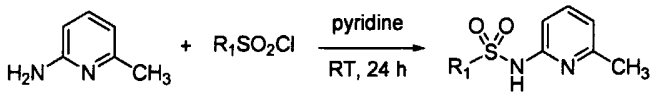
Preparation of Sodium 4'-Cyanobiphenyl-4-sulfonate

(Modification of Himmelsbach, F.; Austel, V.; Pieper, H.; Eisert, W.; Mueller, T.; Weisenberger, J.; Linz, G.; Krueger, G. *Eur. Pat. Appl* **1992**, EP 483667 A2) Chlorosulfonic acid (116.5 mL, 1.744 mmol) was added to a solution of 4-biphenylcarbonitrile (156.2 g, 0.872 mol) in dichloromethane (3 L) at –14 °C while maintaining the reaction temperature below –10 °C. The mixture was warmed to 10 °C over 1 h and maintained at 8–10 °C for 6 h. Triethylamine was added while maintaining the temperature below 12 °C. The mixture was stirred for 15 min until all black / brown solids were dissolved and a while precipitate formed. Water (300 mL) was added, and the slurry was stirred for 10 min and concentrated. A solution of sodium hydroxide (2 L, 15%) was added, and the reaction mixture was concentrated until at least half of the volume was distilled. Concentrated hydrochloric acid (~300 mL) was added until a pH of 7 was reached, and the final volume was adjusted to 2.2 L by the addition of water. A saturated solution of sodium chloride (2.2 L) was added, and the resulting mixture was stirred for 10 min. The solids were filtered and dried in a vacuum oven (80 °C) to afford 251.0 g of the product as a white to yellow solid. The product contains a substantial amount of sodium chloride.

Preparation of 4'-Cyanobiphenyl-4-sulfonyl chloride

(Modification of Himmelsbach, F.; Austel, V.; Pieper, H.; Eisert, W.; Mueller, T.; Weisenberger, J.; Linz, G.; Krueger, G. *Eur. Pat. Appl* **1992**, EP 483667 A2). A mixture of sodium 4'-cyanobiphenyl-4-sulfonate (251 g) and phosphorous oxychloride was refluxed for 16 h. The reaction mixture was poured into a large quantity of ice / water and the resulting slurry was extracted with dichloromethane (1 x 1.8 L). The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated to approximately 200 mL. Hexanes (200 mL) was added. The slurry was stirred for 30 min, filtered, washed with 1:1 dichloromethane / hexanes, and dried to give 82.1 g of product. The mother liquor was concentrated and further purified by flash chromatography on silica gel (40→70% dichloromethane / hexanes) to give an additional 16.2 g of white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13–8.19 (m, 2 H), 7.80–7.86 (m, 4 H), 7.72–7.77 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.2, 144.2, 143.0, 133.2, 128.7, 128.4, 128.0, 118.5, 113.1.

Alternative General Method for Sulfonamide Formation



The sulfonyl chloride (104 μmol, 1.3 equiv 400 μL of a 0.26 M solution in anhydrous pyridine) and 2-amino-6-picoline (80 μmol, 1.0 equiv 400 μL of a 0.2 M solution in anhydrous pyridine) were placed into a test tube (75x10 mm, dried by heating at 110 °C for 16 h) equipped with a stir bar. The test tube was covered with Parafilm® and the reaction was stirred for 24 h at ambient temperature. The solvent was evaporated and the residue was dissolved in EtOAc (1 mL). After dissolution was completed or a fine suspension had formed, $NaHCO_3$ (0.5 mL of a sat aq. solution) was added. The reaction mixture was vortexed and the phases were separated by centrifugation. The organic layer was transferred into a new test tube (95x10 mm) and the aq. phase was extracted with EtOAc (2x 0.8 mL). The organic phases were combined, the solvent was evaporated, and the residue was dissolved in DMSO (1.340 mL).

General Analysis and Purification Procedures

The crude reaction mixtures were analyzed by SFC using Method 2. Prior to purification, all samples were filtered through Whatman® GF/F Unifilter (#7700-7210). Purification of samples was performed by SFC using the method 4. Fractions were collected in 23 mL pre-tared tubes and centrifugal evaporated to dryness. Dried product was weighed and dissolved in DMSO. Products were then analyzed using Method 5 and submitted for screening.

Analytical SFC Method 2 (Pre-purification)

Column: Zymor Pegasus, 150x4.6mm i.d., 5um, Gradient: 5% methanol-modified CO2 ramped to 50% methanol @ 18%/min and held for 0.1 min, Flow rate: 5.6 mL/min, Column Temp.=50C, Isobaric pressure: 140 bar, UV Detection = 260nm.

Preparative SFC Method 4

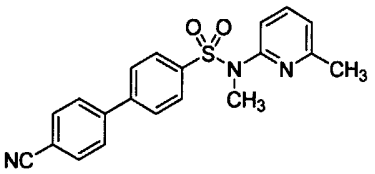
Column: Zymor Pegasus, 150x21.2mm i.d., 5 μm semi-preparative column, Lot 2174, Column Temp: 35 °C, Gradient: 5% methanol-modified CO_2 held for 0.1minute, ramped to 60% methanol @ 10%/min and held for 1.0 minute, Flow Rate: 53 mL/min, Isobaric pressure: 140 bar, UV Detection: 260nm.

Analytical LCMS Method 5 (Post-purification)

Column: Peeke Scientific® HI-Q C-18, 50 x 4.6mm, 5 μm, Eluent A: Water with 0.05% TFA, Eluent B: Acetonitrile with 0.05% TFA, Gradient: linear gradient of 0-100% B in 1.75 min, then 100% B for 0.35 min, then 100-50% B for 0.5 min, Flow: 3.00 mL/min, Column Temperature: 25°C, Injection Amount: 15 μl of a 300 uM solution in methanol/DMSO 99/1, UV Detection: 260 nm, Mass Spectrometry: APCI, positive mode, mass scan range 100-1000 amu, ELSD: gain=9, temp 40°C, nitrogen pressure 3.5 bar.

Method G

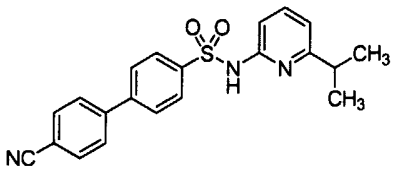
Example 110: 4'-Cyano-biphenyl-4-sulfonic acid methyl-(6-methyl-pyridin-2-yl)-amide



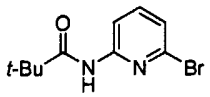
To a solution of *N*,6-dimethylpyridin-2-amine (0.15 g, 1.24 mmol) in THF (5 ml) was added NaHMDS (1.56 mL, 1.56 mmol) at R.T. After 15 min, 4'-cyanobiphenyl-4-sulfonyl chloride (0.28 g, 1.03 mmol) was added to the reaction mixture and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (2 X 30 mL). The collected organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified with radial chromatography (2 mm silica plate, 2:1 hexanes / ethyl acetate) to yield a clear oil. The product was converted to a HCl salt by dissolving in 5 mL diethyl ether and adding 1N HCl in diethyl ether dropwise. The solid was triturated with additional ether and dried on high vacuum to afford the product (0.11 g, 29.5%).

Method H

Example 111: 4'-Cyano-biphenyl-4-sulfonic acid (6-isopropyl-pyridin-2-yl)-amide

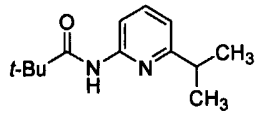


Preparation of N-(6-Bromo-pyridin-2-yl)-2,2-dimethyl-propionamide



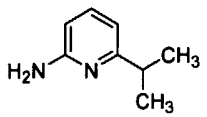
To an ice-cooled solution of 6-bromopyridin-2-amine (7.0 g, 40.5 mmol) in 60 mL of CH_2Cl_2 was added 2,2-dimethylpropanoyl chloride (5.23 mL, 42.48 mL) and diisopropylethylamine (13.6 mL, 82.9 mmol) sequentially. The solution was stirred for 1h then diluted with 50 mL of diethyl ether. The mixture was washed with saturated aqueous sodium bicarbonate (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in ethyl acetate (10 mL) and hexane (20 mL) and allowed to stand for 3 h. The product was filtered, rinsed with 1:1 hexanes / ethyl acetate, and dried *in vacuo* to afford the title compound as a white solid (9.56 g, 93%). ^{1}H NMR (400 MHz, CD_3CN), δ: 8.22 (d, *J* = 8.4 Hz, 1 H), 7.99 (bs, 1 H), 7.55 (t, *J* = 8.1 Hz, 1 H), 7.22 (d, *J* = 7.3 Hz, 1 h), 1.31 (s, 9 H); LCMS (ESI): *m/z*: 258.0.

Preparation of N-(6-Isopropyl-pyridin-2-yl)-2,2-dimethyl-propionamide



Cu(I) (7.40 g, 38.8 mmmol) was added to a solution of *N*-(6-bromopyridin-2-yl)-2,2-dimethylpropanamide (5.0 g, 19.4 mmol) in THF (100 mL) at -78 °C. After 0.5 hours, isopropylmagnesium chloride (48.5 mL, 1M in THF) was added dropwise at -78 °C, and the resulting solution was warmed to 25 °C for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride (50 mL) then diluted with ethyl acetate (100 mL). The solids were removed by filtration. The solution was washed sequentially with saturated aqueous ammonium chloride (2 x 50 mL) and saturated aqueous sodium bicarbonate (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (2:1 hexane / ethyl acetate) afforded the title product as an amber oil (2.60 g, 60.4%). ^{1}H NMR (400 MHz, CD_3CN), δ: 8.04 (d, *J* = 7.8 Hz, 1 H), 7.97 (bs, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 6.90 (d, *J* = 7.5 Hz, 1 H), 2.95-2.88 (m, 1 H), 1.34 (s, 9 H), 1.28 (d, *J* = 7.1 Hz, 6 H); LCMS (ESI): *m/z*: 221.2.

Preparation of 6-Isopropyl-pyridin-2-ylamine



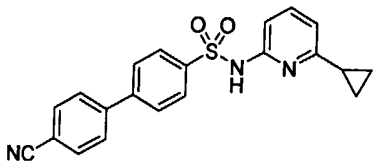
To a solution of *N*-(6-isopropylpyridin-2-yl)-2,2-dimethylpropanlamide (2.0 g, 9.08 mmol) in dioxane (5 mL) was added HCl (9N, 10 mL). The mixture was stirred for 18 hours at 80 °C. After cooling to 25 °C, the pH of the reaction mixture was adjusted with NaOH to achieve pH 9. The solution was diluted with ethyl acetate (120 mL) and washed with saturated aqueous sodium bicarbonate (2 x 30 mL). Next, the organic layer was azeotroped with toluene (10 mL) to afford 6-isopropylpyridin-2-amine as clear oil (0.68 g, 55%). ^{1}H NMR(400 MHz, CD_3CN), δ: 7.36 (t, *J* = 7.8 Hz, 1 H), 6.64 (d, *J* = 8.7, 1 H), 6.32 (d, *J* = 8.1 Hz, 1 H), 1.25 (d, *J* = 4.5 Hz, 9 H); LCMS (ESI): *m/z*: 137.2.

4'-Cyano-biphenyl-4-sulfonic acid (6-isopropyl-pyridin-2-yl)-amide

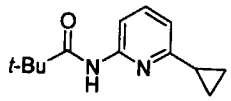
Made following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-isopropyl-pyridin-2-ylamine and making non-critical variations.

Method I

Example 112: 4'-Cyano-biphenyl-4-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide

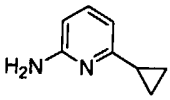


Preparation of N-(6-Cyclopropyl-pyridin-2-yl)-2,2-dimethyl-propionamide



To a solution of *N*-(6-bromopyridin-2-yl)-2,2-dimethylpropanamide (4.20 g, 16.3 mmol), cyclopropylboronic acid (1.82 g, 21.8 mmol), $Pd(OAc)_2$ (0.18 g, 0.82 mmol) and PCy_3 (0.38 g, 1.62 mmol) in toluene (20 mL) was added K_3PO_4 (12.8 g, 60.3 mmol) and water (1 mL). The mixture was stirred at 95 °C for 12h, then cooled to 25 °C. The reaction mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a clear oil. The residue was purified by flash column chromatography (5:1 hexanes/Et_2O) to give the title product as a clear oil (2.25 g, 63.3%). ^1H NMR (400 MHz, $CDCl_3$), δ: 7.98 (d, *J* = 8.3, 1 H), 7.88 (bs, 1 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 1.98-1.91 (m, 1 H), 1.32 (s, 9 H), 0.94 (d, *J* = 6.6 Hz, 4 H); LCMS (ESI): 219.2.

Preparation of 6-Cyclopropyl-pyridin-2-ylamine



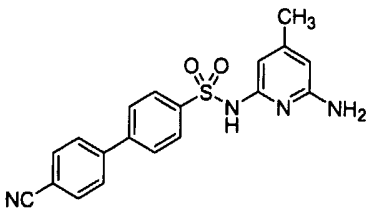
Made by following the procedure described for the preparation of 6-isopropyl-pyridin-2-ylamine but substituting N-(6-cyclopropyl-pyridin-2-yl)-2,2-dimethyl-propionamide and making non-critical variations. ^1H NMR(400 MHz, $CDCl_3$), δ: 7.70 (t, *J* = 7.8, 1 H), 6.85 ((t, *J* = 7.4, 1 H), 6.65 (d, J = 7.5 Hz, 1 H), 4.79 (bs, 2 H); LCMS (ESI): *m/z*: 135.2.

4'-Cyano-biphenyl-4-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-cyclopropyl-pyridin-2-ylamine and making non-critical variations.

Method J

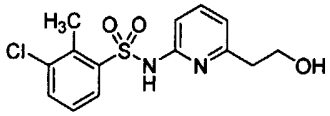
Example 113: 4'-Cyano-biphenyl-4-sulfonic acid (6-amino-4-methyl-pyridin-2-yl)-amide



To a solution of 4-methylpyridine-2,6- diamine (*J. Org. Chem.* **2001**, *61*, 6513)(102 mg, 0.825 mmol) in THF (6 mL) was added diispropylethylamine (287 uL, 1.65 mmol) followed by 4-(dimethylamino)pyridine (5 mg, 0.04 mmol). To the resulting solution was added 4'-cyanobiphenyl-4-sulfonyl chloride in CH_2Cl_2 (3 mL). The heterogeneous mixture was stirred at R.T. overnight. By morning all solids had dissolved and the solution was concentrated *in vacuo*. The residue was dissolved in MeOH/CH_2Cl_2 and to the solution was added DOWEX® 50WX2-400 ion exchange resin, commercially available from DOW Company of Midland, Michigan USA, (2 wt equiv) and the mixture was stirred at R.T. for 1 hour. The mixture was filtered and the resin was washed with MeOH and CH_2Cl_2. The resin was then cleaved by washing with 3.5 N methanolic ammonia and the mother liquor was concentrated *in vacuo*. To the residue was added MeOH, and the solids were filtered to afford the title compound (50 mg, 25%).

Method K

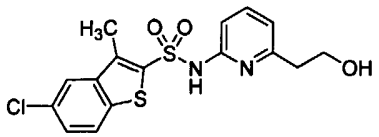
Example 114: 3-Chloro-N-[6-(2-hydroxy-ethyl)-pyridin-2-yl]-2-methyl-benzenesulfonamide



Borane-tetrahydrofuran complex (0.924 mL, 0.924 mmol, 3.0 equiv, 1.0 M tetrahydrofuran solution) was added to an ice-cooled solution of [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid (105 mg, 0.308 mmol, 1 equiv) in tetrahydrofuran. After 1 h, the reaction mixture was warmed to 24 °C for 17.5 h. Aqueous hydrochloric acid (3 mL, 5% wt) was added, and the resulting solution was stirred vigorously. After 30 min, saturated aqueous sodium bicarbonate solution (8 mL) was added, and the mixture was extracted with dichloromethane (3 × 15 mL). The collected organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→5% methanol in dichloromethane) yielded product (45.5 mg, 45%).

Method L

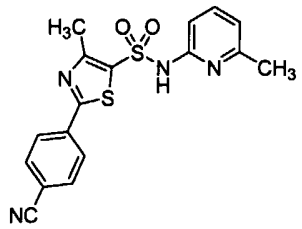
Example 115: 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [6-(2-hydroxy-ethyl)-pyridin-2-yl]-amide



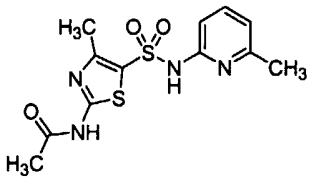
Lithium aluminum hydride (0.015 g, 0.310 mmol, 1.3 equiv) was added in one portion to an ice-cooled solution of [6-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-pyridin-2-yl]-acetic acid ethyl ester (0.100 g, 0.235 mmol, 1 equiv) in tetrahydrofuran (4 mL). After 5 min, the reaction mixture was warmed to 24 °C for 16 h. The reaction mixture was cooled to 0 °C, and excess lithium aluminum hydride was quenched with saturated aqueous ammonium chloride solution (10 mL). The resulting solution was warmed to 24 °C and stirred for an additional 30 min. The reaction mixture was filtered through a plug of Celite®, and the resulting filtrate was extracted with dichloromethane (60 mL). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification of the residue by high performance flash chromatography (0→1% methanol in dichloromethane) yielded product (0.0421 g, 47%).

Method M

Example 118: 2-(4-Cyano-phenyl)-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide

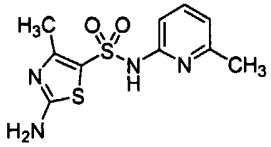


Preparation of N-[4-Methyl-5-(6-methyl-pyridin-2-ylsulfamoyl)-thiazol-2-yl]-acetamide



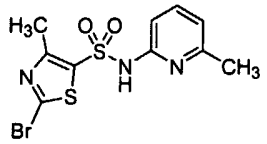
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 2-acetamido-4-methyl-5-thiazole sulfonyl chloride and making non-critical variations. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.56 (dd, J = 8.7, 7.2 Hz, 1 H), 7.10 (d, J = 8.6 Hz, 1 H), 6.58 (d, J = 7.3 Hz, 1 H), 2.53 (s, 3 H), 2.47 (s, 3 H), 2.24 (s, 3 H); MS (ESI) for $C_{12}H_{15}N_4O_3S_2$ *m/z*: 327.0.

Preparation of 2-Amino-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide



A solution of N-[4-methyl-5-(6-methyl-pyridin-2-ylsulfamoyl)-thiazol-2-yl]-acetamide (2.15 g, 6.58 mmol, 1 equiv) and aqueous hydrochloric acid (1.6 mL, 12 M) in ethanol (30 mL) was refluxed overnight. Upon cooling to 24 °C, the reaction mixture was concentrated *in vacuo* (~25 mm Hg). The resulting solid was dissolved in water (10 mL). The solution was neutralized with saturated aqueous sodium bicarbonate until pH = 7. The resulting solid was collected by filtration. Lyophilization of the solid provided an off-white solid (1.67 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.64 (t, J = 8.0 Hz, 1 H), 7.44 (s, 2 H), 6.93 (m, 1 H), 6.70 (m, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H); MS (ESI) for $C_{10}H_{13}N_4O_2S_2$ *m/z*: 285.1.

Preparation of 2-Bromo-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide



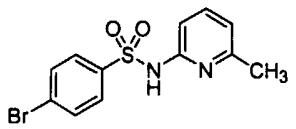
To a suspension of 2-amino-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide (0.200 g, 0.703 mmol, 1 equiv) and copper (II) bromide (0.098 g, 0.68 mmol, 0.62 equiv) in acetonitrile (6 mL) at 65 °C was added *tert*-butyl nitrite (0.128 mL, 1.08 mmol, 1.5 equiv). The reaction mixture changed from green to red and gas evolution was observed. After 10 min when gas evolution ceased, the reaction mixture was cooled to 24 °C and diluted with ethyl acetate (60 mL). The resulting mixture was washed with saturated aqueous sodium chloride (2 × 30 mL). The collect organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→2% methanol in dichloromethane) provided product (0.156 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.61 (dd, J = 8.8, 7.1 Hz, 1 H), 7.00 (d, J = 8.8 Hz, 1 H), 6.58 (d, J = 7.3 Hz, 1 H), 2.65 (s, 3 H), 2.49 (s, 3 H); MS (ESI) for $C_{10}H_{11}BrN_3O_2S_2$ *m/z*: 349.9.

2-(4-Cyano-phenyl)-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide

A solution of 2-bromo-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide (0.080 g, 0.23 mmol, 1 equiv), 4-cyanophenylboronic acid (0.034 g, 0.23 mmol, 1.0 equiv), and cesium carbonate (0.225 g, 0.690 mmol, 3.00 equiv) in 2:1 dimethoxyethane / water (1.5 mL) was purged with nitrogen for 15 min. Dichloro[1,1'-bis(diphenylphosphine)ferrocene] palladium (II) chloride (0.008 g, 0.009 mmol, 0.04 equiv) was then added, and the resulting mixture was purged with nitrogen for another 15 minutes. The reaction mixture was heated to 80 °C for 1 h. After cooling to 24 °C, the resulting solution was diluted with ethyl acetate (40 mL) and washed with saturated aqueous sodium chloride (2 × 30 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→1% methanol in dichloromethane) provided the titled compound (62 mg, 73%).

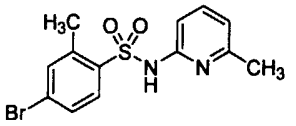
Method N

Preparation of 4-Bromo-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide



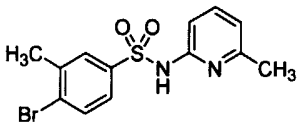
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromobenzenesulfonyl chloride and making non-critical variations. 1H NMR (400 MHz, $CDCl_3$), δ ppm 7.61 - 7.68 (m, 2 H) 7.40 - 7.46 (m, 2 H) 7.36 (dd, *J*=8.6, 7.3 Hz, 1 H) 6.77 - 6.83 (d, *J*=8.8 Hz, 1 H) 6.42 (d, *J*=7.1 Hz, 1 H) 2.28 (s, 3 H).

Preparation of 4-Bromo-2-methyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide



Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-2-methylbenzene-1-sulfonyl chloride (commercially available from ASDI, Inc. of Newark, Delaware USA) and making non-critical variations. $APCI^+$ 342 $[M+H]^+$ 100%.

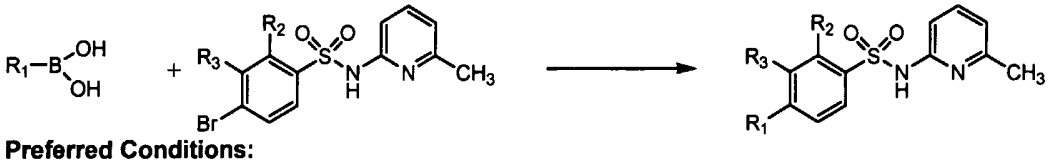
Preparation of 4-Bromo-3-methyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide



Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-3-methylbenzene-1-sulfonyl chloride (available from Lancaster) and making non-critical variations. $APCI^+$ 342 $[M+H]^+$ 100%.

General Method for Microwave Assisted Suzuki-Miyaura Cross-Coupling

This protocol discloses a procedure for the synthesis of biaryls through a Suzuki-Miyaura cross-coupling of an 4-bromobenzenesulfonamide (***Reactant A***) and an aryl boronic-acid (***Reactant B***).



Preferred Conditions:

In a glove box, the following was added to a 2.0 mL Personal Chemistry Microwave reaction tube:

(1) one triangular stir bar,

(2) 4-Bromobenzenesulfonamide (***Reactant A,*** 320 µL, 80 µmol, 1.0 equiv, 0.25 M in anhydrous DMF),

(3) the appropriate aromatic boronic acid (***Reactant B***, 320 µL, 80 µmol, 1.0 equiv, 0.25 M in anhydrous DMF),

(4) the catalyst $Pd(PPh_3)_4$ (320 µL, 4 µmol, 0.05 equiv, 0.0125 M in anhydrous THF), and

(5) K_2CO_3 (100 µL, 200 µmol, 2.5 equiv, 2 M in degassed DI water).

(6) The microwave tube was sealed with a septum cap.

Outside the glove box, the reaction mixtures were heated in a Personal Chemistry Microwave Synthesizer (SmithCreator™) for 15 min at 130 °C (energy-control setting for a high absorbing sample). The septum caps were removed and the reaction mixture was transferred into a 13x100 mm test tube while leaving any solid material behind. The microwave tubes were washed with DMF (1 mL) and the DMF was added to the receiving test tube.

Next, the solvent was evaporated (SpeedVac, vaccum, medium heating, 16 h). EtOAc (1 mL) and water (1.0 mL) were added and the mixture was vortexed at ambient temperature until the residue had dissolved (*Note: Some of the palladium in the reaction mixture will form a small amount of a black material that will not dissolve*). The test tubes were centrifuged until the phases had separated (some of the black palladium material will settle at the organic/aqueous interface). The organic layer was transferred into a new test tube (13x100 mm). The aq. layer was extracted with EtOAc (2x 1 mL) and the extracts were added to the test tube with the organic layer. The combined organic phase was washed with water (1 mL) followed by brine (1 mL). The solvent was evaporated and the residue dissolved in DMSO. Purification was peformed by reverse phase preparative HPLC.

General Analysis and Purification Procedures

The crude reaction mixtures were analyzed by HPLC using Method 1. Prior to purification, all samples were filtered through Whatman® GF/F Unifilter (#7700-7210). Purification of samples was performed by reverse phase HPLC using the method 3. Fractions were collected in 23 mL pre-tared tubes and centrifugal evaporated to dryness. Dried product was weighed and dissolved in DMSO. Products were then analyzed using Method 5 and submitted for screening.

Analytical LCMS Method 1 (Pre-purification)

Column: Peeke Scientific® HI-Q C-18, 50 x 4.6 mm, 5µm, Eluent A: Water with 0.05% TFA, Eluent B: Acetonitrile with 0.05% TFA, Gradient: linear gradient of 0-100% B in 3.0 min, then 100% B for 0.5 min, then 100-0% B in 0.25 min, hold 100% A for 0.75 min, Flow: 2.25 ml/min, Column Temperature: 25°C, Injection Amount: 15 µl of a 286 µM crude solution in methanol/DMSO/water 90/5/5, UV Detection: 260 and 210 nm, Mass Spectrometry: APCI, positive mode, mass scan range 111.6-1000 amu.

Preparative LC Method 3 (Gilson)

Column: Peeke Scientific® HI-Q C18, 50mm X 20mm, 5µm, Eluent A: 0.05% TFA in Water, Eluent B: 0.05% TFA in Acetonitrile, Pre-inject Equilibration: 0.50 min, Post-inject Hold: 0.16 min, Gradient: 0-100% B in 2.55 minutes, then ramp 100% back to 0% in 0.09 min,

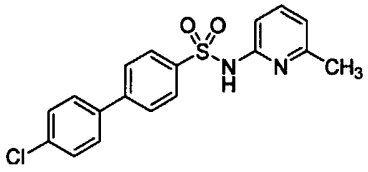
Flow: 50.0 mL/min, Column Temp: Ambient, Injection Amount: 1200 µL of filtered crude reaction mixture in DMSO, Detection: UV at 210 nm or 260 nm.

Analytical LCMS Method 5 (Post-purification)

Column: Peeke Scientific® HI-Q C-18, 50 x 4.6mm, 5 µm, Eluent A: Water with 0.05% TFA, Eluent B: Acetonitrile with 0.05% TFA, Gradient: linear gradient of 0-100% B in 1.75 min, then 100% B for 0.35 min, then 100-50% B for 0.5 min, Flow: 3.00 mL/min, Column Temperature: 25°C, Injection Amount: 15 µl of a 300 µM solution in methanol/DMSO 99/1, UV Detection: 260 nm, Mass Spectrometry: APCI, positive mode, mass scan range 100-1000 amu, ELSD: gain=9, temperature 40°C, nitrogen pressure 3.5 bar.

Method O

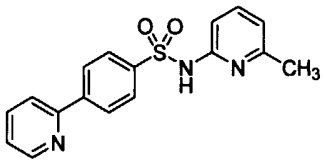
Example 249: 4'-Chloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



To a mixture of 4-Bromo-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide (160 mg, 0.489 mmol) and 4-chlorophenylboronic acid (76.5 mg, 0.489 mmol) in DMF (2 mL) was added aqueous Na_2CO_3 (2.0 M, 0.625 mL; 1.25 mmol) followed by $Pd(PPh_3)_4$ (28 mg, 0.0245 mmol). The resulting mixture was heated at 130 °C for 15 min in microwave oven. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (50% EtOAc/Hexane) to yield the title compound as a yellow solid (130 mg, 74%).

Method P

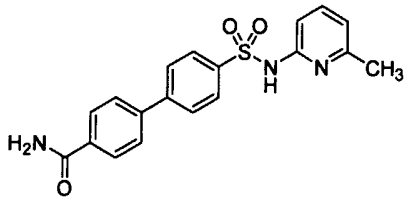
Example 259: *N*-(6-Methyl-pyridin-2-yl)-4-pyridin-2-yl-benzenesulfonamide trifuoroacetate



A mixture of 4-Bromo-*N*- (6-methyl-pyridin-2-yl)-benzenesulfonamide (117 mg, 0.358 mmol), 2-pyridyltributyltin (197 mg, 0.536 mol) and Pd $(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol) in DMF (2 mL) was heated in a microwave oven for 1 h. DMF was removed under vacuum. The residue was purified by reverse phase preparative HPLC to yield the title compound as white solid (42 mg, 0.129 mmol; 36%).

Method Q

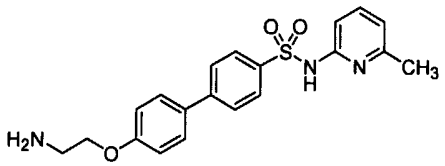
Example 262: 4'-(6-Methyl-pyridin-2-ylsulfamoyl)-biphenyl-4-carboxylic acid amide



To a solution of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide (144 mg, 0.286 mmol) in 30% H_2O_2 (1 mL) and EtOH (1 mL) was added 4N NaOH (0.2 mL). The mixture become clear. After 12 h, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over sodium sulphate and concentrated. The residue was chromatographed over silica gel (60% EtOAc/hexane) to give the title compound as a white solid.

Method R

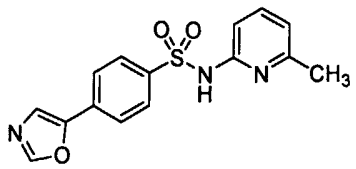
Example 263: 4'-(2-Amino-ethoxy)-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



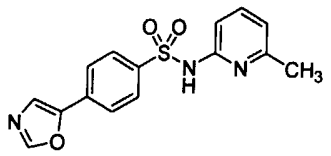
To a yellow solution of 4-hydroxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide (129 mg, 0.378 mmol), N-hydroxyethylphthaliamide (80 mg, 0.416 mmol), triphenylphosphine (119 mg, 0.454 mmol) in THF (3 mL) was added DEAD (72 µL, 0.454 mmol). After stirring overnight, the mixture was concentrated. The residue was chromatographed on silica gel (40-70% EtOAc/hexane) to give the ether intermediate (152 mg, 79%). To a solution of the above ether intermediate (152 mg, 0.3 mmol) in MeOH (3 mL) was added hydrazine (74 µL, 1.5 mmol). The mixture was stirred at R.T. for 2 h and concentrated to give a residue, which was purified by preparative HPLC to give the final product as a white solid (60 mg, 52%).

Method S

Example 264: N-(6-Methyl-pyridin-2-yl)-4-oxazol-5-yl-benzenesulfonamide



Preparation of 4-Formyl-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide



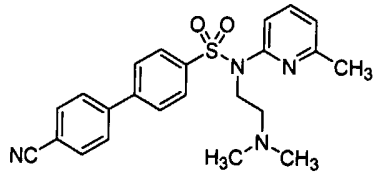
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-formylbenzensulfonyl chloride.

N-(6-Methyl-pyridin-2-yl)-4-oxazol-5-yl-benzenesulfonamide

A solution of sulfonamide from step 1 (449 mg, 1.63 mmol), $TsCH_2NC$ (349 mg, 1.79 mmol) and K_2CO_3 (450 mg, 3.25 mmol) in MeOH (5 mL) was refluxed for 12 h. The mixture was cooled to R.T. and partitioned between EtOAc and water. The organic layer was dried over sodium sulfate and concentrated to give a residue, which was purified by flash column chromatography (60% EtOAc / hexanes) to give the title compound as a white solid (301 mg, 58% yield). ^1H NMR (400 MHz, $CDCl_3$), δ: 8.21 (s, 1 H), 7.90 (d, *J*=8.3 Hz, 1 H), 7.62 (d, *J*=8.3 Hz, 1 H), 7.56 (s, 1 H), 7.54 (m, 1 H), 7.04 (m, 1 H), 6.56 (m, 1 H), 2.30 (s, 3 H). Anal. Calcd for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33; Found: C, 57.31; H, 4.22; N, 12.92.

Method T

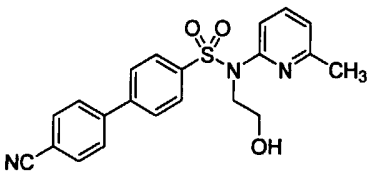
Example 265: 4'-Cyano-biphenyl-4-sulfonic acid (2-dimethylamino-ethyl)-(6-methyl-pyridin-2-yl)-amide



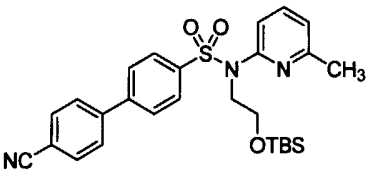
2-(Dimethylamino)ethyl chloride hydrochloride (70 mg, 0.49 mmol, 1.8 equiv) was added to a solution of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide (93.1 mg, 0.266 mmol, 1 equiv), potassium carbonate (184 mg, 1.33 mmol, 5.00 equiv) in dimethylformamide (2.5 mL) at 24 °C. The heterogenous solution was heated to 50 °C for 22 h. Upon cooling to 24 °C, the reaction mixture was concentrated *in vacuo* (<1 mm Hg). The resulting residue was diluted with saturated aqueous sodium chloride (5 mL), saturated aqueous sodium bicarbonate (5 mL), and ethyl acetate (5 mL). The organic phase was separated, and the resulting aqueous solution was extracted with ethyl acetate (2 × 5 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→5% methanol / dichloromethane + 0.1% ammonium hydroxide) yielded alkylation product, which was converted to the hydrochloride salt by treatment with a methanolic hydrogen chloride solution (96.6 mg, 76%).

Method U

Example 266: 4'-Cyano-biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-(6-methyl-pyridin-2-yl)-amide



Preparation of 4'-Cyano-biphenyl-4-sulfonic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(6-methyl-pyridin-2-yl)-amide



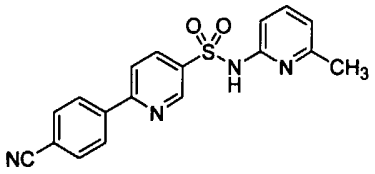
(2-Bromoethoxy)-*tert*-butyldimethylsilane (91 μL, 0.42 mmol, 1.5 equiv) was added to a solution of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide (99.1 mg, 0.284 mmol, 1 equiv) and potassium carbonate (202 mg, 1.46 mmol, 5.2 equiv) in dimethylformamide (2.5 mL) at 24 °C. The reaction mixture was maintained at 24 °C for 4.7 h before warming to 70 °C for 15.7 h. The reaction mixture was cooled to 24 °C and concentrated *in vacuo* (<1 mm Hg). The resulting residue was diluted with ethyl acetate (5 mL), saturated aqueous sodium chloride (3 mL), and saturated aqueous sodium bicarbonate (3 mL). The organic layer was separated, and the resulting aqueous layer was extracted with ethyl acetate (2 × 5 mL). The collected organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (12→50% ethyl acetate in hexanes) provided product (85.3 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.57–7.83 (m, 9 H), 7.40 (d, J = 8.1 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 4.00 (t, J = 6.2 Hz, 2 H), 3.78 (t, J = 6.2 Hz, 2 H), 2.41 (s, 3 H), 0.78 (s, 9 H), –0.03 (s, 6 H).

4'-Cyano-biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-(6-methyl-pyridin-2-yl)-amide

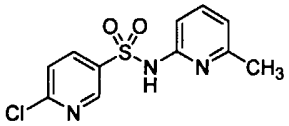
Tetrabutylammonium flouride (371 mL, 0.371 mmol, 2.0 equiv, 1.0 M in tetrahydrofuran) was added dropwise to an ice-cooled solution of 4'-Cyano-biphenyl-4-sulfonic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(6-methyl-pyridin-2-yl)-amide (85.3 mg, 0.186 mmol, 1 equiv) in tetrahydrofuran (3 mL). After 50 min, saturated aqueous sodium chloride was added to the reaction mixture, and the resulting solution was extracted with ethyl acetate (3 × 5 mL). The collected organic extracts were dried over sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (13% ethyl acetate in hexanes → ethyl acetate) provided product which was converted to the hydrochloride salt by treatment with a methanolic hydrogen chloride solution (58 mg, 76%).

Method V

Example 267: **6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide**



Preparation of 6-Chloro-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide



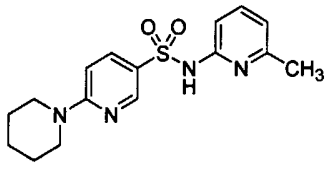
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-chloro-3-pyridylsulfonyl chloride (Naegeli, C.; Kundig, W.; Brandenburger, H. *Helv. Chem. Acta.* **1939**, *21*, 1746) and making non-critical variations. $APCI^+$ 284 $[M+H]^+$ 100%.

6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide

A solution of 6-chloro-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide (188 mg, 0.573 mmol), 4-cyanoboronic acid (88 mg, 0.602 mmol), $Pd(PPh_3)_4$ (33 mg, 0.03 mmol), aqueous Na_2CO_3 (0.72 mL, 1.43 mmol) in DMF (3 mL) was heated in microwave for 30 min. The black mixture was partitioned between EtOAc and water. The organic layer was then washed with brine, dried over Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica gel to give title compound (86.3 mg, 43%) as a yellow solid.

Method W

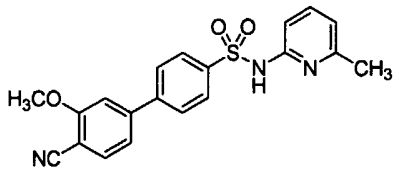
Example 269: **N-(6-methylpyridin-2-yl)-6-piperidin-1-ylpyridine-3-sulfonamide**



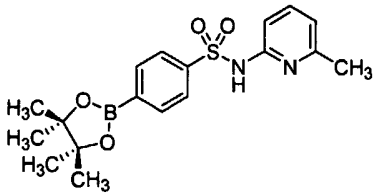
A mixture of 6-chloro-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide (233 mg, 0.823 mmol) and piperidine (4.17 mmol) in dioxane (5 mL) was heated at 100 °C in a Personal Chemistry Microwave oven for 30 min. The mixture was cooled and partitioned between EtOAc and water. The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (50 to 70% EtOAc / Hexanes) furnished the title compound as a brown solid (177 mg, 65%).

Method X

Example 270: 4'-Cyano-3'-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of N-(6-Methyl-pyridin-2-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide



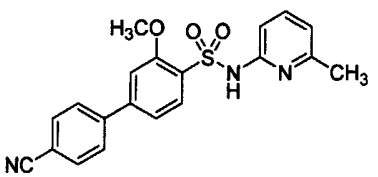
A mixture of 4-bromo-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide (13.7 g, 41.9 mmol), bis(pinacolato)diboron (10.7 g, 41.9 mmol), KOAc (14 g, 143mmol) and $Pd(dppf)Cl_2$ (1.7 g, 2.1 mmol) in DMSO (100 mL) was heated at 100 °C for 12 h. The mixture was cooled to room temperature, partitioned between EtOAc and water and filtered through Celite®. The organic layer was dried and concentrated. Purification by flash column chromatography (50% EtOAc / hexanes) furnished the boronate as a solid (15.5 g, 98%).

4'-Cyano-3'-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting N-(6-methyl-pyridin-2-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide and 4-bromo-2-methoxybenzonitrile and making non-critical variations.

Method Y

Example 276: 4'-Cyano-3-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of 4-Bromo-2-methoxy-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide

To a solution of 1-bromo-3-methoxybenzene (3.1 g, 16.6 mmol) in CH_2Cl_2 at 0 °C was added $ClSO_3H$ (3.3 mL, 48 mmol). The mixture was warmed to R.T. and stirred for 2 h. The mixture was poured into ice and water and extracted with CH_2Cl_2 (3X30 mL). The organic

layer was dried over Na_2SO_4, filtered, and concentrated to give a mixture of sulfonyl chlorides as an oil, which was used for the next reaction without purification.

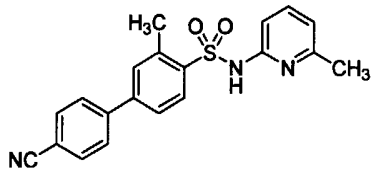
The above sulfonyl chloride was dissolved in pyridine (50 mL) and 2-methyl-6-aminopyridine (1.7 g, 16mmol) was added. The mixture was stirred overnight at R.T. The mixture was partitioned between EtOAc and water. The organic layer was dried and concentrated to the mixture of sulfonamides (3 to 1 by LCMS). The residue was purified by flash column chromatography to give the desired isomer as a white solid (0.87 g, 15% for two steps).

4'-Cyano-3-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'-chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-2-methoxy-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide and 4-cyanophenylboronic acid and making non-critical variations.

Method Z

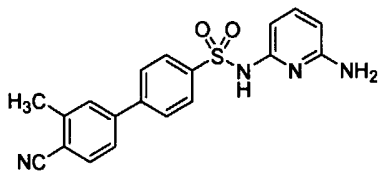
Example 277: 4'-Cyano-3-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



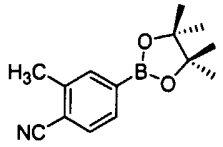
To a mixture of 4-bromo-2-methyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide (200mg, 0.6mmol) 4-cyanophenyl boronic acid (102mg, 0.7mmol) and cesium carbonate (585mg, 1.8mmol) in 1,4-dioxane (6mL) was added [2-[(D-κN)METHYL]PHENYL-κC](TRICYCLOHEXYLPHOSPHINE)(TRIFLUOROACETATO-κO-(SP-4-3)-PALLADIUM, (Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987), (2mg, 0.5mol%). Mixture heated at reflux for 4 hours. After such time reaction mixture was allowed to cool to ambient temperature, filtered through a pad of Celite® and concentrated *in vacuo*. Residue was purified by flash column chromatography (SiO_2 2g, dichloromenthane, methanol 0% & 1%) to return desired product as a white solid (19mg, 0.05mmol, 9% yield).

Method AA

Example 282: 4'-Cyano-3'-methyl-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide



Preparation of 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile



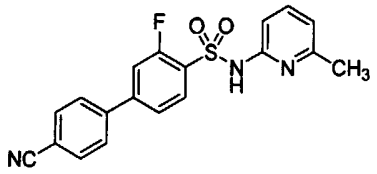
Made following the procedure described for the preparation of N-(6-methyl-pyridin-2-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide but substituting 4-bromo-2-methyl-benzonitrile and making non-critical variations. ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm 7.63 (s, 1 H) 7.56 (d, *J*=7.6 Hz, 1 H) 7.45 (d, *J*=7.6 Hz, 1 H) 2.42 (s, 3 H) 1.24 (s, 12 H).

4'-Cyano-3'-methyl-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile and N-(6-amino-pyridin-2-yl)-4-bromo-benzenesulfonamide and making non-critical variations.

Method AB

Example 283: 4'-Cyano-3-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of 4-Bromo-2-fluoro-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide

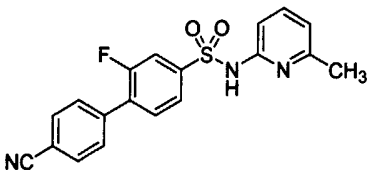
Made following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-2-fluorobenzenesulfonyl chloride and making non-critical variations. The crude material was carried to the next step.

4'-Cyano-3-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Made following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-2-fluoro-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide and 4-cyanophenylboronic acid and making non-critical variations.

Method AC

Example 284: 4'-Cyano-2-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of 4-Bromo-3-fluoro-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide

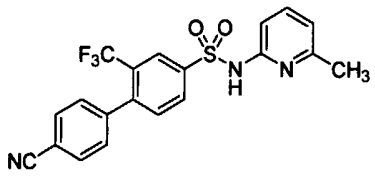
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride and making non-critical variations. The crude material was carried to the next step.

4'-Cyano-2-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-3-fluoro-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide and 4-cyanophenylboronic acid and making non-critical variations.

Method AD

Example 285: 4'-Cyano-2-trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of 4-Bromo-N-(6-methyl-pyridin-2-yl)-3-trifluoromethyl-benzenesulfonamide

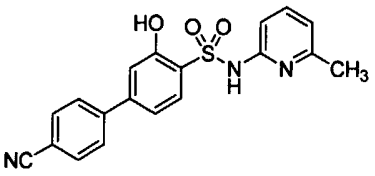
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride and making non-critical variations. The crude material was carried to the next step.

4'-Cyano-2-trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Made by following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 4-bromo-N-(6-methyl-pyridin-2-yl)-3-trifluoromethyl-benzenesulfonamide and 4-cyanophenylboronic acid and making non-critical variations.

Method AE

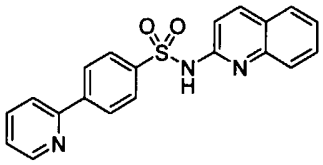
Example 286: 4'-Cyano-3-hydroxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide



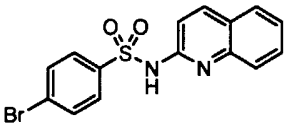
To a solution of 4'-cyano-3-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide (28 mg, 0.073 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (0.2 mL, 1.0 M in CH_2Cl_2) at 0 °C. The mixture was warmed to 23 °C and stirred for 1 h. The mixture was then quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated to give a residue, which was purified by flash column chromatography to furnish the title compound as a white solid (17 mg, 65% yield).

Method AF

Example 287: 4-Pyridin-2-yl-N-quinolin-2-yl-benzenesulfonamide



Preparation of 4-bromo-*N*-quinolin-2-ylbenzenesulfonamide



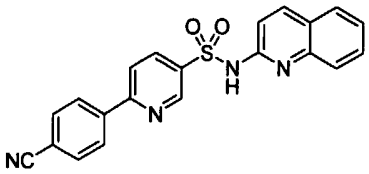
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-bromophenylsulfonyl chloride and 2-aminoquinoline and making non-critical variations. 1H NMR (400 MHz, DMSO-d6), δ ppm 7.37 (t, *J*=7.58 Hz, 1 H) 7.44 - 7.51 (m, 1 H) 7.56 (d, *J*=8.34 Hz, 1 H) 7.64 - 7.70 (m, 1 H) 7.70 - 7.74 (m, 2 H) 7.81 (d, *J*=8.59 Hz, 3 H) 8.23 (d, *J*=9.60 Hz, 1 H); APCI MS: *m/z* 365.0 (M+2).

4-Pyridin-2-yl-N-quinolin-2-yl-benzenesulfonamide

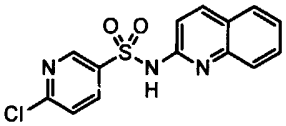
To a solution of 4-bromo-*N*-quinolin-2-ylbenzenesulfonamide (50 mg) in 1,4 dioxane (2.0 ml) was added 2-bromopyridine (22 mg), tetrakis(triphenylphosphine)palladium (16 mg), hexamethylditin (50 mg). After the resulting mixture was heated in microwave at 130°C for 30 mins, it was filtered and concentrated under reduced pressure. To the resulting residue was added 1,4 dioxane (2.0 mL), 2-bromopyridine (30 mg), tetrakis(triphenylphosphine)palladium (20 mg), hexamethylditin (50 mg). After the reaction mixture was heated in microwave at 130°C for 90 min, it was filtered and concentrated under reduced pressure. The residue was purified using reversed phase Kromasil® C18, 0.05% TFA in water and acetonitrile to provide the titled product (5.4 mg).

Method AG

Example 290: 6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid quinolin-2-ylamide



Preparation of 6-chloro-*N*-quinolin-2-ylpyridine-3-sulfonamide



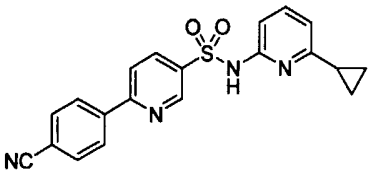
Made by following the procedure describe for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 2-aminoquinoline and 2-chloro-pyridin-5-sulfonyl chloride (Naegeli, C.; Kundig, W.; Brandenburger, H. *Helv. Chem. Acta.* **1939**, *21*, 1746) and making non-critical variations.

6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid quinolin-2-ylamide

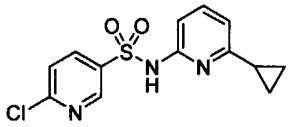
To a flask containing 6-chloro-*N*-quinolin-2-ylpyridine-3-sulfonamide (148 mg, 0.46 mmol) and 4-cyanophenylboronic acid (136 mg, 0.92 mmol) were added DME (1.5 mL), *N,N*-dimethylacetamide (2.0 mL), H_2O (0.5 mL), Cs_2CO_3 (451 mg, 1.39 mmol). The reaction mixture was degassed by alternating between vacuum and nitrogen. After [1,1-bis(diphenylphosphino)-ferrocene]dichloropalladium (II)-dicholoromethane complex (16 mg) was added, the reaction mixture was degassed again. After the resulting mixture was heated at 80°C for 19 hours, it was diluted with EtOAc (30 mL), sat $NaHCO_3$ (5mL). After the resulting mixture was stirred at R.T. for 5 min, it was filtered and diluted with sat $NaHCO_3$ (5mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried with K_2CO_3, filtered, and concentrated to give a solid. After triturating the resulting solid with CH_2Cl_2, the desired product was obtained (59.7 mg). The mother liquor was purified using high performance flash chromatography (0→30% dichloromethane in acetone) to give an additional batch of desired product (33.3 mg).

Method AH

Example 293: 6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide



Preparation of 6-Chloro-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide



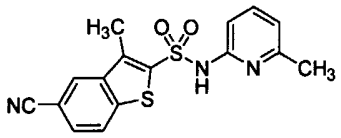
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-cyclopropyl-pyridin-2-ylamine and 6-chloro-3-pyridylsulfonyl chloride (Naegeli, C.; Kundig, W.; Brandenburger, H. *Helv. Chem. Acta.* **1939**, 21, 1746) and making non-critical variations. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.91 (d, J = 2.5 Hz, 1 H), 8.18 (dd, *J* = 8.4, 2.5 Hz, 1 H), 7.53 (t, J = 7.5 Hz, 1 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 6.55 (d, *J* = 7.3 Hz, 1 H), 6.27 (d, *J* = 8.1 Hz, 1 H), 1.98-1.92 (m, 1 H), 1.14-1.09 (m, 2 H) 0.93-0.89 (m, 2 H); LCMS (ESI): 310.1.

6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide

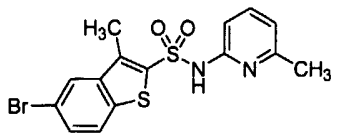
Made by following the procedure described for the preparation of 4'chlorobiphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 6-chloro-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide and 4-cyanophenyl boronic acid and making non-critical variations.

Method AI

Example 295: 5-Cyano-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of 5-Bromo-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide



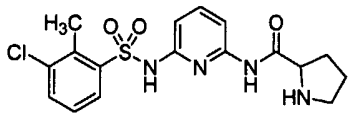
Made by following the procedure described for the preparation of 4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide but substituting 5-bromo-3-methyl-benzo[b]thiophene-2-sulfonyl chloride and making non-critical variations. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.88 (d, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.47–7.58 (m, 2 H), 7.11 (d, *J* = 9.1 Hz, 1 H), 6.54 (d, *J* = 7.3 Hz, 1 H), 2.68 (s, 3 H), 2.51 (s, 3 H); MS (ESI) for $C_{15}H_{14}BrN_2O_2S_2$ *m/z*: 398.0.

5-Cyano-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide

Copper (I) cyanide (43 mg, 0.476 mmol, 1.5 equiv) was added to a solution of 5-bromo-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide (126 mg, 0.317 mmol, 1 equiv) in dimethylformamide (2.5 mL) at 24 °C. The solution was heated to 250 °C by microwave for 10 min. Deionized water (5 mL), hexanes (2.5 mL), and diethyl ether (2.5 mL) were added, and the resulting tan solid was collected by filtration. Purification of the solid by preparative reverse phase HPLC (Kromasil® C18, 10μm, 250 × 50.8 mm, mobile phase: water / acetonitrile / 0.05% trifluoroacetic acid) provided the titled compound (30 mg, 27.5%).

Method AJ

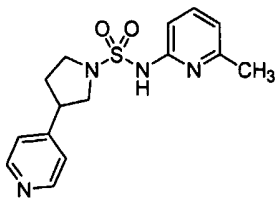
Example 296: Pyrrolidine-2-carboxylic acid [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-amide



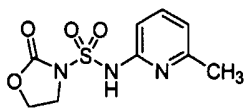
A mixture of (6-amino-pyridin-2-yl)-3-chloro-2-methyl-benzenesulfonamide (140 mg, 0.47 mmol), pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (106 mg, 0.50 mmol), HATU (215 mg, 0.57 mmol) and Et_3N (0.2 mL) in DMF (3 mL) was stirred at 23 °C for 12 h. The mixture was partitioned between EtOAc and water. The organic layer was dried and concentrated to give the crude amide as an oil, which was used directly in the next reaction. The amide was dissolved in CH_2Cl_2 (2 mL), and HCl (4 ml; 4 N in dioxane) was added. The mixture was stirred at 23 °C for 12 h. The mixture was concentrated and the residue was purified by reverse-phase HPLC to give the title compound as a white solid (99 mg, 53%).

Method AK

Example 297: 3-Pyridin-4-yl-pyrrolidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide



Preparation of *N*-(6-methylpyridin-2-yl)-2-oxo-1,3-oxazolidine-3-sulfonamide



Chlorosulfonyl isocyanate (0.27 mL, 4.1 mmol) was dissolved in 40 mL of CH_2Cl_2 and cooled to 0 °C. Chloroethanol (0.27 mL, 4.1 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 1.5 h. A solution of 6-methyl-2-aminopyridine (444 mg, 4.1

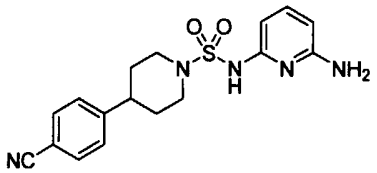
mmol) and Et_3N (1.3 ml, 12.4 mmol) in 50 mL of CH_2Cl_2 was slowly added so that the reaction temperature did not exceed 5 °C. The reaction solution was slowly warmed to room temperature and stirred overnight. After acidic workup, the crude product was purified by triturating with CH_2Cl_2 and hexane. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.34 (s, 1 H) 7.62 (dd, *J*=8.8, 7.3 Hz, 1 H) 6.77 (d, *J*=8.8 Hz, 1 H) 6.57 (d, *J*=7.1 Hz, 1 H) 4.39 (t, *J*=8.0 Hz , 2 H) 4.15 (t, *J*=7.8 Hz, 2 H) 2.50 (s, 3 H).

3-Pyridin-4-yl-pyrrolidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide

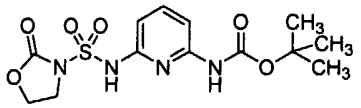
A solution of *N*-(6-methylpyridin-2-yl)-2-oxo-1,3-oxazolidine-3-sulfonamide (0.23 g, 0.894 mmol), 4-pyrrolidin-3-ylpyridine (0.40 g, 2.23 mmol), and diisopropylethylamine (1 mL) in acetonitrile (3 mL) was heated to 130 °C using microwave heating for 0.5 hour. The reaction mixture was cooled to 25 °C, and diluted with ethyl acetate (50 mL). The resulting mixture was washed with saturated aqueous ammonium chloride (2 x 30 mL) and saturated aqueous sodium bicarbonate (2 x 30 mL). The organic layer was concentrated to give a clear oil. The residue was purified using radial chromatography (2 mm silica plate; 1:1:0.1 dichloromethane / ethyl acetate / methanol). The product was triturated with additional diethyl ether and dried *in vacuo* to afford the title compound (0.19 g, 65.4%). Sulfamide formation may also occur without microwave by heating the reaction overnight to 82 °C in acetonitrile or 110 °C in dimethylformamide.

Method AL

Example 317: 4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid (6-amino-pyridin-2-yl)-amide



Preparation of tert-Butyl (6-{[(2-oxo-1,3-oxazolidin-3-yl)sulfonyl]amino}pyridin-2-yl)carbamate



Made by following the procedure described for the preparation of *N*-(6-methylpyridin-2-yl)-2-oxo-1,3-oxazolidine-3-sulfonamide but substituting *tert*-butyl (6-aminopyridin-2-yl)carbamate (Berl, et al *Chem Eur J* **2001**, *7*, 2798) and making non-critical variations. ^1H NMR (400 MHz, CD_2Cl_2), δ: 1.50 (s, 9 H) 4.05 - 4.11 (m, 2 H) 4.24 - 4.30 (m, 2 H) 6.64 (d, *J*=7.83 Hz, 1 H) 7.32 (d, *J*=8.08 Hz, 1 H) 7.50 (t, *J*=8.08 Hz, 1 H).

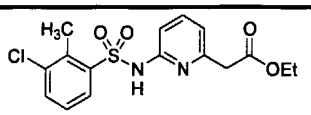
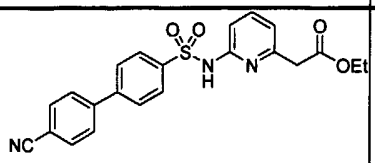
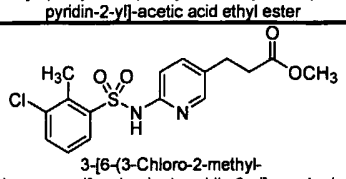
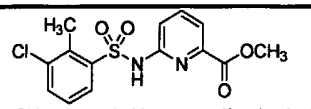
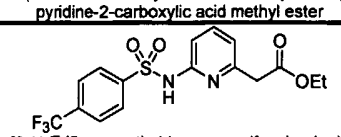
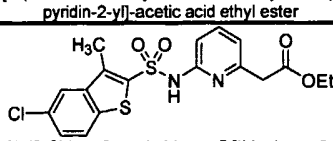
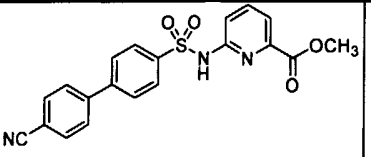
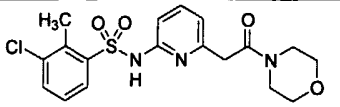
4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid (6-amino-pyridin-2-yl)-amide

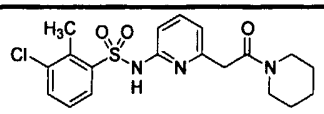
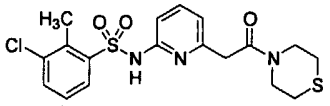
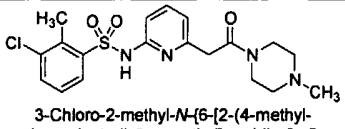
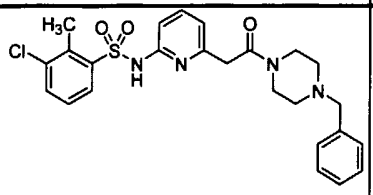
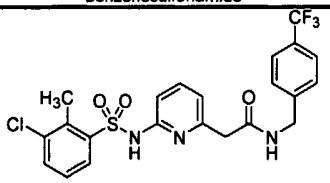
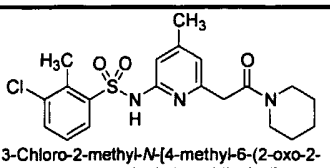
A solution of tert-butyl (6-{[(2-oxo-1,3-oxazolidin-3-yl)sulfonyl]amino}pyridin-2-yl)carbamate (150 mg, 0.420 mmol), diisopropylethylamine (219 µL, 1.26 mmol), and 4-(4-

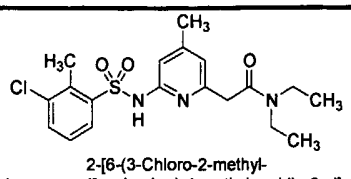
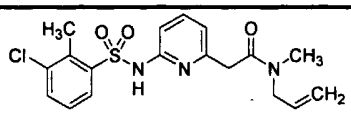
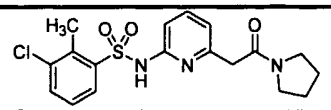
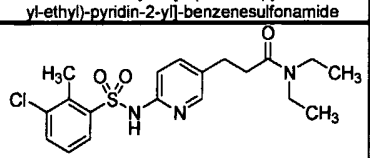
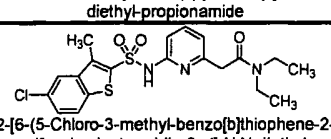
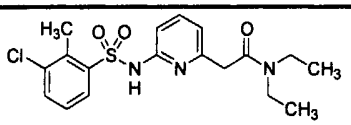
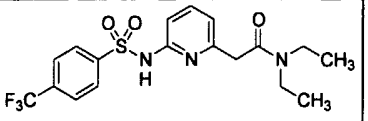
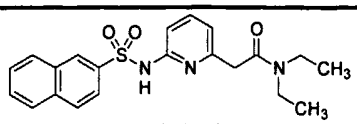
cyanophenyl)piperidine (82 mg, 0.44 mmol) was subjected to microwaves at 110°C for 30 min. The reaction mixture was concentrated and the crude product was purified by flash chromatography eluting with hexanes/ ethyl acetate (0-25%). To a cooled (0-5°C) solution of the afforded material in CH_2Cl_2 (1 mL) was added TFA (1 mL). After 2 hours, the reaction mixture was concentrated and the residue was partitioned between EtOAc (50 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was separated and washed with brine (10 mL), dried (MgSO4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (0-5%) to afford the title compound (30 mg, 20%).

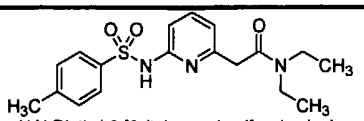
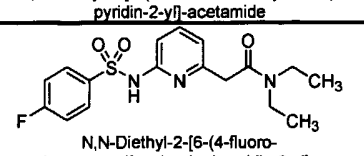
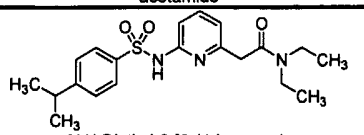
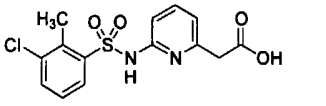
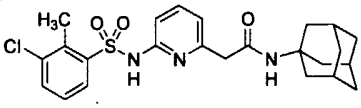
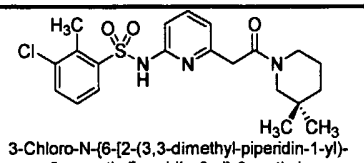
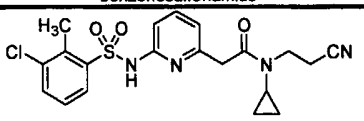
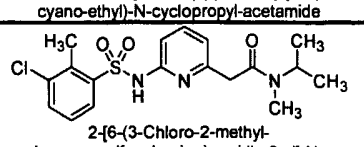
The structure, name, physical and biological data, and Methods are further described in tabular form below in Table 1.

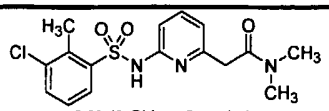
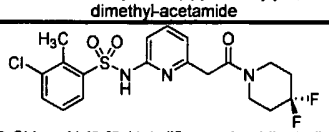
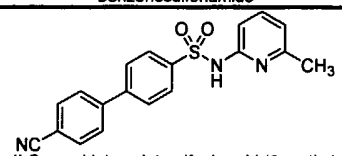
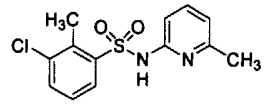
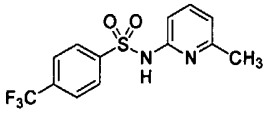
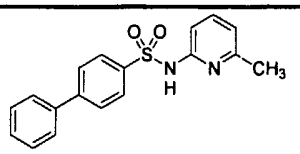
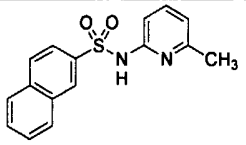
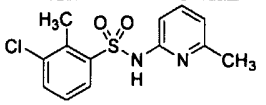
Table 1

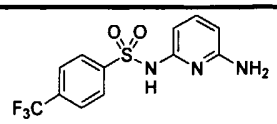
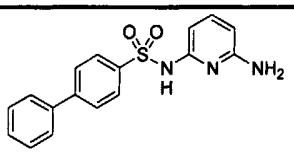
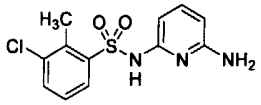
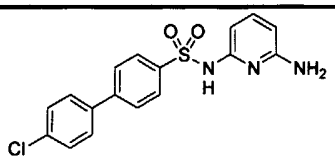
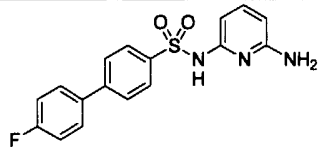
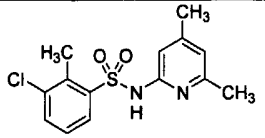
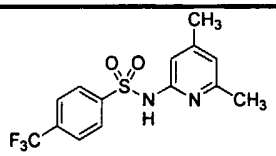
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
1	42	72.3	 Ethyl [6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetate	A	(400 MHz, $CDCl_3$) δ: 8.02 (dd, *J* = 7.96, 1.14 Hz, 1 H), 7.52 (dd, *J* = 8.46, 7.45 Hz, 2 H), 7.22 (t, *J* = 7.96 Hz, 1 H), 7.01 (d, *J* = 8.34 Hz, 1 H), 6.80 (d, *J* = 7.33 Hz, 1 H), 4.17 (q, *J* = 7.07 Hz, 2 H), 3.68 (s, 2H), 2.73 (s, 3 H), 1.25 (t, *J* = 7.07 Hz, 3 H)	369.0677
2	16	85.4	 [6-(4'-Cyano-biphenyl-4-sulfonylamino)-pyridin-2-yl]-acetic acid ethyl ester	A	(400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.6 Hz, 2 H), 7.74 (m, 2 H), 7.66 (d, *J* = 7.8 Hz, 4 H), 7.58 (m, 1 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 6.88 (d, *J* = 7.3 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.67 (s, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H)	422.1
3	NA	19.6	 3-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-3-yl]-propionic acid methyl ester	A	(400 MHz, $CDCl_3$) δ: 14.18 (s, 1 H) 8.14 (d, *J*=1.8 Hz, 1 H) 8.08 (m, 1 H) 7.56 (dd, *J*=9.3, 2.3 Hz, 1 H) 7.48 - 7.53 (m, 1 H) 7.20 - 7.30 (m, 2 H) 3.64 (s, 3 H) 2.81 (t, *J*=7.3 Hz, 2 H) 2.66 (s, 3 H) 2.55 (t, *J*=7.3 Hz, 2 H)	NA
4	NA	23.9	 6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridine-2-carboxylic acid methyl ester	A	(500 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.1 Hz, 1 H), 7.60–7.75 (m, 2 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.20–7.27 (m, 1 H), 3.97 (s, 3 H), 2.74 (s, 3 H)	341.0359
5	NA	0.3	 [6-(4-Trifluoromethyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid ethyl ester	A	(400 MHz, $CDCl_3$) δ: 9.03 (br s, 1 H), 8.06 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.58 (m, 1 H), 7.12 (d, *J* = 8.3 Hz, 1 H), 6.83 (d, *J* = 7.3 Hz, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 3.66 (s, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H)	389.0789
6	2.8	100	 [6-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-pyridin-2-yl]-acetic acid ethyl ester	A	(400 MHz, $CDCl_3$) δ: 9.31 (br s, 1 H), 7.65–7.75 (m, 2 H), 7.58 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.40 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.24 (m, 1 H), 6.81 (d, *J* = 7.3 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.68 (s, 2 H), 2.63 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H)	425.0
7	NA	7.7	 6-(4'-Cyano-biphenyl-4-sulfonylamino)-pyridine-2-carboxylic acid methyl ester	A	NA	393.9
8	NA	5.52	 3-Chloro-2-methyl-*N*-[6-(2-morpholin-4-yl-2-oxo-ethyl)-pyridin-2-yl]-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.01 (dd, *J* = 8.08, 1.01 Hz, 1 H), 7.53 (t, *J* = 8.08 Hz, 2 H), 7.23 (m, 1 H), 7.03 (d, *J* = 8.34 Hz, 1 H), 6.84 (d, *J* = 7.33 Hz, 1 H), 3.77 (s, 2 H), 3.63 (m, 4 H), 3.56 (m, 2 H)	410.0936

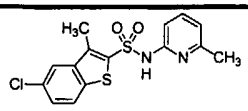
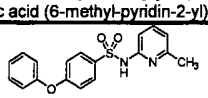
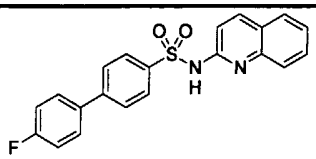
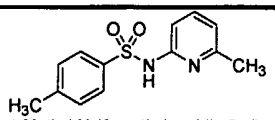
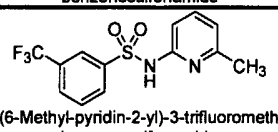
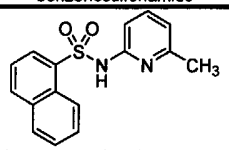
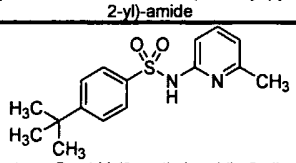
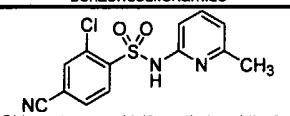
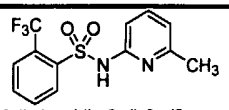
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
9	169	54.8	 3-Chloro-2-methyl-*N*-[6-(2-oxo-2-piperidin-1-yl-ethyl)-pyridin-2-yl]-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 9.57 (br s, 1 H), 8.02 (m, 1 H), 7.37–7.59 (m, 2 H), 7.21 (t, *J* = 8.1 Hz, 1 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.75 (d, *J* = 7.3 Hz, 1 H), 3.76 (s, 2 H), 3.54 (m, 2 H), 3.39 (m, 2 H), 2.73 (s, 3 H) 1.33–1.67 (m, 6 H)	408.1169
10	NA	38.7	 3-Chloro-2-methyl-*N*-[6-(2-oxo-2-thiomorpholin-4-yl-ethyl)-pyridin-2-yl]-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.01 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.42–7.59 (m, 2 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 8.6 Hz, 1 H), 6.79 (d, *J* = 7.3 Hz, 1 H), 3.77–3.90 (m, 4 H), 3.72 (m, 2 H), 2.70 (s, 3 H), 2.57 (m, 2 H), 2.46 (m, 2 H)	426.0715
11	NA	8.05	 3-Chloro-2-methyl-*N*-{6-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-pyridin-2-yl}-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.02 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.41–7.60 (m, 2 H), 7.19–7.24 (m, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.80 (d, *J* = 7.3 Hz, 1 H), 3.76 (s, 2 H), 3.65 (br s, 2 H), 3.53 (br s, 2 H), 2.73 (s, 3 H), 2.18 - 2.49 (m, 7 H)	423.1251
12	NA	21.5	 *N*-{6-[2-(4-Benzyl-piperazin-1-yl)-2-oxo-ethyl]-pyridin-2-yl}-3-chloro-2-methyl-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.00 (m, 1 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.22–7.34 (m, 5 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.74 (d, *J* = 7.1 Hz, 1 H), 3.80 (s, 2 H), 3.60 (m, 2 H), 3.48 (s, 2 H), 3.44 (m, 2 H), 2.70 (s, 3 H), 2.39 (m, 2 H), 2.32 (m, 2 H)	499.1554
13	NA	9.1	 2-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-*N*-(4-trifluoromethyl-benzyl)-acetamide	B	NA	498.0870
14	NA	25.9	 3-Chloro-2-methyl-*N*-[4-methyl-6-(2-oxo-2-piperidin-1-yl-ethyl)-pyridin-2-yl]-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.03 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.50 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.15 - 7.23 (m, 1 H), 6.84 (s, 1 H), 6.52 (s, 1 H), 3.70 (s, 2 H), 3.55 (m, 2 H), 3.41 (m, 2 H), 2.75 (s, 3 H), 2.23 (s, 3 H), 1.62 (m, 2 H), 1.44 - 1.58 (m, 4 H)	422.1295

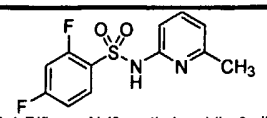
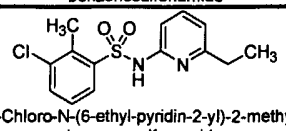
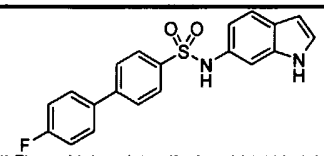
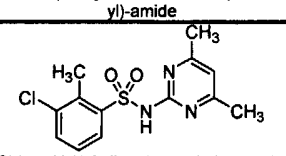
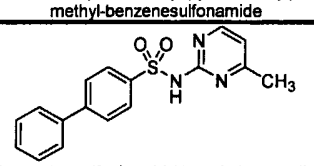
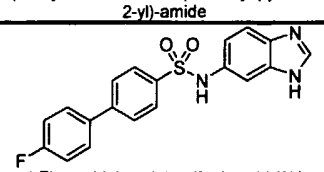
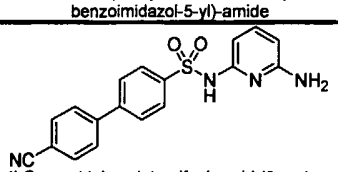
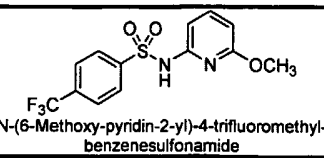
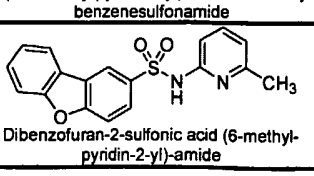
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
15	NA	23.6	 2-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-4-methyl-pyridin-2-yl]-*N,N*-diethyl-acetamide	B	(400 MHz, $CDCl_3$) δ: 10.29 (br s, 1 H), 8.04 (m, 1 H), 7.48 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 6.84 (s, 1 H), 6.46 (s, 1 H), 3.66 (s, 2 H), 3.28 - 3.44 (m, 4 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H)	410.1291
16	NA	10.9	 *N*-Allyl-2-[6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-*N*-methyl-acetamide	B	(1:1 rotamer ratio, 400 MHz, $CDCl_3$) δ: 7.96 - 8.06 (m, 1 H), 7.42 - 7.57 (m, 2 H), 7.16 - 7.23 (m, 1 H), 6.96 - 7.10 (m, 1 H), 6.69 - 6.78 (m, 1 H), 5.63 - 5.79 (m, 1 H), 5.03 - 5.25 (m, 2 H), 3.90 - 4.02 (m, 2 H), 3.81 (s, 2 H), 3.74 (s, 2 H), 2.96 (s, 3 H), 2.93 (s, 3 H), 2.73 (s, 3 H), 2.72 (s, 3 H)	394.2
17	NA	11.4	 3-Chloro-2-methyl-N-[6-(2-oxo-2-pyrrolidin-1-yl-ethyl)-pyridin-2-yl]-benzenesulfonamide	B	(400 MHz, $CDCl_3$) δ: 8.02 (m, 1 H), 7.42–7.56 (m, 2 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 6.69 (d, *J* = 7.3 Hz, 1 H), 3.72 (s, 2 H), 3.46 (t, *J* = 6.7 Hz, 4 H), 2.73 (s, 3 H), 1.78–2.02 (m, 4 H)	394.0988
18	NA	34.6	 3-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-3-yl]-N,N-diethyl-propionamide	B	(400 MHz, $CDCl_3$) δ: 13.56 (s, 1 H) 8.01 - 8.13 (m, 2 H) 7.62 (dd, *J*=9.1, 2.3 Hz, 1 H) 7.48 - 7.54 (m, 1 H) 7.15 - 7.30 (m, 2 H) 3.32 (q, *J*=7.1 Hz, 2 H) 3.21 (q, *J*=7.1 Hz, 2 H) 2.85 (t, *J*=7.2 Hz, 2 H) 2.68 (s, 3 H) 2.52 (t, *J*=7.2 Hz, 2 H) 1.02 - 1.15 (m, 6 H)	NA
19	4.8	96.9	 2-[6-(5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonylamino)-pyridin-2-yl]-N,N-diethyl-acetamide	C	(400 MHz, $CDCl_3$) δ: 10.72 (br s, 1 H), 7.61–7.71 (m, 2 H), 7.55 (dd, *J* = 8.7, 7.5 Hz, 1 H), 7.36 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 6.72 (d, *J* = 7.1 Hz, 1 H), 3.77 (s, 2 H), 3.28–3.40 (m, 4 H), 2.62 (s, 3 H), 1.04–1.16 (m, 6 H)	452.1
20	220	NA	 *N,N*-diethyl 2-[6-(3-Chloro-2-methylbenzenesulfonylamino)pyridin-2-yl]acetamide	C	(400 MHz, $CDCl_3$) δ: 9.80 (br s, 1 H), 8.04 (m, 1 H), 7.41–7.58 (m, 2 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 8.6 Hz, 1 H), 6.72 (d, *J* = 7.3 Hz, 1 H), 3.69 (s, 2 H), 3.31–3.41 (m, 4H), 2.75 (s, 3 H), 1.07–1.17 (m, 6 H)	396.1146
21	480	NA	 N,N-diethyl 2-[6-(4-trifluoromethylbenzenesulfonylamino)pyridin-2-yl]acetamide	C	(400 MHz, $CDCl_3$), δ: 10.28 (br s, 1 H), 8.09 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.54 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.10 (d, *J* = 8.6 Hz, 1 H), 6.70 (d, *J* = 7.3 Hz, 1 H), 3.70 (s, 2 H), 3.39 (q, *J* = 7.1 Hz, 2 H), 3.33 (q, *J* = 7.2 Hz, 2 H), 1.04–1.19 (m, 6 H)	416.3
22	170	44.7	 *N,N*-Diethyl-2-[6-(naphthalene-2-sulfonylamino)-pyridin-2-yl]-acetamide	C	(400 MHz, $CDCl_3$), δ: 8.60 (br s, 1 H), 8.52 (s, 1 H), 7.76–8.00 (m, 4 H), 7.43–7.69 (m, 3 H), 7.19 (d, *J* = 8.3 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 3.66 (s, 2 H), 3.32 (q, *J* = 7.1 Hz, 2 H), 3.23 (q, *J* = 7.2 Hz, 2 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 1.00 (t, *J* = 7.2 Hz, 3 H)	398.2

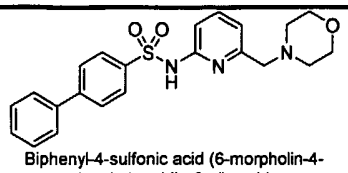
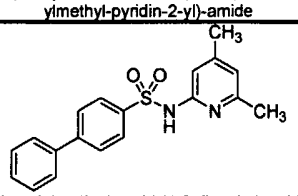
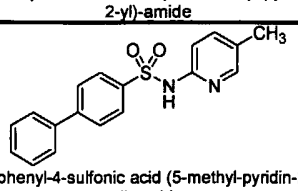
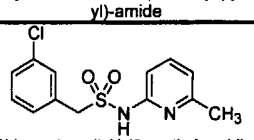
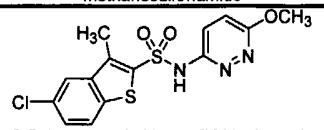
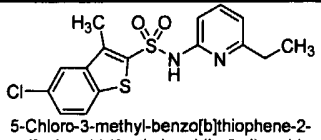
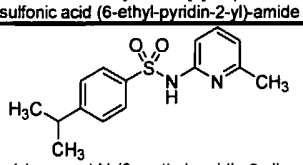
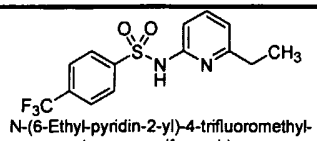
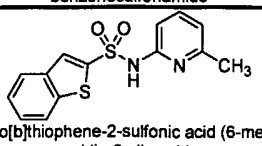
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
23	NA	4.9	 N,N-Diethyl-2-[6-(toluene-4-sulfonylamino)-pyridin-2-yl]-acetamide	C	(400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.8 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.24 (m, 2 H), 7.15 (d, *J* = 8.3 Hz, 1 H), 6.90 (d, *J* = 7.3 Hz, 1 H), 3.70 (s, 2 H), 3.21–3.44 (m, 4 H), 2.37 (s, 3 H), 1.00–1.14 (m, 6 H)	362.1538
24	NA	3.7	 N,N-Diethyl-2-[6-(4-fluoro-benzenesulfonylamino)-pyridin-2-yl]-acetamide	C	(400 MHz, $CDCl_3$) δ: 8.88 (br s, 1 H), 7.94 (dd, *J* = 8.7, 4.9 Hz, 2 H), 7.54 (m, 1 H), 7.02–7.19 (m, 3 H), 6.83 (d, *J* = 7.3 Hz, 1 H), 3.69 (s, 2 H), 3.37 (q, *J* = 7.1 Hz, 2 H), 3.31 (q, *J* = 7.2 Hz, 2 H), 1.10 (m, 6 H)	366.1272
25	NA	42.8	 N,N-Diethyl-2-[6-(4-isopropyl-benzenesulfonylamino)-pyridin-2-yl]-acetamide	C	(400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.1 Hz, 2 H), 7.75 (m, 1 H),7.44 (m, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.09 (m, 1 H), 3.82 (s, 2 H), 3.25–3.46 (m, 4 H), 2.94 (m, 1 H), 1.23 (d, *J* = 7.1 Hz, 6 H), 1.03–1.18 (m, 6 H)	390.1837
26	NA	25.2	 [6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetic acid	D	(400 MHz, $CDCl_3$) δ: 8.05 (m, 1 H), 7.64 (m, 1 H), 7.57 (m, 1 H), 7.24 (m, 1 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 6.87 (d, *J* = 7.3 Hz, 1 H), 3.76 (s, 2 H), 2.73 (s, 3 H)	341.0371
27	NA	1.9	 *N*-Adamantan-1-yl-2-[6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetamide	E	(1:1 rotamer ratio, 400 MHz, $CDCl_3$) δ: 8.06 (m, 1 H), 7.54 (m, 2 H), 7.24 (m, 1 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 6.84 (d, *J* = 7.3 Hz, 1 H), 6.14 (s, 1 H), 3.53 (s, 2 H), 2.75 (s, 3 H), 2.03 (s, 3 H), 1.92 (d, *J* = 2.5 Hz, 6 H), 1.64 (m, 6 H)	474.3
28	NA	45.6	 3-Chloro-N-{6-[2-(3,3-dimethyl-piperidin-1-yl)-2-oxo-ethyl]-pyridin-2-yl}-2-methyl-benzenesulfonamide	E	NA	436
29	NA	10.9	 2-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-N-(2-cyano-ethyl)-N-cyclopropyl-acetamide	E	NA	433
30	NA	15.9	 2-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-N-isopropyl-N-methyl-acetamide	E	NA	396.1

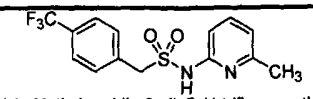
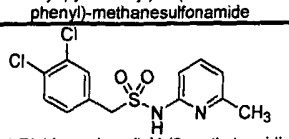
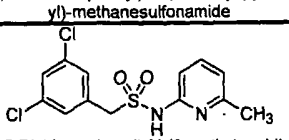
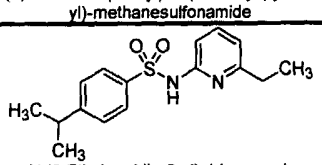
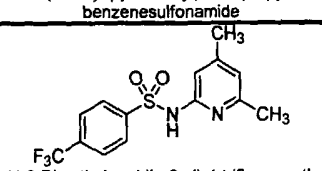
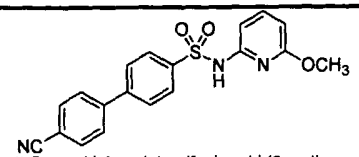
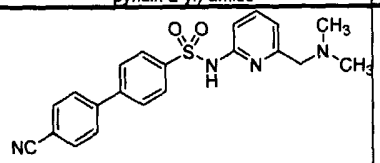
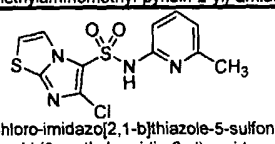
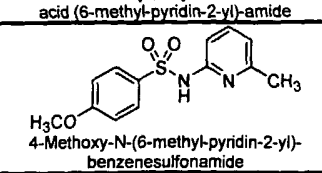
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
31	NA	11.3	 2-[6-(3-Chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-N,N-dimethyl-acetamide	E	NA	368
32	NA	20.4	 3-Chloro-N-{6-[2-(4,4-difluoro-piperidin-1-yl)-2-oxo-ethyl]-pyridin-2-yl}-2-methyl-benzenesulfonamide	E	NA	443.9
33	6.4	97	 4'-Cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 2.42 (s, 3 H), 6.59 (d, *J* = 6.8 Hz, 1 H), 6.97 (m, 1 H), 7.52 (dd, *J* = 8.8,7.73 Hz, 1 H), 7.67 (m, 4 H), 7.75 (m, 2 H), 8.05 (m, 1 H)	350.1
34	169	48.8	 3-Chloro-2-methyl-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.1 Hz, 1 H), 7.41–7.55 (m, 2 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 8.8 Hz, 1 H), 6.51 (d, *J* = 7.1 Hz, 1 H), 2.77 (s, 3 H), 2.49 (s, 3 H)	297.2
35	108	98	 *N*-(6-Methyl-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.06 (d, 2 H, *J* = 8.08 Hz), 7.70 (d, 2 H, *J* = 8.08 Hz), 7.55 (m, 1 H), 7.05 (d, 1 H, *J* = 8.84 Hz), 6.57 (d, 1 H, *J* = 7.07 Hz), 2.48 (s, 3H)	317.0566
36	48	52	 Biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.00 (m, 2 H), 7.67 (m, 2 H), 7.50–7.59 (m, 3 H), 7.35–7.49 (m, 3 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 6.63 (d, *J* = 7.3 Hz, 1 H), 2.44 (s, 3 H)	325.1019
37	84	45	 Naphthalene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.51 (s, 1 H), 7.77–8.00 (m, 4 H), 7.58 (m, 2 H), 7.49 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.13 (d, *J* = 8.6 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 2.44 (s, 3 H)	299.0859
38	169	49	 3-Chloro-2-methyl-*N*-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.1 Hz, 1 H), 7.41–7.55 (m, 2 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 8.8 Hz, 1 H), 6.51 (d, *J* = 7.1 Hz, 1 H), 2.77 (s, 3 H), 2.49 (s, 3 H)	297.0458

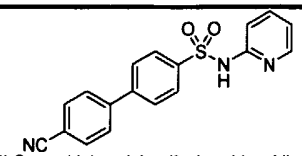
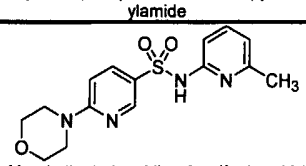
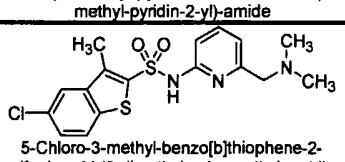
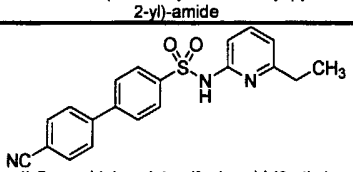
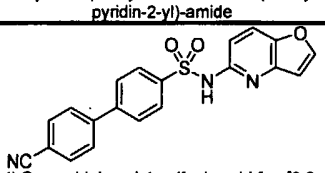
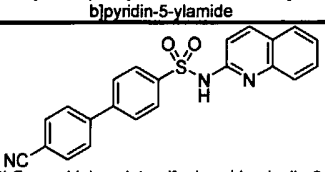
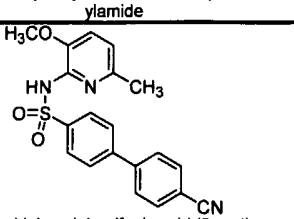
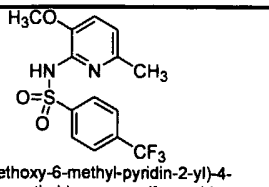
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
39	9	96	 *N*-(6-Amino-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, pyridine-d_5) δ ppm 5.92 (d, *J*=8.34 Hz, 1 H) 6.20 (d, *J*=8.34 Hz, 1 H) 7.27 (t, *J*=8.21 Hz, 1 H) 7.70 (d, *J*=8.34 Hz, 2 H), 7.98 (d, *J*=8.34 Hz)	318.1
40	4.3	98	 Biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 5.93 (d, *J* = 8.1 Hz, 1 H), 6.23 (d, *J* = 8.1 Hz, 1 H), 7.24 (t, *J* = 8.3 Hz, 1 H), 7.28 (m, 1 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.54 (d, *J* = 7.1 Hz, 2 H), 7.64 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H)	326.1
41	17	94	 *N*-(6-Amino-pyridin-2-yl)-3-chloro-2-methyl-benzenesulfonamide	F	(400 MHz, CD_3OD) δ: 7.90 (m, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.24 (t, *J* = 8.2 Hz, 1 H), 7.18 (t, *J* = 8.1 Hz, 1 H), 6.13 (d, *J* = 7.6 Hz, 1 H), 5.87 (d, *J* = 8.1 Hz, 1 H), 2.62 (s, 3 H)	298.1
42	4.6	96	 4'-Chloro-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 5.93 (d, *J* = 8.1 Hz, 1 H), 6.23 (d, *J* = 8.1 Hz, 1 H), 7.24 (t, *J* = 8.3 Hz, 1 H), 7.28 (m, 1 H), 7.35 (t, *J* = 7.3 Hz, 2 H), 7.54 (d, *J* = 7.07 Hz, 2 H), 7.64 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H)	NA
43	8.1	98	 4'-Fluoro-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, MeOD) δ: 7.96 (d, *J*=8.3 Hz, 2 H), 7.70 (d, *J*=8.3 Hz, 2 H), 7.60 - 7.68 (m, 2 H), 7.33 (t, *J*=8.1 Hz, 1 H), 7.18 (t, *J*=8.7 Hz, 2 H), 6.33 (d, *J*=8.1 Hz, 1 H), 6.03 (d, *J*=8.3 Hz, 1 H)	NA
44	NA	16	 3-Chloro-*N*-(4,6-dimethyl-pyridin-2-yl)-2-methyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.01 (m, 1 H), 7.48 (m, 1 H), 7.19 (m, 1 H), 6.74 (s, 1 H), 6.32 (s, 1 H), 2.77 (s, 3 H), 2.43 (s, 3 H), 2.23 (s, 3 H)	311.0612
45	NA	35	 *N*-(4,6-Dimethyl-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 11.59 (br s, 1 H), 8.05 (d, *J* = 8.3 Hz, 2 H), 7.69 (d, *J* = 8.1 Hz, 2 H), 6.80 (s, 1 H), 6.35 (s, 1 H), 2.43 (s, 3 H), 2.25 (s, 3 H)	331.0738

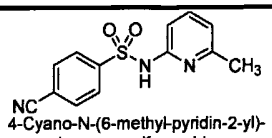
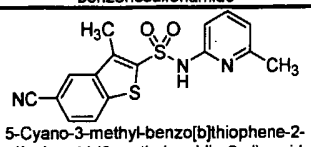
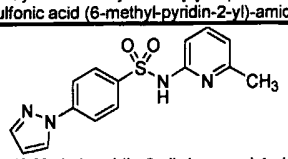
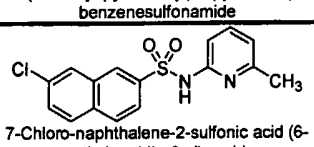
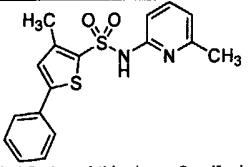
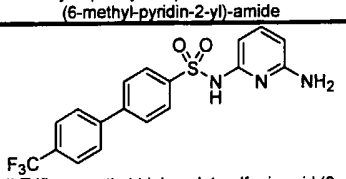
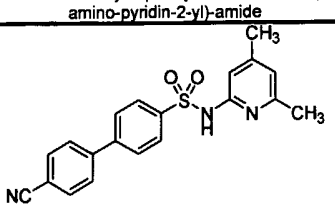
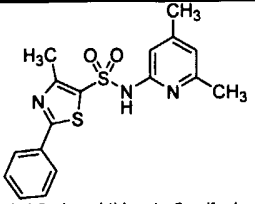
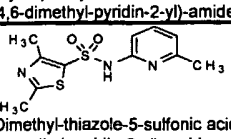
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
46	3.2	98	 5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.65–7.73 (m, 2 H), 7.56 (dd, *J* = 8.8, 7.3 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.14 (d, *J* = 8.8 Hz, 1 H), 6.55 (d, *J* = 7.3 Hz, 1 H), 2.68 (s, 3 H), 2.52 (s, 3 H)	353.0197
47	NA	21	 N-(6-Methyl-pyridin-2-yl)-4-phenoxy-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 9.65 (br s, 1 H), 7.86 (m, 2 H), 7.49 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.37 (m, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 6.91–7.06 (m, 5 H), 6.62 (d, *J* = 7.3 Hz, 1 H), 2.41 (s, 3 H)	341.0946
48	14.5	90	 4'-Fluoro-biphenyl-4-sulfonic acid quinolin-2-ylamide	F	(400 MHz, $CDCl_3$) δ: 8.02 - 8.10 (m, 2 H), 8.06 (d, 2 H), 7.88 (d, *J*=9.3 Hz, 1 H), 7.60 - 7.69 (m, 4 H), 7.50 - 7.58 (m, 2 H), 7.40 - 7.45 (m, 1 H), 7.35 - 7.40 (m, 1 H), 7.11 - 7.19 (m, 1 H), 6.88 (d, *J*=9.3 Hz, 1 H)	NA
49	NA	82.6	 4-Methyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.3 Hz, 2 H), 7.48 (dd, *J* = 8.5, 7.4 Hz, 1 H), 7.24 (m, 2 H), 7.06 (d, *J* = 8.6 Hz, 1 H), 6.62 (d, *J* = 7.3 Hz, 1 H), 2.42 (s, 3 H), 2.37 (s, 3 H)	263.0855
50	NA	10.1	 N-(6-Methyl-pyridin-2-yl)-3-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.22 (s, 1 H), 8.14 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.50–7.64 (m, 2 H), 7.06 (d, *J* = 8.8 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 2.49 (s, 3 H)	317.0563
51	NA	10.2	 Naphthalene-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.88 (d, *J* = 8.6 Hz, 1 H), 8.33 (dd, *J* = 7.3, 1.0 Hz, 1 H), 7.99 (d, *J* = 8.1 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 7.63 (m, 1 H), 7.40–7.57 (m, 3 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 6.48 (d, *J* = 7.3 Hz, 1 H), 2.41 (s, 3 H)	299.0849
52	NA	32	 4-tert-Butyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 7.84 (m, 2 H), 7.41–7.53 (m, 3 H), 7.11 (d, *J* = 8.6 Hz, 1 H), 6.60 (d, *J* = 7.3 Hz, 1 H), 2.45 (s, 3 H), 1.29 (s, 9 H)	305.1325
53	NA	10.1	 2-Chloro-4-cyano-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.33 (d, *J* = 8.3 Hz, 1 H), 7.73 (d, *J* = 1.5 Hz, 1 H), 7.66 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.58 (dd, *J* = 8.8, 7.1 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 6.55 (d, *J* = 7.1 Hz, 1 H), 2.48 (s, 3 H)	308.0266
54	NA	1.0	 N-(6-Methyl-pyridin-2-yl)-2-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$), δ: 8.37 (d, *J* = 7.6 Hz, 1 H), 7.80 (m, 1 H), 7.57–7.70 (m, 2 H), 7.51 (dd, *J* = 8.7, 7.2 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 6.52 (d, *J* = 7.3 Hz, 1 H), 2.44 (s, 3 H)	317.0570

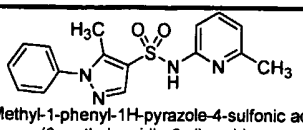
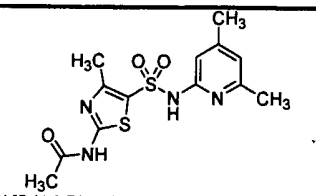
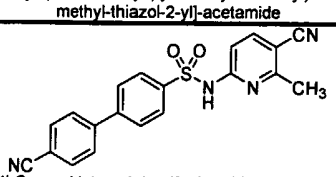
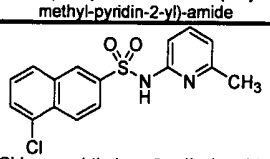
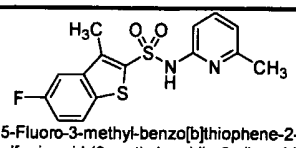
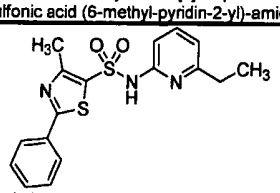
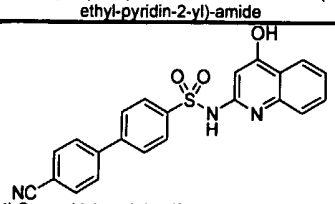
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
55	NA	7.4	 2,4-Difluoro-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$), δ: 8.02 (m, 1 H), 7.54 (dd, *J* = 8.8, 7.1 Hz, 1 H), 6.95 (m, 1 H), 6.79–6.90 (m, 2 H), 6.55 (d, *J* = 7.1 Hz, 1 H), 2.46 (s, 3 H)	285.0509
56	47.6	66.8	 3-Chloro-N-(6-ethyl-pyridin-2-yl)-2-methyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.02 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.42–7.59 (m, 2 H), 7.20 (m, 1 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 6.51 (d, *J* = 7.1 Hz, 1 H), 2.76 (s, 3 H), 2.72 (q, *J* = 7.7 Hz, 2 H), 1.29 (t, *J* = 7.6 Hz, 3 H)	311.0627
57	NA	4.5	 4'-Fluoro-biphenyl-4-sulfonic acid (1H-indol-6-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 6.43 (s, 1 H), 6.50 (m, 1 H), 6.65 (t, *J* = 8.2, 1.9 Hz, 1 H), 7.14 (m, 2 H), 7.22 (d, *J* = 2.53 Hz, 2 H), 7.38 (s, 1 H), 7.47 (s, 1 H), 7.50 (m, 1 H), 7.52 (d, *J* = 3.5 Hz, 2 H), 7.55 (d, *J* = 8.6 Hz, 2 H), 7.75 (d, *J* = 8.34 Hz, 2 H)	367.1
58	NA	4.0	 3-Chloro-N-(4,6-dimethyl-pyrimidin-2-yl)-2-methyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.76 (br s, 1 H), 8.24 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.55 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.26–7.31 (m, 1 H), 6.59 (s, 1 H), 2.71 (s, 3 H), 2.29 (s, 6 H)	312.0558
59	NA	3.8	 Biphenyl-4-sulfonic acid (4-methyl-pyrimidin-2-yl)-amide	F	(400 MHz, DMSO-d_6) δ: 11.77 (br s, 1 H), 8.32 (d, *J* = 5.3 Hz, 1 H), 8.04 (d, *J* = 8.3 Hz, 2 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 7.71 (d, *J* = 7.3 Hz, 2 H), 7.38–7.52 (m, 3 H), 6.91 (d, *J* = 5.1 Hz, 1 H), 2.32 (s, 3 H)	326.0974
60	NA	31.9	 4'-Fluoro-biphenyl-4-sulfonic acid (3H-benzoimidazol-5-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 6.78 (d, *J* = 8.59Hz, 1 H), 7.02 (s, 1 H), 7.14 (m, 2 H), 7.49 (m, 2 H), 7.64 (m, 3H), 7.99 (m, 2 H), 8.29 (s, 1 H)	368.0
61	2.3	98.6	 4'-Cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, MeOD) δ: 6.22 (d, *J* = 7.8 Hz, 1 H), 6.28 (d, *J* = 8.3 Hz, 1 H), 7.45 (t, *J* = 8.2 Hz, 1 H), 7.70–7.81 (m, 6 H), 7.90 (d, *J* = 8.3 Hz, 2 H)	351.1
62	NA	1.3	 N-(6-Methoxy-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ ppm 3.71 (s, 3 H) 6.42 (d, *J*=8.08 Hz, 1 H) 6.77 (d, *J*=7.83 Hz, 1 H) 7.49 (t, *J*=7.96 Hz, 1 H) 7.74 (d, *J*=8.59 Hz, 2 H) 8.10 (d, *J*=8.08 Hz, 2 H)	333.1
63	NA	32.7	 Dibenzofuran-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.58 (d, *J*=2.0 Hz, 1 H) 8.03 (dd, *J*=8.7, 1.9 Hz, 1 H) 7.97 (d, *J*=7.8 Hz, 1 H) 7.57 - 7.62 (m, 2 H) 7.45 - 7.54 (m, 2 H) 7.39 (t, *J*=7.5 Hz, 1 H) 7.01 (d, *J*=8.6 Hz, 1 H) 6.59 (d, *J*=7.6 Hz, 1 H) 2.39 (s, 3 H)	339.0792

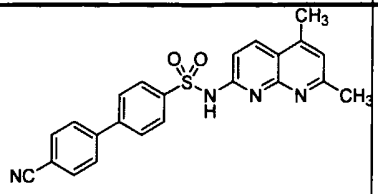
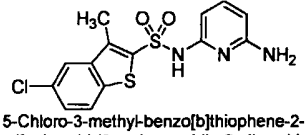
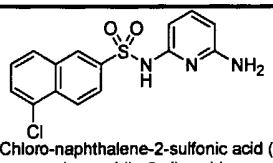
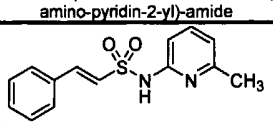
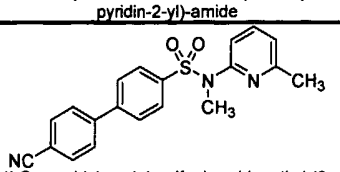
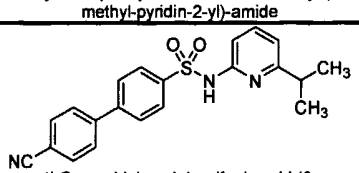
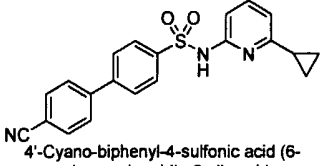
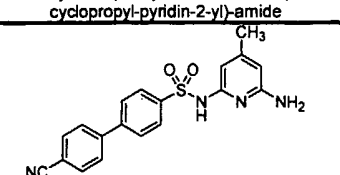
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
64	NA	8.9	 Biphenyl-4-sulfonic acid (6-morpholin-4-ylmethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 11.21 (s, 1 H) 8.01 (d, *J*=8.3 Hz, 2 H) 7.65 (d, *J*=8.3 Hz, 2 H) 7.35 - 7.59 (m, 6 H) 6.98 (d, *J*=8.8 Hz, 1 H) 6.55 (d, *J*=7.1 Hz, 1 H) 3.80 (m, 4 H) 3.52 (s, 2 H) 2.51 (m, 4 H)	410.1520
65	18.3	59.4	 Biphenyl-4-sulfonic acid (4,6-dimethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.00 (m, 2 H), 7.64 (m, 2 H), 7.55 (m, 2 H), 7.34–7.47 (m, 3 H), 6.95 (s, 1 H), 6.40 (s, 1 H), 2.44 (s, 3 H), 2.26 (s, 3 H)	339.1157
66	NA	33.8	 Biphenyl-4-sulfonic acid (5-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.13 (s, 1 H), 7.97 (d, *J* = 8.3 Hz, 2 H), 7.64 (d, *J* = 8.6 Hz, 2 H), 7.50–7.58 (m, 3 H), 7.36–7.48 (m, 4 H), 2.22 (s, 3 H)	325.0997
67	NA	49.6	 C-(3-Chloro-phenyl)-N-(6-methyl-pyridin-2-yl)-methanesulfonamide	F	(400 MHz, $CDCl_3$) δ: 10.35 (s, *J* = 16.2 Hz, 1 H), 7.36 - 7.48 (m, 2 H), 7.23 - 7.31 (m, 1 H), 7.14 - 7.23 (m, 2 H), 6.71 (d, *J* = 8.8 Hz, 1 H), 6.41 (d, *J*=7.3 Hz, 1 H), 4.33 - 4.41 (m, 2 H) 2.25 (s, 3 H)	297.0451
68	8.3	100	 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methoxy-pyridazin-3-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.66–7.78 (m, 2 H), 7.39 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.25 (d, *J* = 9.8 Hz, 1 H), 7.07 (d, *J* = 9.6 Hz, 1 H), 3.89 (s, 3 H), 2.68 (s, 3 H)	370.0
69	1.1	100	 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-ethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 11.43 (br s, 1 H), 7.64– 7.76 (m, 2 H), 7.56 (dd, *J* = 8.8, 7.3 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.0 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 1 H), 6.53 (d, *J* = 7.3 Hz, 1 H), 2.74 (q, *J* = 7.6 Hz, 2 H), 2.68 (s, 3 H) 1.31 (t, *J* = 7.6 Hz, 3 H)	367.0
70	216	78.7	 4-Isopropyl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 9.73 (br s, 1 H), 7.83 (d, *J* = 8.6 Hz, 2 H), 7.48 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 6.61 (d, *J* = 7.3 Hz, 1 H), 2.92 (m, 1 H), 2.41 (s, 3 H), 1.22 (d, *J* = 7.1 Hz, 6 H)	291.1158
71	34.6	66	 N-(6-Ethyl-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 11.17 (br s, 1 H), 8.06 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 7.55 (dd, *J* = 8.6, 7.3 Hz, 1 H), 6.94 (d, *J* = 8.8 Hz, 1 H), 6.55 (d, *J* = 7.3 Hz, 1 H), 2.73 (q, *J* = 7.6 Hz, 2 H), 1.29 (t, *J* = 7.6 Hz, 3 H)	331.0716
72	30.9	74.6	 Benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.90 (s, 1 H), 7.71–7.86 (m, 2 H), 7.57 (dd, *J* = 8.8, 7.3 Hz, 1 H), 7.32–7.47 (m, 2 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 2.52 (s, 3 H)	305.0

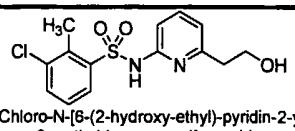
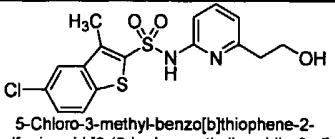
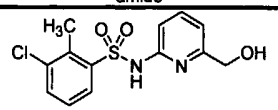
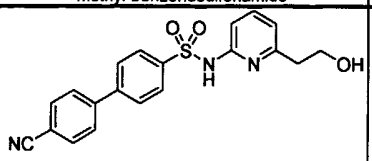
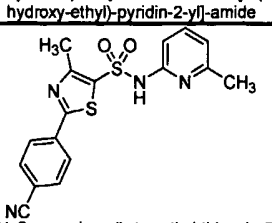
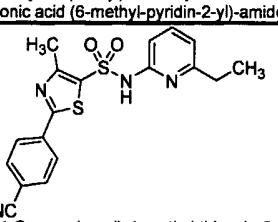
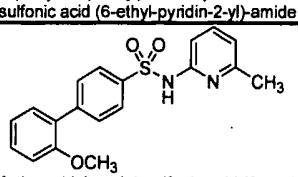
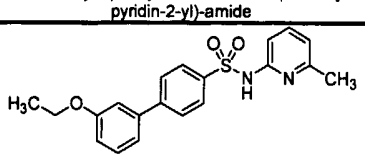
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
73	NA	17.3	 N-(6-Methyl-pyridin-2-yl)-C-(4-trifluoromethyl-phenyl)-methanesulfonamide	F	(400 MHz, $CDCl_3$) δ: 7.51 (m, 4 H), 7.43 (dd, J = 8.7, 7.2 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.39 (d, J = 7.1 Hz, 1 H), 4.45 (s, 2 H), 2.20 (s, 3 H)	331.1
74	NA	28.9	 C-(3,4-Dichloro-phenyl)-N-(6-methyl-pyridin-2-yl)-methanesulfonamide	F	(400 MHz, $CDCl_3$) δ: 7.42–7.51 (m, 2 H), 7.31 (m, 1 H), 7.21–7.25 (m, 1 H), 6.72 (d, J = 8.8 Hz, 1 H), 6.44 (d, J = 7.3 Hz, 1 H), 4.33 (s, 2 H), 2.27 (s, 3 H)	333.0
75	NA	19.2	 C-(3,5-Dichloro-phenyl)-N-(6-methyl-pyridin-2-yl)-methanesulfonamide	F	(400 MHz, $CDCl_3$), δ: 7.47 (dd, J = 8.8, 7.3 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 2 H), 7.22 (t, J = 1.9 Hz, 1 H), 6.71 (d, J = 8.6 Hz, 1 H), 6.43 (d, J = 7.1 Hz, 1 H), 4.31 (s, 2 H), 2.28 (s, 3 H)	333.0
76	NA	15.6	 N-(6-Ethyl-pyridin-2-yl)-4-isopropyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 9.75 (br s, 1 H), 7.84 (d, J = 8.6 Hz, 2 H), 7.49 (dd, J = 8.5, 7.5 Hz, 1 H), 7.29 (d, J = 8.3 Hz, 2 H), 6.98 (d, J = 8.6 Hz, 1 H), 6.60 (d, J = 7.3 Hz, 1 H), 2.92 (m, 1 H), 2.67 (q, J = 7.6 Hz, 2 H), 1.12–1.29 (m, 9 H)	305.1309
77	NA	35.4	 N-(4,6-Dimethyl-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	NA	331.0738
78	NA	8.2	 4'-Cyano-biphenyl-4-sulfonic acid (6-methoxy-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 3.74 (s, 3 H), 6.40 (d, J = 8.1 Hz, 1 H), 6.81 (d, J = 7.8 Hz, 1 H), 7.49 (t, J = 8.0 Hz, 1 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.75 (m, 2 H), 8.09 (d, J = 8.3 Hz, 2 H)	366.1
79	NA	8.1	 4'-Cyano-biphenyl-4-sulfonic acid (6-dimethylaminomethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.07 (d, J=8.3 Hz, 2 H) 7.72 - 7.76 (m, 2 H) 7.62 - 7.68 (m, 4 H) 7.52 (dd, J=8.8, 7.1 Hz, 1 H) 7.02 (d, J=8.6 Hz, 1 H) 6.49 (d, J=7.1 Hz, 1 H) 3.47 (s, 2 H) 2.33 (s, 6 H)	393.1377
80	NA	8	 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, DMSO-d_6) δ: 13.60 (br s, 1 H), 7.91 (m, 1 H), 7.77 (m, 1 H), 7.55 (m, 1 H), 7.09 (m, 1 H), 6.71 (m, 1 H), 2.33 (s, 3 H)	329.0
81	NA	23.4	 4-Methoxy-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 7.90 (d, J = 7.6 Hz, 2 H), 7.69 (m, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 6.94 (d, J = 7.8 Hz, 2 H), 6.81 (d, J = 6.8 Hz, 1 H), 3.83 (s, 3 H), 2.52 (s, 3 H)	279.0797

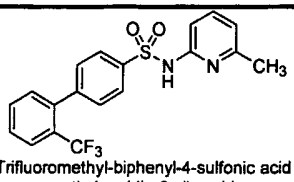
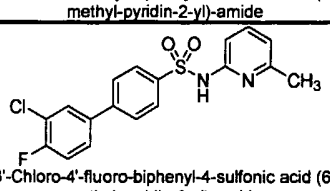
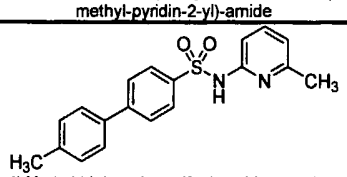
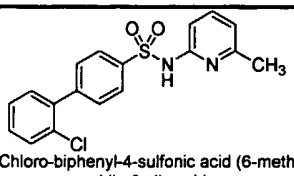
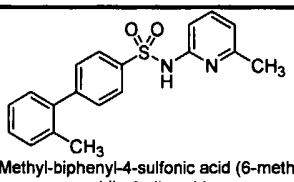
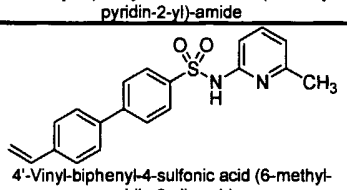
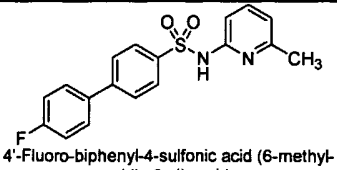
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
82	NA	53.4	 4'-Cyano-biphenyl-4-sulfonic acid pyridin-2-ylamide	F	(400 MHz, DMSO-d_6) δ: 12.30 (br s, 1 H), 7.84–8.04 (m, 9 H), 7.74 (m, 1 H), 7.21 (d, *J* = 8.6 Hz, 1 H), 6.85 (t, *J* = 6.3 Hz, 1 H)	336.1
83	NA	11.1	 6-Morpholin-4-yl-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$), δ: 9.45 (br s, 1 H), 8.66 (d, *J* = 2.5 Hz, 1 H), 7.91 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.41 - 7.56 (m, 1 H), 7.01 (d, *J* = 8.6 Hz, 1 H), 6.63 (d, *J* = 7.3 Hz, 1 H), 6.56 (d, *J* = 9.1 Hz, 1 H), 3.70–3.83 (m, 4 H), 3.54–3.66 (m, 4 H), 2.41 (s, 3 H)	335.0
84	NA	26.4	 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-dimethylaminomethyl-pyridin-2-yl)-amide	F	(400 MHz, CDC l_3) δ: 7.72 (d, *J*=2.0 Hz, 1 H) 7.67 (d, *J*=8.6 Hz, 1 H) 7.54 (dd, *J*=8.8, 7.1 Hz, 1 H) 7.36 (dd, *J*=8.6, 1.8 Hz, 1 H) 7.04 (d, *J*=8.8 Hz, 1 H) 6.46 (d, *J*=7.1 Hz, 1 H) 3.47 (s, 2 H) 2.69 (s, 3 H) 2.33 (s, 6 H)	396.0597
85	6.6	100	 4'-Cyano-biphenyl-4-sulfonic acid (6-ethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 7.8 Hz, 2 H), 7.65–7.78 (m, 7 H), 7.33 (d, *J* = 8.6 Hz, 1 H), 6.80 (d, *J* = 7.1 Hz, 1 H), 2.82 (q, *J* = 7.3 Hz, 2 H), 1.34 (t, *J* = 7.3 Hz, 3 H)	364.1102
86	14.3	100	 4'-Cyano-biphenyl-4-sulfonic acid furo[3,2-b]pyridin-5-ylamide	F	(400 MHz, $CDCl_3$) δ: 3.74 (s, 3 H), 6.40 (d, *J* = 8.1 Hz, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.68 (t, *J* = 7.58 Hz, 4 H), 7.75 (m, 2 H), 8.09 (d, *J* = 8.3 Hz, 2 H)	376.0
87	3.6	100	 4'-Cyano-biphenyl-4-sulfonic acid quinolin-2-ylamide	F	(400 MHz, $CDCl_3$) δ: 7.20–7.34 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.58–7.85 (m, 8 H), 8.07 (d, *J* = 9.4 Hz, 1 H), 8.13 (d, *J* = 8.1 Hz, 2 H)	386
88	NA	7.7	 4'-Cyano-biphenyl-4-sulfonic acid (3-methoxy-6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.27 (s, 2H), 7.63 - 7.84 (m, 6 H), 6.91 (d, *J* = 7.8 Hz, 2 H), 3.81 (s, 3H), 2.36 (s, 3H)	380.1
89	NA	3.7	 N-(3-Methoxy-6-methyl-pyridin-2-yl)-4-trifluoromethyl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.28-8.26 (m, 1H), 7.75-7.73 (m, 1H), 6.93-6.91 (m, 1H), 6.86-6.84 (m, 1H), 6.61-6.59 (m, 1H), 6.45-6.43 (m, 1H), 3.81 (s, 3H), 2.35 (s, 3H)	347.0660

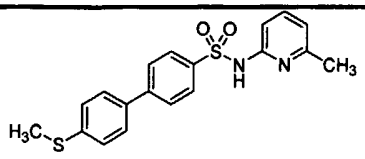
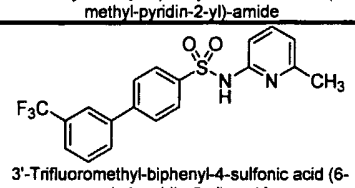
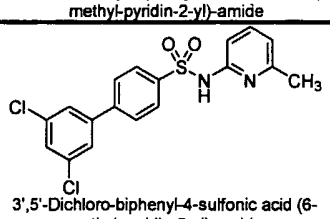
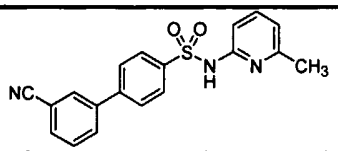
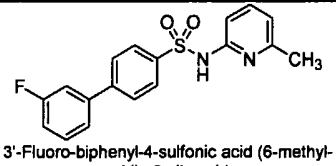
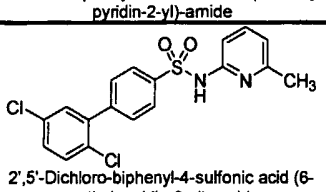
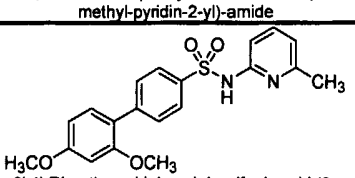
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
90	NA	24.8	 4-Cyano-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 8.1 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.59 (m, 1 H), 7.01 (d, *J* = 8.9 Hz, 1 H), 6.60 (m, 1 H), 2.48 (s, 3 H)	274.0634
91	2.3	100	 5-Cyano-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, DMSO-d_6) δ: 13.58 (br s, 1 H), 8.43 (s, 1 H), 8.21 (d, *J* = 8.3 Hz, 1 H), 7.82 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.72 (m, 1 H), 7.16 (m, 1 H), 6.68 (br d, *J* = 7.3 Hz, 1 H), 2.63 (s, 3 H), 2.34 (s, 3 H)	344.0520
92	NA	29.8	 N-(6-Methyl-pyridin-2-yl)-4-pyrazol-1-yl-benzenesulfonamide	F	(400 MHz, $CDCl_3$) δ: 8.01 (m, 2 H), 7.96 (d, *J* = 2.5 Hz, 1 H), 7.79 (m, 2 H), 7.73 (d, *J* = 1.5 Hz, 1 H), 7.51 (dd, *J* = 8.7, 7.5 Hz, 1 H), 7.04 (d, *J* = 8.8 Hz, 1 H), 6.60 (d, *J* = 7.3 Hz, 1 H), 6.49 (m, 1 H), 2.43 (s, 3 H)	315.0
93	42.3	70	 7-Chloro-naphthalene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.40 (s, 1 H), 7.83–7.96 (m, 3 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 7.47–7.55 (m, 2 H), 7.05 (d, *J* = 8.8 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 2.44 (s, 3 H)	333.0
94	32.8	76.3	 3-Methyl-5-phenyl-thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$), δ: 7.86 (m, 2 H), 7.58 (dd, *J* = 8.8, 7.3 Hz, 1 H), 7.35–7.49 (m, 3 H), 7.10 (d, *J* = 8.8 Hz, 1 H), 6.58 (d, *J* = 7.1 Hz, 1 H), 2.74 (s, 3 H) 2.51 (s, 3 H)	346.0
95	4.4	100	 4'-Trifluoromethyl-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, MeOD) δ: 4.74 (d, *J*=8.08 Hz, 2 H) 5.04 (d, *J*=8.08 Hz, 1 H) 6.06 (t, *J*=8.08 Hz, 1 H) 6.45 - 6.49 (m, 2 H) 6.50 - 6.54 (m, 2 H) 6.54 - 6.59 (m, 2 H) 6.73 (d, *J*=8.59 Hz, 2 H)	NA
96	7	100	 4'-Cyano-biphenyl-4-sulfonic acid (4,6-dimethyl-pyridin-2-yl)-amide	F	(400 MHz, DMSO-d_6), δ: 12.97 (br s, 1 H), 7.84–7.97 (m, 8 H), 6.94 (s, 1 H), 6.48 (s, 1 H), 2.25 (s, 3 H), 2.19 (s, 3 H)	364.1
97	NA	31.7	 4-Methyl-2-phenyl-thiazole-5-sulfonic acid (4,6-dimethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.79–7.91 (m, 2 H), 7.33–7.49 (m, 3 H), 6.95 (s, 1 H), 6.39 (s, 1 H), 2.75 (s, 3 H), 2.49 (s, 3 H), 2.28 (s, 3 H)	360.1
98	NA	8.9	 2,4-Dimethyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 8.8, 7.3 Hz, 1 H), 7.11 (d, *J* = 8.8 Hz, 1 H), 6.58 (d, *J* = 7.1 Hz, 1 H), 2.63 (s, 3 H), 2.62 (s, 3 H), 2.52 (s, 3 H)	284.1

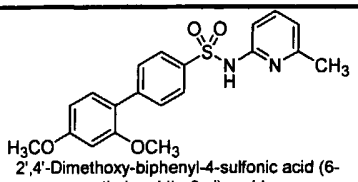
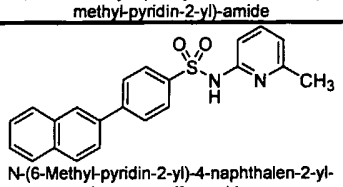
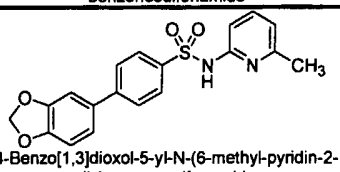
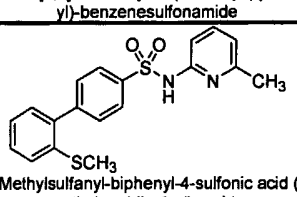
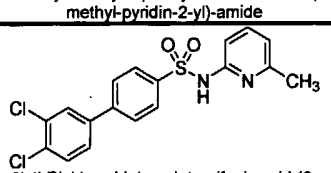
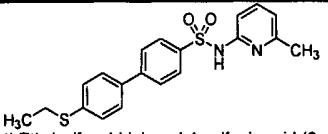
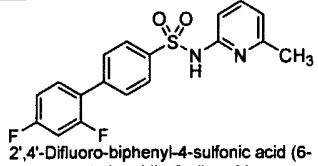
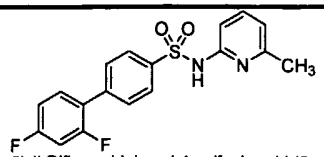
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
99	NA	1.5	 5-Methyl-1-phenyl-1H-pyrazole-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.86– 8.01 (m, 1 H), 7.41–7.59 (m, 4 H), 7.33–7.41 (m, 2 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 2.52 (s, 3 H), 2.44 (s, 3 H)	329.1
100	NA	19.2	 N-[5-(4,6-Dimethyl-pyridin-2-ylsulfamoyl)-4-methyl-thiazol-2-yl]-acetamide	F	(400 MHz, $CDCl_3$) δ: 6.97 (s, 1 H), 6.37 (s, 1 H), 4.56 (br s, 1 H), 2.52 (s, 3 H), 2.44 (s, 3 H), 2.27 (s, 3 H), 2.23 (s, 3 H)	341.1
101	NA	32	 4'-Cyano-biphenyl-4-sulfonic acid (5-cyano-6-methyl-pyridin-2-yl)-amide	F	(400 MHz, DMSO-d_6), δ: 7.90–8.11 (m, 10 H), 2.50 (s, 3 H)	375.1
102	<1	100	 5-Chloro-naphthalene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	NA	332.9
103	<1	100	 5-Fluoro-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	F	NA	337
104	23	89.6	 4-Methyl-2-phenyl-thiazole-5-sulfonic acid (6-ethyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.86 (m, 2 H), 7.59 (dd, *J* = 8.7, 7.2 Hz, 1 H), 7.35–7.48 (m, 3 H), 7.00 (d, *J* = 8.8 Hz, 1 H), 6.57 (d, *J* = 7.3 Hz, 1 H), 2.76 (m, 2 H), 2.73 (s, 3 H), 1.31 (t, *J* = 7.6 Hz, 3 H)	360.1
105	NA	16.9	 4'-Cyano-biphenyl-4-sulfonic acid (4-hydroxy-quinolin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 8.11 - 8.14 (m, 2 H), 7.87 (d, *J*=8.1 Hz, 1 H), 7.81 (dd, *J*=8.5, 1.9 Hz, 4 H), 7.66 - 7.75 (m, 4 H), 7.37 (t, 1 H) 6.95 (s, 1 H)	402.1

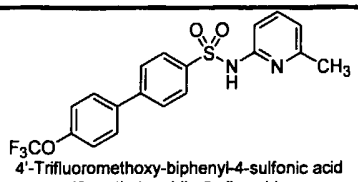
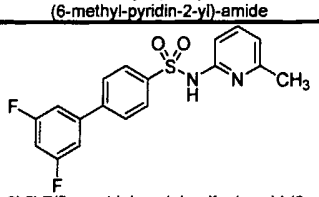
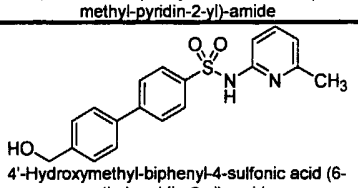
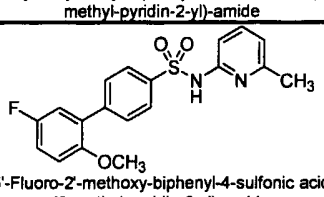
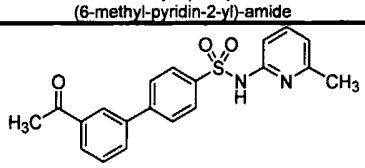
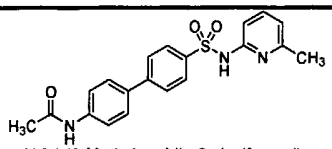
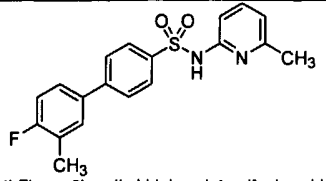
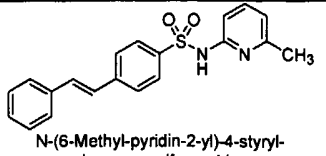
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
106	NA	5.4	 4'-Cyano-biphenyl-4-sulfonic acid (5,7-dimethyl-[1,8]naphthyridin-2-yl)-amide	F	(400 MHz, CD_3OD) δ: 8.56 (s, 1 H) 8.33 (d, *J*=7.8 Hz, 1 H) 7.88 - 7.94 (m, 1 H) 7.86 (s, 4 H) 7.44 (d, *J*=9.3 Hz, 1 H) 2.87 (s, 3 H) 2.81 (s, 3 H)	NA
107	<1	100	 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.63–7.69 (m, 2 H), 7.37–7.46 (m, 2 H), 6.88 (d, *J* = 8.3 Hz, 1 H), 5.97 (d, *J* = 8.1 Hz, 1 H), 2.61 (s, 3 H)	354.0
108	<1	100	 5-Chloro-naphthalene-2-sulfonic acid (6-amino-pyridin-2-yl)-amide	F	(400 MHz, DMSO-d_6) δ: 8.62 (br s, 1 H), 8.28 (d, *J* = 9.0 Hz, 1 H), 8.20 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1 H), 7.84 (d, *J* = 7.3 Hz, 1 H), 7.62 (t, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 8.1 Hz, 1 H), 6.46 (bs, 2 H), 6.19 (d, *J* = 8.3 Hz, 1 H), 5.88 (d, *J* = 8.1 Hz, 1 H)	334.2
109	NA		 2-Phenyl-ethenesulfonic acid (6-methyl-pyridin-2-yl)-amide	F	(400 MHz, $CDCl_3$) δ: 7.69 (dd, *J*=8.6, 7.6 Hz, 1 H) 7.56 (d, *J*=15.4 Hz, 1 H) 7.39 - 7.45 (m, 2 H) 7.26 - 7.37 (m, 4 H) 6.87 (d, *J*=15.4 Hz, 1 H) 6.78 (d, *J*=7.6 Hz, 1 H) 2.49 (s, 3 H)	NA
110	NA	8.1	 4'-Cyano-biphenyl-4-sulfonic acid methyl-(6-methyl-pyridin-2-yl)-amide	G	(400 MHz, CD_3CN), δ: 7.83-7.74 (m, 9 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.50-7.47 (m, 1H) , 7.32 (d, *J* = 8.1 Hz, 1 H), 3.30 (m, 3 H), 2.57 (s, 3 H)	364.1
111	1.7	100	 4'-Cyano-biphenyl-4-sulfonic acid (6-isopropyl-pyridin-2-yl)-amide	H	(400 MHz, CD_3CN) δ: 9.45 (br s, 1 H), 8.05 (dd, *J* = 6.6, 1.8 Hz, 1 H), 7.90-7.78 (m, 6 H), 7.62 (t, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 7.8 Hz, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 2.90-2.86 (m, 1 H), 1.18 (d, *J* = 8.7 Hz, 6 H)	364.1
112	NA		 4'-Cyano-biphenyl-4-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide	I	(400 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.5, 1 H), 7.76 (d, *J* = 8.3 Hz, 1 H), 7.67 (d, *J* = 8.5 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 7.6 Hz, 1 H), 1.93-1.87 (m, 1 H), 1.01-0.97 (m, 2 H), 0.88-0.85 (m, 1 H)	376.1112
113	NA		 4'-Cyano-biphenyl-4-sulfonic acid (6-amino-4-methyl-pyridin-2-yl)-amide	J	(400 MHz, DMSO-D6, D_2O) δ 2.04 (s, 3 H) 5.72 (s, 1 H) 6.09 (s, 1 H) 7.83 - 7.88 (m, 2 H) 7.89 - 7.96 (m, *J*=8.51, 8.51, 8.51 Hz, 6 H)	365.1

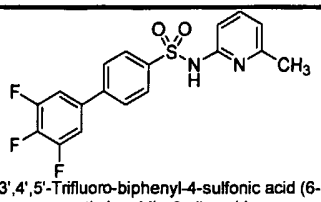
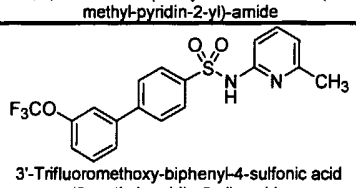
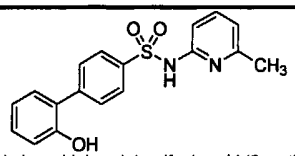
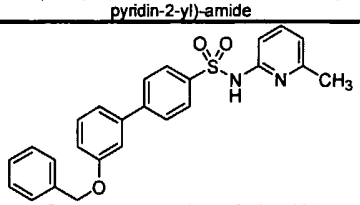
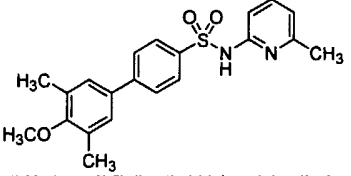
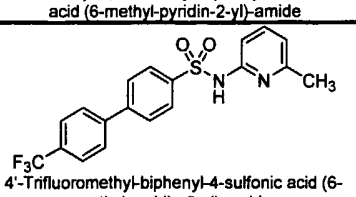
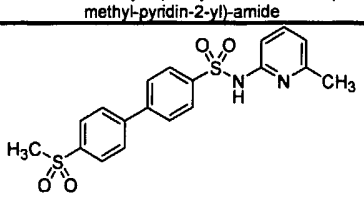
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
114	NA	11.3	 3-Chloro-N-[6-(2-hydroxy-ethyl)-pyridin-2-yl]-2-methyl-benzenesulfonamide	K	(400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.8 Hz, 1 H), 7.41–7.65 (m, 2 H), 7.20–7.26 (m, 1 H), 7.01 (d, *J* = 8.8 Hz, 1 H), 6.61 (d, *J* = 7.3 Hz, 1 H), 3.98 (t, *J* = 5.4 Hz, 2 H), 2.93 (t, *J* = 5.6 Hz, 2 H), 2.77 (s, 3 H)	327.0573
115	4.8	93.6	 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [6-(2-hydroxy-ethyl)-pyridin-2-yl]-amide	L	(400 MHz, DMSO-d_6) δ: 8.02 (d, *J* = 8.6 Hz, 1 H), 7.92 (m, 1 H), 7.72 (m, 1 H), 7.50 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.15 (br s, 1 H), 6.71 (d, *J* = 6.8 Hz, 1 H), 4.75 (br s, 1 H), 3.64 (m, 2 H), 2.76 (t, *J* = 5.9 Hz, 2 H), 2.58 (s, 3 H)	384.0
116	NA	37.2	 3-Chloro-N-(6-hydroxymethyl-pyridin-2-yl)-2-methyl-benzenesulfonamide	L	(400 MHz, DMSO-d_6) δ: 7.97 (br s, 1 H); 7.50-7.80 (m, 2 H), 7.37 (br s, 1 H), 7.04 (br s, 1 H), 6.74 (br s, 1 H), 5.15–5.70 (m, 1 H), 4.20–4.50 (m, 2 H), 2.64 (s, 3H)	313.0400
117	26.2	84.8	 4'-Cyano-biphenyl-4-sulfonic acid [6-(2-hydroxy-ethyl)-pyridin-2-yl]-amide	L	(400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 8.3 Hz, 2 H), 7.74 (m, 2 H), 7.63–7.68 (m, 4 H), 7.55 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.11 (d, *J* = 8.6 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 4.00 (t, *J* = 5.4 Hz, 2 H), 2.91 (t, *J* = 5.4 Hz, 2 H), 1.24 (s, 1 H)	380.0
118	2.5	100	 2-(4-Cyano-phenyl)-4-methyl-thiazole-5-sulfonic acid (6-methyl-pyridin-2-yl)-amide	M	(400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 7.61 (dd, *J* = 8.7, 7.2 Hz, 1 H), 7.11 (d, *J* = 8.8 Hz, 1 H), 6.59 (d, *J* = 7.3 Hz, 1 H), 2.74 (s, 3 H), 2.53 (s, 3 H)	371.2
119	NA	95.0	 2-(4-Cyano-phenyl)-4-methyl-thiazole-5-sulfonic acid (6-ethyl-pyridin-2-yl)-amide	M	(400 MHz, $CDCl_3$) δ: 11.64 (br s, 1 H), 7.98 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.62 (dd, *J* = 9.0, 7.2 Hz, 1 H), 7.01 (d, *J* = 8.6 Hz, 1 H), 6.58 (d, *J* = 7.3 Hz, 1 H), 2.78 (q, *J* = 7.6 Hz, 2 H), 2.73 (s, 3 H), 1.32 (t, *J* = 7.6 Hz, 3 H)	NA
120	NA	71.7	 2'-Methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	355
121	NA	61.4	 3'-Ethoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	369.1

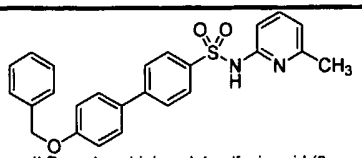
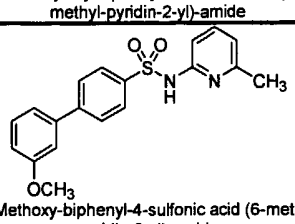
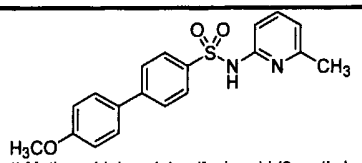
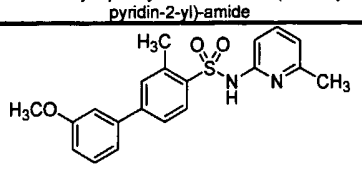
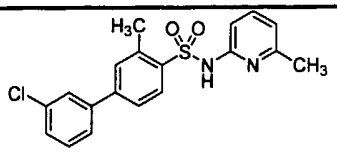
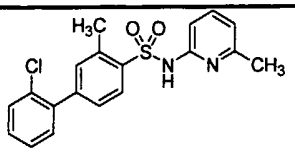
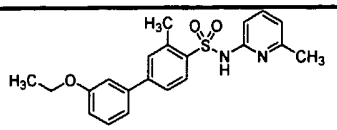
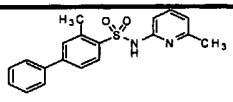
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
122	NA	85.7	 2'-Trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	393.1
123	NA	89.9	 3'-Chloro-4'-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	377
124	NA	84	 4'-Methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	339.1
125	NA	87.8	 2'-Chloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	359
126	NA	77.6	 2'-Methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	339.1
127	NA	100	 4'-Vinyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	351.1
128	19.7	86.8	 4'-Fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	343

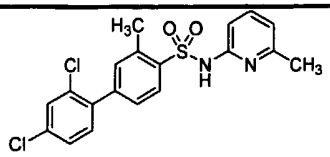
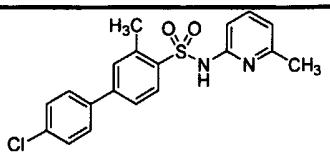
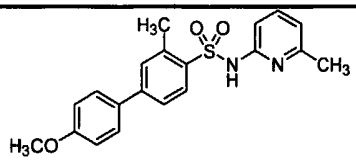
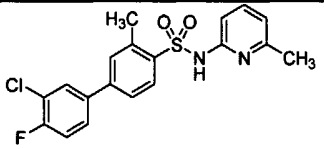
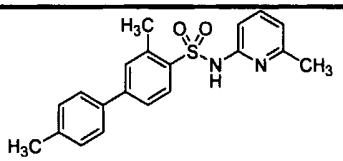
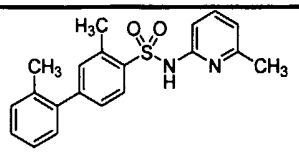
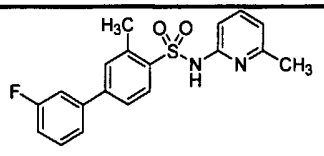
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
129	NA	86.3	 4'-Methylsulfanyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	371
130	NA	78.9	 3'-Trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	393.1
131	NA	100	 3',5'-Dichloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	392.9
132	NA	61.7	 3'-Cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	350
133	24.7	84.8	 3'-Fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	343
134	NA	83.5	 2',5'-Dichloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	392.9
135	NA	49.1	 2',4'-Dimethoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	385

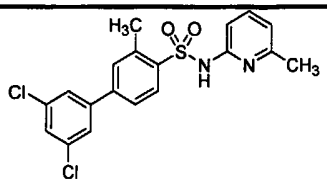
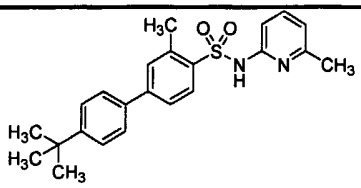
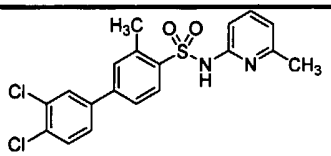
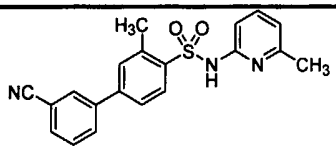
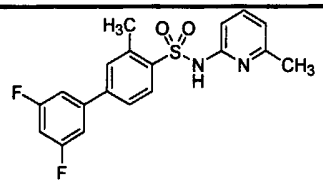
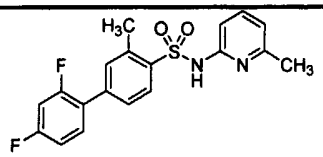
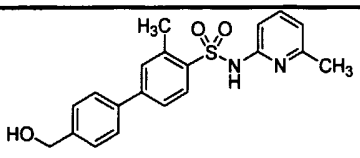
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
136	NA	49.1	 2',4'-Dimethoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	385
137	NA	79	 N-(6-Methyl-pyridin-2-yl)-4-naphthalen-2-yl-benzenesulfonamide	N	NA	375.1
138	NA	91.2	 4-Benzo[1,3]dioxol-5-yl-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	N	NA	368.9
139	NA	37.9	 2'-Methylsulfanyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	371
140	NA	91%	 3',4'-Dichloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	392.9
141	NA	83.8	 4'-Ethylsulfanyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	385
142	NA	84.5	 2',4'-Difluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	361
143	NA	84.5	 2',4'-Difluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	361

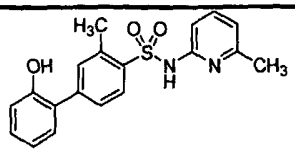
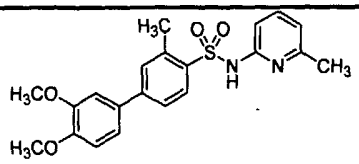
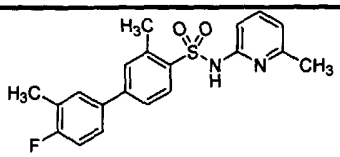
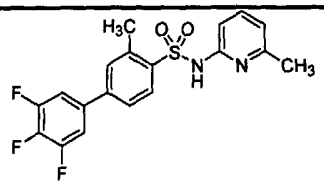
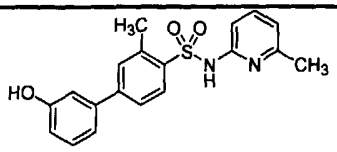
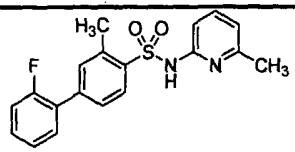
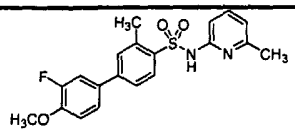
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
144	NA	86.8	 4'-Trifluoromethoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	409
145	NA	80.6	 3',5'-Difluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	361
146	NA	46.5	 4'-Hydroxymethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	355
147	NA	29.5	 5'-Fluoro-2'-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	373
148	NA	57.2	 3'-Acetyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	367
149	NA	20.4	 N-[4'-(6-Methyl-pyridin-2-ylsulfamoyl)-biphenyl-4-yl]-acetamide	N	NA	382
150	NA	79.3	 4'-Fluoro-3'-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	357
151	NA	59.8	 N-(6-Methyl-pyridin-2-yl)-4-styryl-benzenesulfonamide	N	NA	351.1

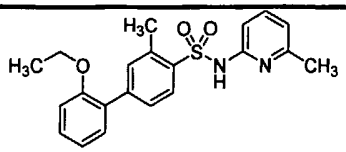
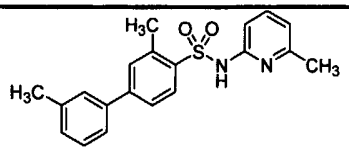
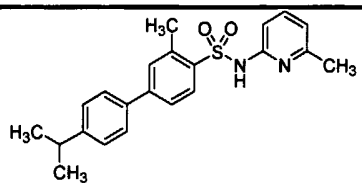
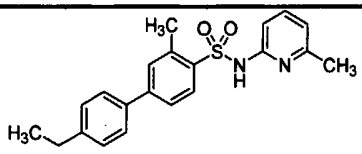
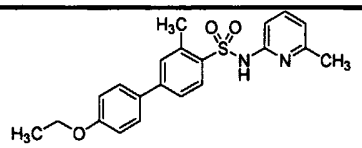
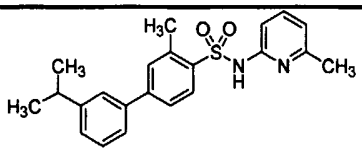
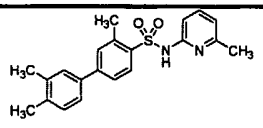
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
152	NA	72.7	 3',4',5'-Trifluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	379
153	NA	75.3	 3'-Trifluoromethoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	409
154	NA	43.6	 2'-Hydroxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	341
155	NA	83.3	 3'-Benzyloxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	431
156	NA	65.6	 4'-Methoxy-3',5'-dimethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	383
157	NA	100	 4'-Trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	392.9
158	NA	71	 4'-Methanesulfonyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	403

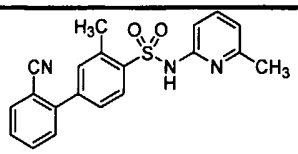
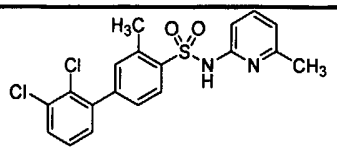
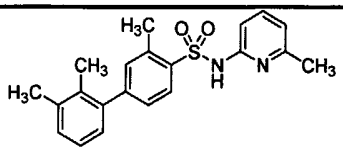
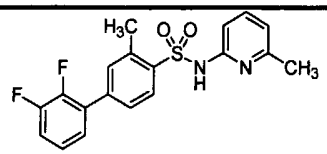
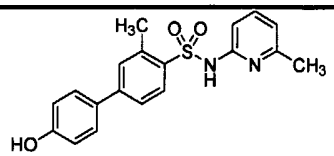
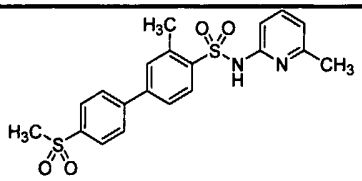
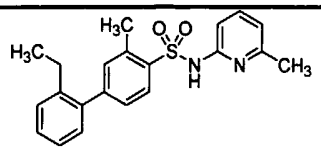
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
159	NA	90.4	 4'-Benzyloxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	431
160	36.2	86.8	 3'-Methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	355
161	22.5	90.3	 4'-Methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	N	NA	355.1
162	21	89	 3'-Methoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	369.1
163	8	97	 3'-Chloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
164	13	93	 2'-Chloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
165	43	71	 3'-Ethoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383
166	12	95	 3-Methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	339.1

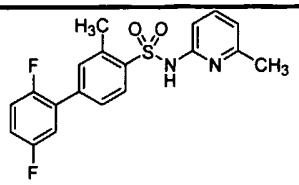
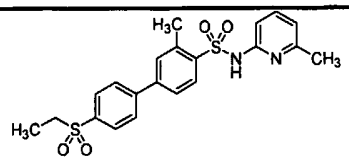
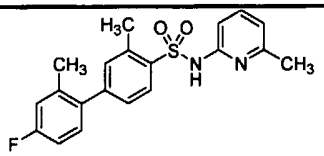
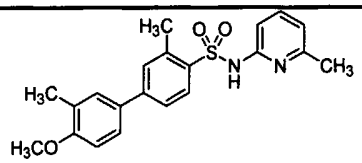
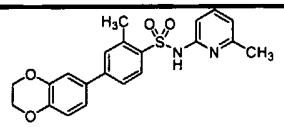
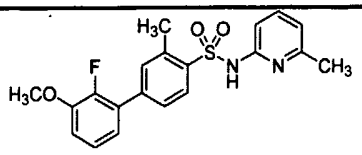
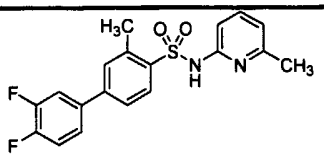
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
167	3.6	100	 2',4'-Dichloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
168	2.8	96	 4'-Chloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
169	19	93	 4'-Methoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	369.1
170	8.1	93	 3'-Chloro-4'-fluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	391
171	6.9	93	 3,4'-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353
172	48	82	 2',3-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353
173	9.6	97	 3'-Fluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	356.9

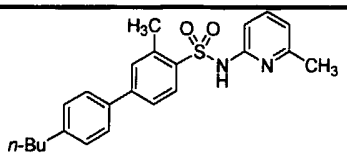
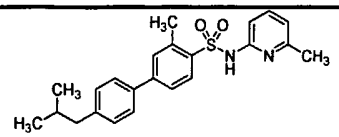
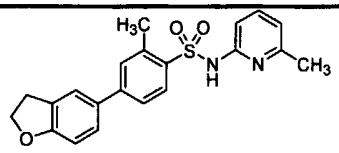
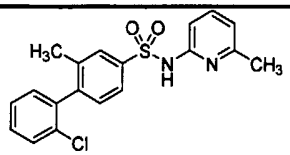
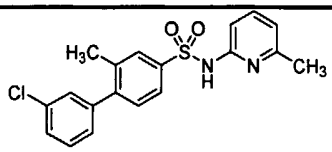
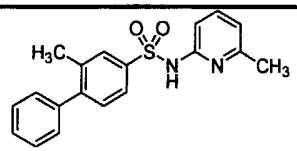
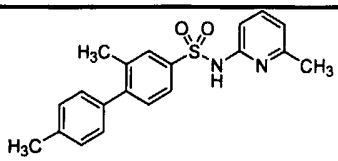
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
174	3.2	98	 3',5'-Dichloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
175	NA	59	 4'-Tert-butyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	395
176	5.2	100	 3',4'-Dichloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
177	20	85	 3'-Cyano-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	364
178	8.2	95	 3',5'-Difluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
179	6.2	95	 2',4'-Difluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
180	75	65	 4'-(Hydroxymethyl)-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	369.1

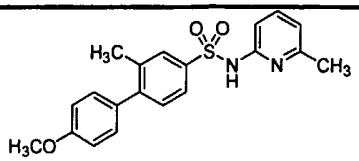
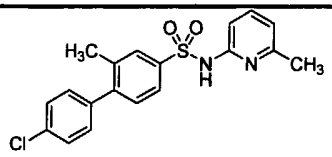
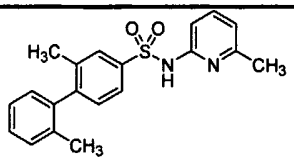
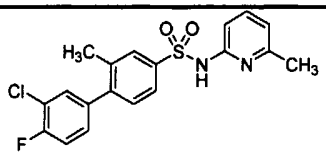
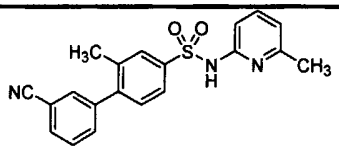
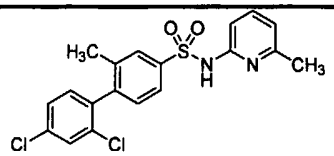
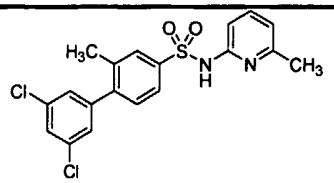
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
181	53	83	 2'-Hydroxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	355
182	23	79	 3',4'-Dimethoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	399.1
183	14	91	 4'-Fluoro-3,3'-dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	371
184	12	97	 3',4',5'-Trifluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	392.9
185	46	71	 3'-Hydroxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	355
186	9.3	95	 2'-Fluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	356.9
187	9.5	93	 3'-Fluoro-4'-methoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	386.9

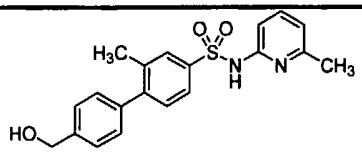
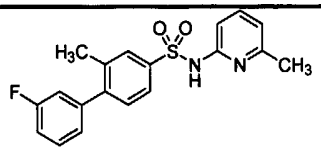
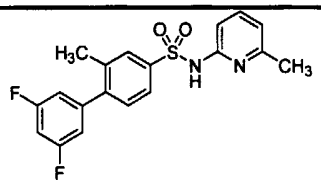
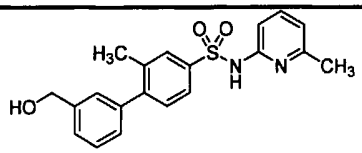
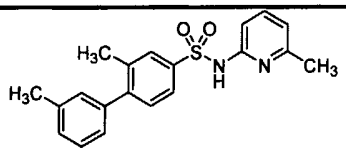
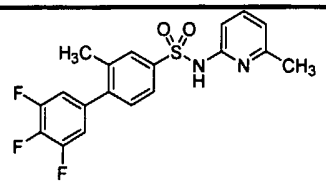
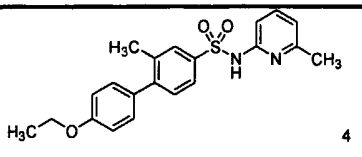
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
188	NA	53	 2'-Ethoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383
189	NA	88	 3,3'-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353
190	35	78	 4'-Isopropyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	381.1
191	11	100	 4'-Ethyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367
192	15	81	 4'-Ethoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383
193	39	78	 3'-Isopropyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	381.1
194	47	74	 3,3',4'-Trimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367

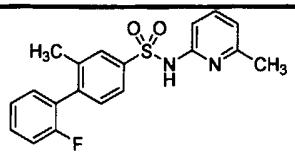
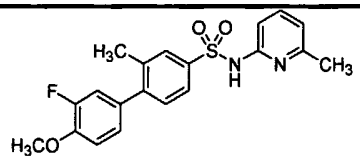
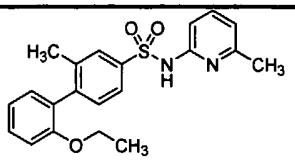
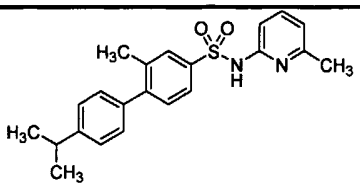
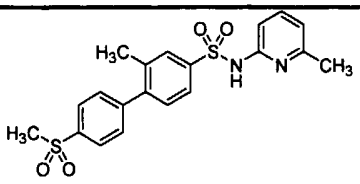
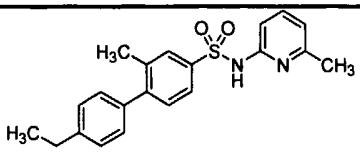
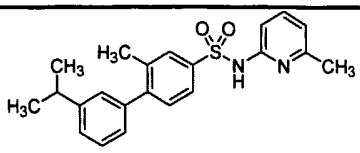
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
195	17	82	 2'-Cyano-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	364
196	7.1	90	 2',3'-Dichloro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
197	29	89	 2',3,3'-trimethyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367
198	7.5	100	 2',3'-Difluoro-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
199	NA	55	 4'-hydroxy-3-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	355
200	21	88	 3-Methyl-N-(6-methylpyridin-2-yl)-4'-(methylsulfonyl)biphenyl-4-sulfonamide	N	NA	416.9
201	43	75	 2'-ethyl-3-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367

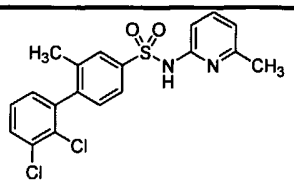
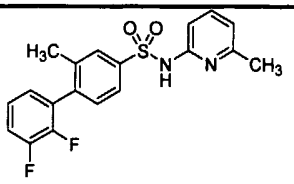
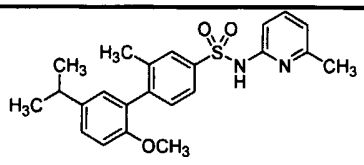
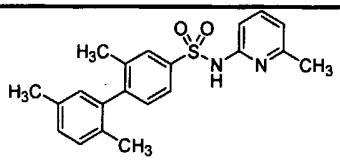
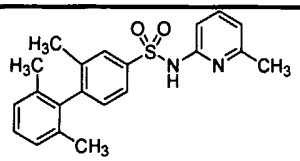
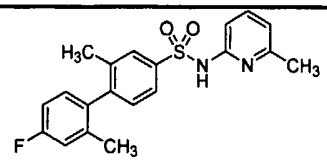
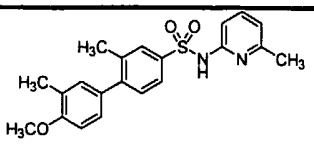
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
202	14	88	 2',5'-difluoro-3-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
203	19	86	 4'-(ethylsulfonyl)-3-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	431
204	10	85	 4'-fluoro-2',3-dimethyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	371
205	19	86	 4'-Methoxy-3,3'-dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383
206	20	87	 4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methyl-N-(6-methylpyridin-2-yl)benzenesulfonamide	N	NA	397
207	NA	63	 2'-Fluoro-3'-methoxy-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	396.9
208	6.7	95	 3',4'-difluoro-3-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9

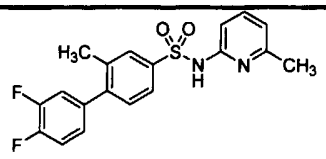
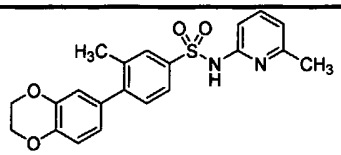
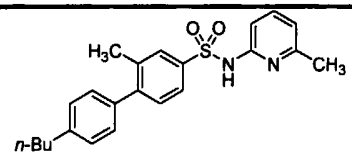
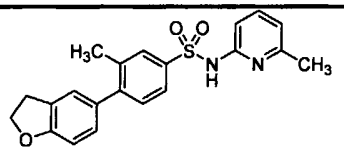
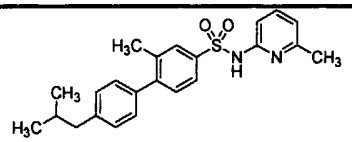
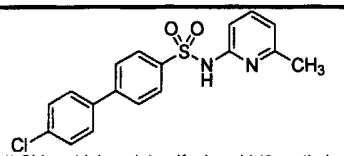
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
209	18	88	 4'-Butyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	395
210	47	74	 4'-Isobutyl-3-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	395
211	23	81	 4-(2,3-Dihydro-1-benzofuran-5-yl)-2-methyl-N-(6-methylpyridin-2-yl)benzenesulfonamide	N	NA	380.9
212	47	75	 2'-Chloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
213	31	77	 3'-Chloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
214	36	72	 2-Methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	338.9
215	16	90	 2,4'-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353

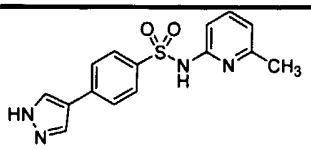
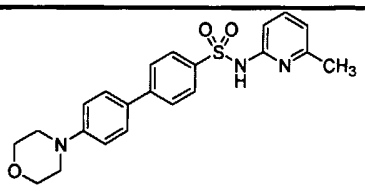
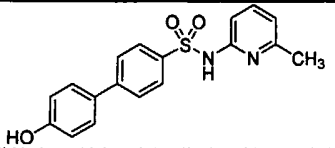
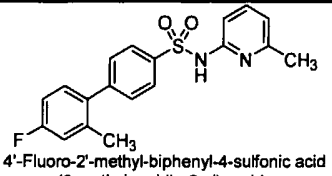
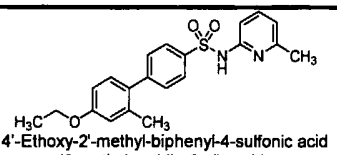
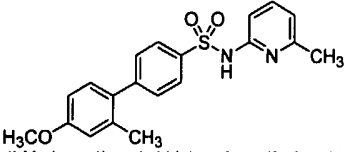
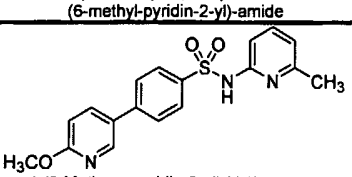
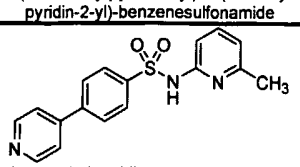
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
216	43	73	 4'-Methoxy-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	368.9
217	5	95	 4'-Chloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	373
218	NA	56	 2,2'-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353
219	17	88	 3'-Chloro-4'-fluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	391
220	NA	67	 3'-Cyano-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	364
221	18	87	 2',4'-Dichloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
222	10	90	 3',5'-Dichloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9

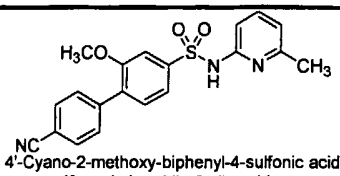
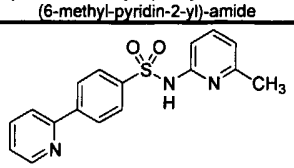
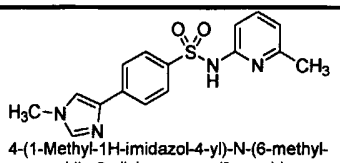
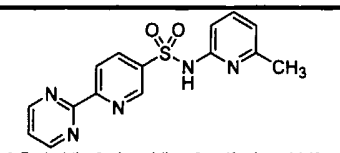
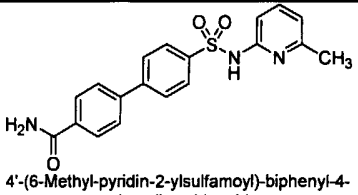
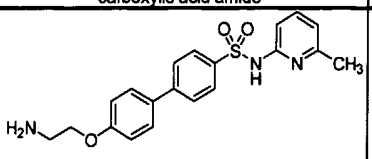
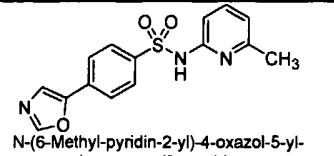
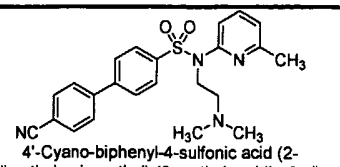
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
223	320	79	 4'-(Hydroxymethyl)-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	368.9
224	19	93	 3'-Fluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	356.9
225	NA	28	 3',5'-Difluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
226	460	94	 3'-(Hydroxymethyl)-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	369.1
227	NA	40	 2,3'-Dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	353
228	29	74	 3',4',5'-Trifluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	392.9
229	NA	9	 4'-Ethoxy-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383

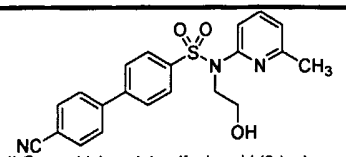
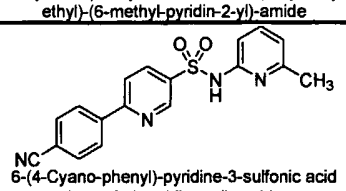
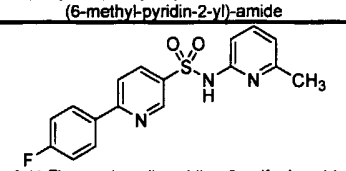
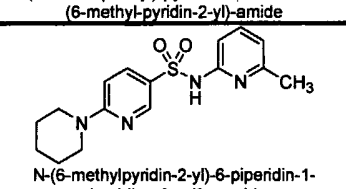
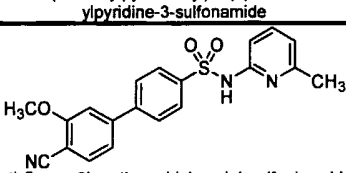
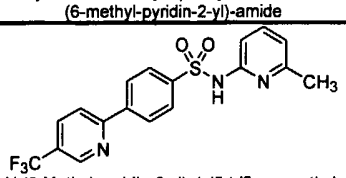
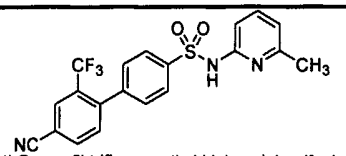
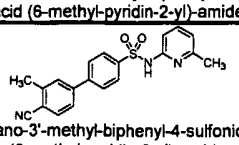
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
230	NA	23	 2'-Fluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	356.9
231	NA	63	 3'-Fluoro-4'-methoxy-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	386.9
232	660	78	 2'-Ethoxy-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383
233	110	78	 4'-Isopropyl-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	381.1
234	NA	57	 2-Methyl-N-(6-methylpyridin-2-yl)-4'-(methylsulfonyl)biphenyl-4-sulfonamide	N	NA	416.9
235	NA	87	 4'-Ethyl-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367
236	110	81	 3'-Isopropyl-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	381.1

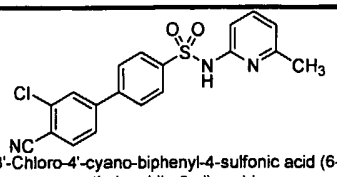
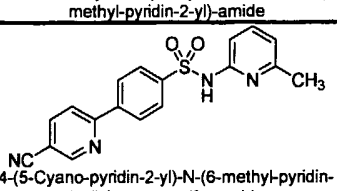
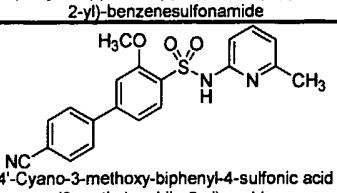
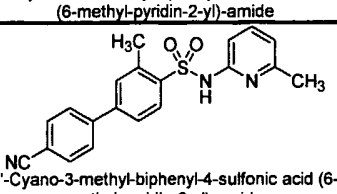
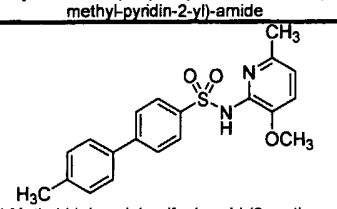
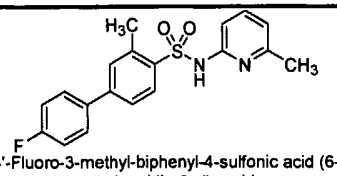
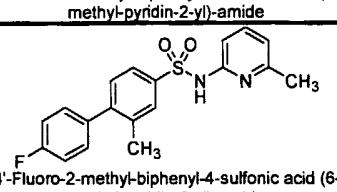
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
237	NA	58	 2',3'-Dichloro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	406.9
238	27	82	 2',3'-Difluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
239	NA	65	 5'-Isopropyl-2'-methoxy-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	411.1
240	NA	89	 2,2',5'-Trimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367
241	NA	64	 2,2',6'-Trimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	367
242	NA	61	 4'-Fluoro-2,2'-dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	371
243	NA	70	 4'-Methoxy-2,3'-dimethyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	383

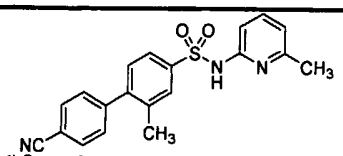
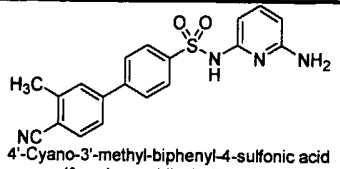
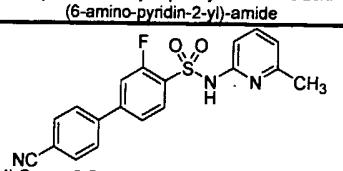
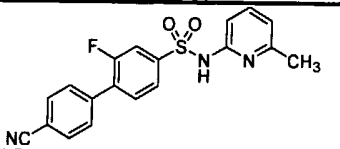
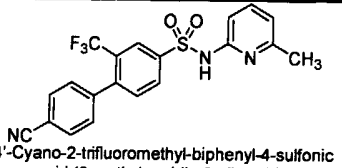
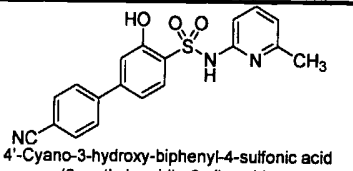
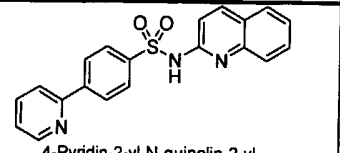
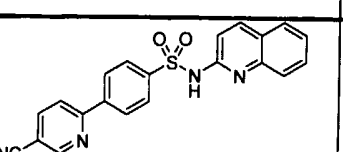
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
244	NA	86	 3',4'-Difluoro-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	374.9
245	NA	62	 4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-methyl-N-(6-methylpyridin-2-yl)benzenesulfonamide	N	NA	397
246	NA	65	 4'-Butyl-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	395
247	NA	65	 4-(2,3-Dihydro-1-benzofuran-5-yl)-3-methyl-N-(6-methylpyridin-2-yl)benzenesulfonamide	N	NA	380.9
248	NA	57	 4'-Isobutyl-2-methyl-N-(6-methylpyridin-2-yl)biphenyl-4-sulfonamide	N	NA	395
249	5.8	96	 4'-Chloro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, CD_3OD) δ: 8.01 (m, 2 H), 7.64 (m, 2 H), 7.55 (s, 1 H), 7.51 (m, 1 H), 7.44 (m, 1 H), 7.37 (m, 2 H), 7.00 (d, *J*=8.59 Hz, 1 H), 6.61 (d, *J*=7.33 Hz, 1 H), 2.42 (s, 3 H)	359.1

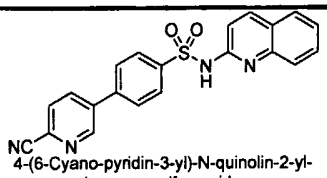
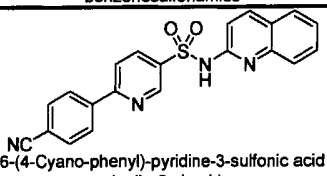
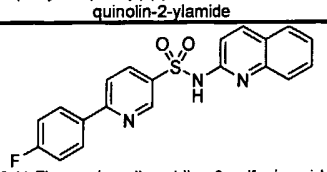
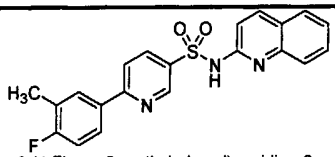
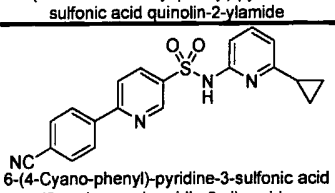
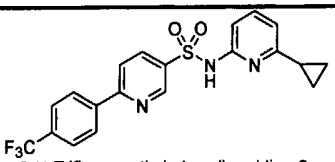
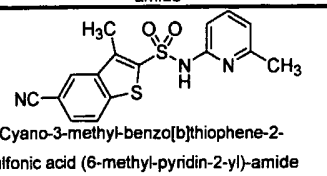
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
250	NA	17	 *N*-(6-Methyl-pyridin-2-yl)-4-(1H-pyrazol-4-yl)-benzenesulfonamide	O	(400 MHz, $CDCl_3$) δ: 7.97 (s, 2 H), 7.80 (d, *J*=8.3 Hz, 2 H), 7.62 (d, *J*=8.3 Hz, 2 H), 7.53 (dd, *J*=8.6, 7.6 Hz, 1 H), 7.03 (d, *J*=8.8 Hz, 1 H), 6.63 (d, *J*=7.3 Hz, 1 H), 2.30 (s, 3 H)	315.1
251	29	83.6	 4'-Morpholin-4-yl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, $CDCl_3$) δ: 2.54 (s, 3 H), 3.18 (m, 4 H), 3.82 (m, 4 H), 6.92 (m, 3 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.61 (m, 3 H), 7.84 (m, 1 H), 7.94 (d, *J* = 8.6 Hz, 2 H)	410.1
252	NA	44	 4'-Hydroxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, $CDCl_3$) δ: 2.34 (s, 3 H), 6.58 (d, *J* = 7.3 Hz, 1 H), 6.78 (m, 2 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.35 (m, 2H), 7.45 (m, 1H), 7.49 (m, 2H), 7.85 (m, 2H)	341.1
253	33.4	79.3	 4'-Fluoro-2'-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.0 Hz, 3 H), 6.61 (d, *J* = 7.3 Hz, 1 H), 6.76 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.79 (d, *J* = 2.5 Hz, 1 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 7.19 (d, *J* = 8.6 Hz, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.54 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 2 H)	357.1
254	22.4	85.4	 4'-Ethoxy-2'-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, $CDCl_3$) δ: 6.89 (d, *J* = 1.8 Hz, 1 H), 7.38 (d, *J* = 9.1 Hz, 1 H), 7.50–7.59 (m, 4 H), 7.63–7.68 (m, 1 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.74 (d, *J* = 2.3 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 2 H), 9.34 (s, 1 H)	383.1
255	NA	64.6	 4'-Methoxy-2'-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.0 Hz, 3 H), 4.05 (q, 3 H), 6.61 (d, *J* = 7.3 Hz, 1 H), 6.76 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.79 (d, *J* = 2.5 Hz, 1 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 7.19 (d, *J* = 8.6 Hz, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.54 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 2 H)	369.1
256	34.9	89.3	 4-(6-Methoxy-pyridin-3-yl)-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	O	(400 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 2.5 Hz, 1 H), 8.00 (d, *J* = 8.1 Hz, 2 H), 7.77 (dd, *J* = 8.6, 2.5 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 2 H) 7.46-7.54 (m, 1 H), 7.00 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H),6.60 (d, *J* = 7.3 Hz, 2 H) 3.98 (s, 3 H), 2.42 (s, 3 H)	356.1
257	NA	74.7	 N-(6-Methyl-pyridin-2-yl)-4-pyridin-4-yl-benzenesulfonamide	O	(400 MHz, $CDCl_3$) δ: 8.83 (s, 2 H), 8.14 (d, *J*=8.3 Hz, 2 H), 7.69 - 7.77 (m, 3 H), 7.29 - 7.33 (m, 1 H), 6.78 (d, *J*=7.1 Hz, 1 H), 2.45 (m, 3 H)	NA

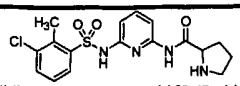
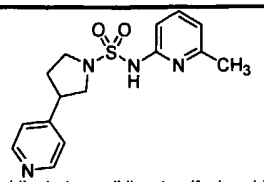
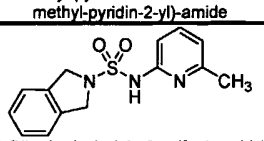
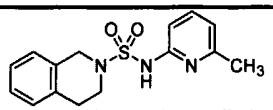
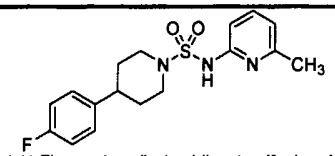
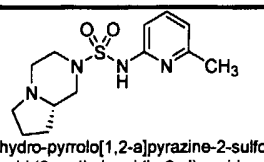
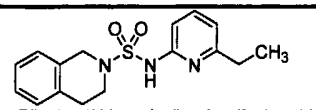
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
258	NA	100	 4'-Cyano-2-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	O	(400 MHz, DMSO-d_6) δ: 7.89 (d, *J*=8.3 Hz, 2 H) 7.70 (d, *J*=8.3 Hz, 2 H) 7.66 (d, *J*=8.1 Hz, 1 H) 7.45 - 7.56 (m, 3 H) 7.13 (s, 1 H) 3.84 (s, 3 H) 2.33 (s, 3 H)	NA
259	NA	30	 *N*-(6-Methyl-pyridin-2-yl)-4-pyridin-2-yl-benzenesulfonamide	P	(400 MHz, $CDCl_3$) δ 8.78 (d, *J*=4.80 Hz, 1 H), 8.10 (s, 2 H), 7.90 (m, 2 H), 7.81 (d, *J*=7.83 Hz, 1 H), 7.59 (d, *J*=8.84 Hz, 1 H), 7.42 (m, 1 H), 6.95 (d, *J*=7.58 Hz, 1 H), 2.59 (s, 3 H)	326.1
260	NA	14.8	 4-(1-Methyl-1H-imidazol-4-yl)-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	P	(400 MHz, DMSO-d_6) δ: 9.37 (s, 1 H), 8.45 (s, 1 H), 8.15 (t, *J* = 8.7 Hz, 4 H), 7.85 (d, *J* = 7.8 Hz, 1 H) 7.28 (s, 1 H), 6.88 (s, 1 H), 4.09 (s, 3 H), 2.52 (s, 3 H)	329.1
261	NA	2.6	 6-Pyrimidin-2-yl-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide	P	(400 MHz, $CDCl_3$) δ: 8.97 (s, 1 H), 8.16 - 8.22 (m, 2 H), 8.11 - 8.16 (m, 2 H), 8.04 (d, *J*=2.3 Hz, 1 H), 7.93 (d, *J*=8.6 Hz, 1 H), 7.86 - 7.91 (m, 1 H), 7.68 (d, *J*=8.8 Hz, 1 H), 6.99 (d, *J*=7.6 Hz, 1 H), 2.62 (s, 3 H)	327.1
262	NA	45.7	 4'-(6-Methyl-pyridin-2-ylsulfamoyl)-biphenyl-4-carboxylic acid amide	Q	(400 MHz, $CDCl_3$) δ: 2.34 (s, 3 H), 6.58 (d, *J* = 7.3 Hz, 1 H), 6.78 (m, 2 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.35 (m, 2H), 7.45 (m, 1H), 7.49 (m, 2H), 7.85 (m, 2H)	368.1
263	NA	11.8	 4'-(2-Amino-ethoxy)-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	R	(400 MHz, $CDCl_3$) δ: 2.30 (s, 3 H), 3.04 (m, 2 H), 4.05 (t, *J* = 5.8 Hz, 1 H), 6.79 (m, 1 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.44 (m, 2 H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.64 (m, 3H)	383.1
264	NA	39.7	 N-(6-Methyl-pyridin-2-yl)-4-oxazol-5-yl-benzenesulfonamide	S	(400 MHz, $CDCl_3$) δ: 8.21 (s, 1 H), 7.90 (d, *J* = 8.3 Hz, 1 H), 7.62 (d, *J* = 8.3 Hz, 1 H), 7.56 (s, 1 H), 7.54 (m, 1 H), 7.04 (m, 1 H), 6.56 (m, 1 H), 2.30 (s, 3 H)	316.1
265	NA	11.4	 4'-Cyano-biphenyl-4-sulfonic acid (2-dimethylamino-ethyl)-(6-methyl-pyridin-2-yl)-amide	T	(400 MHz, DMSO-d_6) δ: 10.10 (br s, *J* = 3.8 Hz, 1 H), 7.90–8.07 (m, 6 H), 7.71–7.86 (m, 3 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 4.17 (t, *J* = 6.6 Hz, 2 H), 3.24 (m, 2 H), 2.82 (s, 6 H), 2.33 (s, 3 H)	421.1693

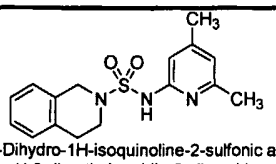
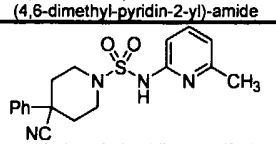
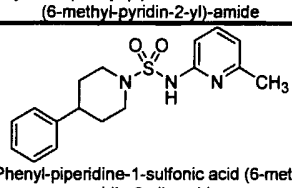
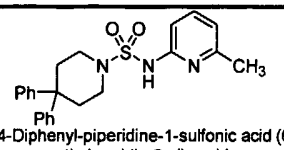
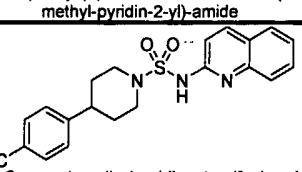
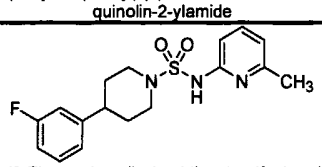
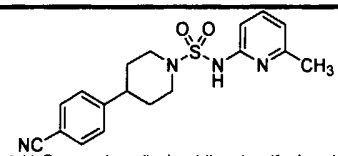
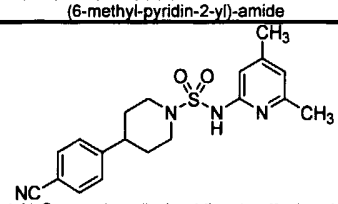
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
266	NA	9.6	 4'-Cyano-biphenyl-4-sulfonic acid (2-hydroxy-ethyl)-(6-methyl-pyridin-2-yl)-amide	U	(400 MHz, DMSO-d_6) δ: 7.91–8.01 (m, 6 H), 7.79 (d, *J* = 8.3 Hz, 2 H), 7.73 (t, *J* = 7.8 Hz, 1 H), 7.27 (d, *J* = 7.8 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 1 H), 3.83 (t, *J* = 6.3 Hz, 2 H), 3.47 (t, *J* = 6.3 Hz, 2 H), 2.31 (s, 3 H)	394.1218
267	22.6	81.8	 6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide	V	(400 MHz, DMSO-d_6) δ: 2.16 (s, 3 H), 6.51 (s, 1 H), 7.01 (s, 1 H), 7.54 (s, 1 H), 7.83 (d, *J* = 8.3 Hz, 2 H), 8.03–8.10 (m, 1 H), 8.12 (s, 2 H), 8.94 (s, 1 H)	351.0
268	40	70	 6-(4-Fluoro-phenyl)-pyridine-3-sulfonic acid (6-methyl-pyridin-2-yl)-amide	V	(400 MHz, $CDCl_3$) δ: 9.18 (1H, s); 8.28 (1H, d); 8.01 (1H, dd), 7.77 (1H, d); 7.56 (1H, t); 7.18 (1H, d); 7.16 (1H, d); 7.10 (1H, d); 7.04 (1H, d); 6.58 (1H, d); 2.47 (1H, s); N-H not observed	342
269	NA	2.4	 N-(6-methylpyridin-2-yl)-6-piperidin-1-ylpyridine-3-sulfonamide	W	(400 MHz, $CDCl_3$) δ: 8.65 (d, *J*=2.3 Hz, 1 H) 7.88 (dd, *J*=9.1, 2.5 Hz, 1 H) 7.26 - 7.46 (m, 1 H) 7.00 (d, *J*=8.6 Hz, 1 H) 6.40 - 6.61 (m, 2 H) 3.58 (d, *J*=5.1 Hz, 3 H) 2.93 - 3.14 (m, 3 H) 2.29 (s, 3 H) 1.47 - 1.81 (m, 6 H)	333.1
270	10.7	94.8	 4'-Cyano-3'-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	X	(400 MHz, $CDCl_3$) δ: 2.46 (s, 3 H) 4.10 (s, 3 H) 6.60 (d, *J*=7.33 Hz, 1 H) 7.04 (d, *J*=8.84 Hz, 1 H) 7.10 (s, 1 H) 7.19 (dd, *J*=7.96, 1.14 Hz, 1 H) 7.44 - 7.50 (m, 1 H) 7.54 (d, *J*=7.58 Hz, 1 H) 7.62 - 7.67 (m, 2 H) 8.05 (d, *J*=8.34 Hz, 2 H)	380.1
271	20	87.7	 N-(6-Methyl-pyridin-2-yl)-4-(5-trifluoromethyl-pyridin-2-yl)-benzenesulfonamide	X	(400 MHz, $CDCl_3$), δ: 8.97 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 2 H), 8.13 (d, *J* = 8.3 Hz, 1 H), 8.06 (dd, *J* = 8.4, 2.15 Hz, 1 H) 7.93 (d, *J* = 8.6 Hz, 1 H) 7.89 (m, 1 H) 7.68 (d, *J* = 8.8 Hz, 1 H) 6.99 (d, *J* = 7.58 Hz, 1 H) 2.62 (s, 3 H)	393.0
272	12	100	 4'-Cyano-2'-trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	X	(400 MHz, $CDCl_3$) δ: 7.98 (s, 1 H) 7.97 - 8.02 (m, 1 H) 7.95 (d, *J*=8.3 Hz, 2 H) 7.95 (d, *J*=8.3 Hz, 2 H) 7.80 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.56 - 7.66 (m, 1 H) 7.44 - 7.52 (m, 1 H) 7.35 - 7.44 (m, 2 H) 7.32 (d, *J*=8.3 Hz, 2 H) 6.96 (d, *J*=8.8 Hz, 1 H) 6.52 (d, *J*=7.3 Hz, 1 H) 2.37 - 2.49 (m, 3 H)	418.1
273	5.3	95.5	 4'-Cyano-3'-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	X	(400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.1 Hz, 2 H), 7.82 - 7.91 (m, 4 H), 7.72 (d, *J*=8.1 Hz, 1 H), 7.31 (t, *J*=8.0 Hz, 1 H), 6.21 (d, *J*=8.1 Hz, 1 H), 5.92 (d, *J*=7.6 Hz, 1 H), 2.56 (s, 3 H)	364.1

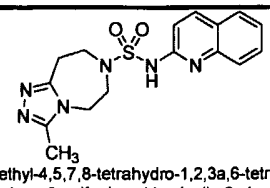
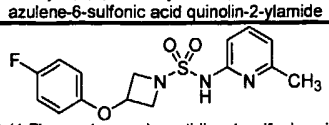
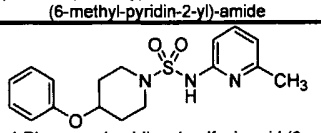
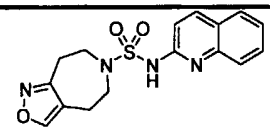
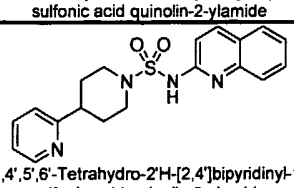
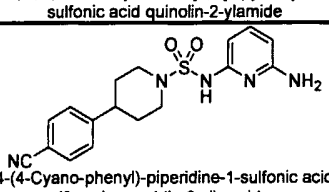
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
274	3.5	94.4	 3'-Chloro-4'-cyano-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	X	(400 MHz, $CDCl_3$) δ: 8.11 (d, *J*=8.3 Hz, 2 H) 7.86 (t, *J*=8.1 Hz, 1 H) 7.77 (d, *J*=8.3 Hz, 1 H) 7.71 (s, 1 H) 7.70 (d, 1 H) 7.56 (d, *J*=8.6 Hz, 2 H) 6.92 (d, *J*=7.8 Hz, 1 H) 2.58 (s, 3 H)	384.0
275	NA	85.7	 4-(5-Cyano-pyridin-2-yl)-N-(6-methyl-pyridin-2-yl)-benzenesulfonamide	X	(400 MHz, $CDCl_3$) δ: 10.19 (bs, 1 H) 8.94 - 8.96 (m, 1 H) 8.11 - 8.15 (m, 2 H) 8.02 - 8.09 (m, 3 H) 7.85 - 7.88 (m, 1 H) 7.50 (dd, *J*=8.6, 7.3 Hz, 1 H) 6.97 (d, *J*=8.0 Hz, 1 H) 6.57 (d, *J*=7.3 Hz, 1 H) 2.42 (s, 3 H)	351.0910
276	NA	60.1	 4'-Cyano-3-methoxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	Y	(400 MHz, $CDCl_3$) δ: 8.08 (d, *J*=8.1 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 2 H), 7.60 - 7.68 (m, 2 H), 7.43 - 7.51 (m, 1 H), 7.22 (dd, *J*=8.1, 1.5 Hz, 1 H), 7.09 (s, 1 H), 6.98 (d, *J*=8.8 Hz, 1 H), 6.65 (d, *J*=7.3 Hz, 1 H), 3.91 (s, 3 H), 2.43 (s, 2 H)	380.1
277	<1	100	 4'-Cyano-3-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	Z	(400 MHz, DMSO-d_6) δ: 8.05 (1H, d); 7.96 (2H, d); 7.93 (2H, d); 7.89-7.68 (2H, m), 7.62 (1H, t); 7.01 (1H, bs); 6.61 (1H, bs); 2.69 (3H, s); 2.31 (3H, s), N-H proton not observed	364
278	NA	42.8	 4'-Methyl-biphenyl-4-sulfonic acid (3-methoxy-6-methyl-pyridin-2-yl)-amide	Z	(400 MHz, $CDCl_3$) δ: 8.22 (s, 2H), 7.68-7.66 (m, 2H), 7.50-7.48 (m, 2H), 7.28-7.26 (2H, m), 6.90-6.88 (1H, m), 6.65 (s, 1H), 3.80 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H)	369.1259
279	4.5	100	 4'-Fluoro-3-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	Z	(400 MHz, DMSO-d_6) δ: 8.01 (1H, d); 7.77 (1H, d); 7.74 (1H, d); 7.65-7.56 (3H, m), 7.31 (1H, t); 6.98 (1H, bs); 6.62 (1H, bs); 2.67 (3H, s); 2.30 (3H, s), N-H proton not observed	357
280	15	91	 4'-Fluoro-2-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	Z	(400 MHz, DMSO-d_6) δ: 7.80 (1H, s); 7.73 (1H, d); 7.65 (1H, t); 7.42 (1H, d), 7.40 (1H, d); 7.34 (1H, d); 7.28 (1H, t); 7.09 (1H, bs); 6.68 (1H, bs); 2.32 (3H, s); 2.27 (3H, s), N-H proton not observed	357

Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
281	10	92.9	 4'-Cyano-2-methyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	Z	(400 MHz, DMSO-d_6) δ: 7.93 (2H, d); 7.82 (1H, s); 7.75 (1H, d); 7.65 (1H, t), 7.59 (2H, d); 7.38 (1H, d); 7.10 (1H, bs); 6.67 (1H, bs); 2.33 (3H, s); 2.28 (3H, s), N-H proton not observed	364
282	<1	100	 4'-Cyano-3'-methyl-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide	AA	(400 MHz, DMSO-d_6) δ: 7.95 (d, *J*=7.1 Hz, 2 H) 7.82 - 7.91 (m, 4 H) 7.72 (d, *J*=8.1 Hz, 1 H) 7.31 (t, *J*=8.0 Hz, 1 H) 6.21 (d, *J*=8.1 Hz, 1 H) 5.92 (d, *J*=7.6 Hz, 1 H) 2.56 (s, 3 H)	365.1
283	5.7	100	 4'-Cyano-3-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AB	(400 MHz, $CDCl_3$) δ: 8.13 (t, *J*=7.7 Hz, 1 H) 7.77 (d, 2 H) 7.70 - 7.74 (m, 1 H) 7.66 (d, *J*=8.1 Hz, 2 H) 7.48 (d, *J*=8.6 Hz, 1 H) 7.35 (d, *J*=11.1 Hz, 1 H) 7.23 (s, 1 H) 6.78 (d, *J*=7.3 Hz, 1 H) 2.55 (s, 3 H)	368.1
284	3.4	100	 4'-Cyano-2-fluoro-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AC	(400 MHz, $CDCl_3$) δ: 7.88 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.73 - 7.84 (m, 4 H) 7.64 (d, *J*=7.3 Hz, 2 H) 7.57 (t, *J*=7.7 Hz, 1 H) 7.40 (d, *J*=8.8 Hz, 1 H) 6.84 (d, *J*=7.6 Hz, 1 H) 2.57 (s, 2 H)	368.1
285	2.9	100	 4'-Cyano-2-trifluoromethyl-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AD	(400 MHz, $CDCl_3$) δ: 8.37 (d, *J*=1.5 Hz, 1 H) 8.23 (dd, *J*=8.1, 1.8 Hz, 1 H) 7.83 (dd, *J*=8.8, 7.6 Hz, 1 H) 7.73 (d, *J*=8.1 Hz, 2 H) 7.43 - 7.50 (m, 1 H) 7.39 - 7.44 (m, 2 H) 6.86 (d, *J*=7.3 Hz, 1 H) 2.59 (s, 3 H)	418.1
286	NA	100	 4'-Cyano-3-hydroxy-biphenyl-4-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AE	(400 MHz, DMSO-d_6) δ: 7.95 (d, *J*=8.6 Hz, 2 H), 7.80 - 7.90 (m, 3 H), 7.52 - 7.72 (m, 1 H), 7.30 (dd, *J*=8.2, 1.4 Hz, 1 H), 7.22 (d, *J*=1.8 Hz, 1 H), 6.72 (s, 1 H), 2.37 (m, 3 H)	NA
287	NA	67.1	 4-Pyridin-2-yl-N-quinolin-2-yl-benzenesulfonamide	AF	(400 MHz, MeOD) δ ppm 7.38 - 7.44 (m, 1 H) 7.57 (d, *J*=9.35 Hz, 2 H) 7.64 - 7.71 (m, 2 H) 7.78 (d, *J*=8.08 Hz, 1 H) 8.07 - 8.12 (m, 3 H) 8.13 - 8.24 (m, 4 H) 8.73 (d, *J*=4.29 Hz, 1 H)	3626
288	NA	91	 4-(5-Cyano-pyridin-2-yl)-N-quinolin-2-yl-benzenesulfonamide	AF	(400 MHz, $CDCl_3$) δ: 6.89 (d, *J*=9.35 Hz, 1 H) 7.36 - 7.46 (m, 2 H) 7.61 - 7.67 (m, 2 H) 7.88 (t, *J*=8.08 Hz, 2 H) 8.01 - 8.07 (m, 1 H) 8.11 - 8.17 (m, 4 H) 8.95 (s, 1 H)	387.1

Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
289	NA	73.9	 4-(6-Cyano-pyridin-3-yl)-N-quinolin-2-yl-benzenesulfonamide	AF	(400 MHz, $CDCl_3$) δ: 6.94 - 7.00 (m, 1 H) 7.39 - 7.49 (m, 2 H) 7.64 - 7.72 (m, 4 H) 7.79 (d, *J*=8.08 Hz, 1 H) 7.95 (d, *J*=9.35 Hz, 1 H) 8.00 (dd, *J*=8.08, 2.27 Hz, 1 H) 8.16 (d, *J*=8.59 Hz, 2 H) 8.92 (d, *J*=1.77 Hz, 1 H)	387.1
290	NA	100	 6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid quinolin-2-ylamide	AG	(400 MHz, DMSO-d_6) δ: 7.40 (t, *J*=7.58 Hz, 1 H) 7.57 - 7.64 (m, 2 H) 7.70 (t, *J*=7.33 Hz, 1 H) 7.86 (d, *J*=7.83 Hz, 1 H) 7.99 (d, *J*=8.59 Hz, 2 H) 8.24 (d, *J*=8.34 Hz, 1 H) 8.28 - 8.33 (m, 3 H) 8.37 (d, *J*=7.83 Hz, 1 H) 9.16 (s, 1 H)	387.1
291	NA		 6-(4-Fluoro-phenyl)-pyridine-3-sulfonic acid quinolin-2-ylamide	AG	(400 MHz, DMSO-d_6) δ: 7.31 - 7.42 (m, 3 H) 7.56 - 7.62 (m, 2 H) 7.70 (t, *J*=7.33 Hz, 1 H) 7.85 (d, *J*=7.83 Hz, 1 H) 8.07 - 8.13 (m, 1 H) 8.14 - 8.20 (m, 2 H) 8.30 (d, *J*=9.35 Hz, 2 H) 9.10 (s, 1 H)	380.1
292	NA		 6-(4-Fluoro-3-methyl-phenyl)-pyridine-3-sulfonic acid quinolin-2-ylamide	AG	(400 MHz, DMSO-d_6) δ: 2.30 (d, *J*=1.26 Hz, 3 H) 7.26 (t, *J*=9.09 Hz, 1 H) 7.40 (t, *J*=7.45 Hz, 1 H) 7.59 (d, *J*=8.08 Hz, 2 H) 7.69 (t, *J*=7.20 Hz, 1 H) 7.85 (d, *J*=7.58 Hz, 1 H) 7.97 (ddd, *J*=8.21, 5.31, 2.40 Hz, 1 H) 8.05 - 8.13 (m, 2 H) 8.29 (d, *J*=9.35 Hz, 2 H) 9.08 (s, 1 H)	NA
293	NA		 6-(4-Cyano-phenyl)-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide	AH	(400 MHz, $CDCl_3$), δ: 9.19 (d, *J* = 1.5, 1 H), 8.35 (dd, J = 10.8, 2.2 Hz, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 8.6 Hz, 1 H), 7.90 (d, *J* = 8.6 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 8.4, 1 H), 6.82 (d, *J* = 8.5, 1 H), 1.81-1.78 (m, 1 H), 0.93-0.89 (m, 2 H), 0.73-0.70 (m, 1 H)	377.1072
294	NA		 6-(4-Trifluoromethyl-phenyl)-pyridine-3-sulfonic acid (6-cyclopropyl-pyridin-2-yl)-amide	AH	(400 MHz, $CDCl_3$), δ: 9.19 (d, *J* = 1.5, 1 H), 8.35 (dd, J = 10.8, 2.2 Hz, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 8.6 Hz, 1 H), 7.90 (d, *J* = 8.6 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 8.4, 1 H), 6.82 (d, *J* = 8.5, 1 H), 1.95-1.89 (m, 1 H), 0.93-0.89 (m, 2 H), 0.73-0.70 (m, 1 H)	420.0992
295	2.3	100	 5-Cyano-3-methyl-benzo[b]thiophene-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AI	(400 MHz, DMSO-d_6), δ: 13.58 (br s, 1 H), 8.43 (s, 1 H), 8.21 (d, *J* = 8.3 Hz, 1 H), 7.82 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.72 (m, 1 H), 7.16 (m, 1 H), 6.68 (br d, *J* = 7.3 Hz, 1 H), 2.63 (s, 3 H), 2.34 (s, 3 H)	344.0522

Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (m/z)
296	NA	16.0	 Pyrrolidine-2-carboxylic acid [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-amide	AJ	(400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 8.08 Hz, 1 H), 7.57 (s, 1H), 7.51 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.68 (d, *J* = 8.34 Hz, 1H), 3.52 (d, *J* = 6.8 Hz, 1H), 3.28 (m, 4 H), 2.29 (m, 1H), 2.12 (dd, *J*=10.99, 5.68 Hz, 1 H)	394.0
297	NA	3.4	 3-Pyridin-4-yl-pyrrolidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, CD_3CN) δ: 8.35 (br s, 1 H), 8.42 (dd, *J* = 4.6, 1.8 Hz, 2 H), 7.53 (t, *J* = 8.4 Hz, 1 H), 7.15 (d, J = 4.8 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 6.78 (d, *J* = 7.5 Hz, 1 H), 3.90 (dd, *J* = 6.5, 4.6 Hz, 1 H), 3.60-3.57 (m, 1 H), 3.45-3.27 (m, 4 H), 2.28-2.20 (m, 1 H)	319.0
298	NA	13.3	 1,3-Dihydro-isoindole-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 2.43 (3 H, s) 4.76 (4 H, s) 6.65 (1 H, d, *J*=7.3 Hz) 7.05 (1 H, d, *J*=8.6 Hz) 7.19 - 7.23 (2 H, m) 7.25 - 7.29 (2 H, m) 7.52 (1 H, dd, *J*=8.5, 7.4 Hz)	288
299	NA	55.7	 7-Cyano-3,4-dihydro-1H-isoquinoline-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 7.47 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.42 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.33 (s, 1 H), 7.21 (d, *J* = 8.1 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.53 (d, *J* = 7.1 Hz, 1 H), 4.45 (s, 2 H), 3.56 (t, *J* = 5.9 Hz, 2 H), 2.99 (t, *J* = 5.8 Hz, 2 H), 2.39 (s, 3 H)	304.2
300	11	88.3	 3,4-Dihydro-1H-isoquinoline-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 7.50 (dd, *J* = 8.5, 7.4 Hz, 1 H), 7.13–7.16 (m, 2 H), 7.07–7.11 (m, 1 H), 7.01–7.05 (m, 1 H), 6.97 (s, 1 H), 6.62 (d, *J* = 7.3 Hz, 1 H), 4.48 (s, 2 H), 3.57 (t, *J* = 5.9 Hz, 2 H), 2.93 (t, *J* = 5.9 Hz, 2 H), 2.41 (s, 3 H)	329.2
301	4.9	100	 4-(4-Fluoro-phenyl)-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 8.3, 7.6 Hz, 1 H), 7.07 - 7.13 (m, 2 H), 6.97 (td, *J* = 8.8, 2.3 Hz, 3 H), 6.65 (d, *J* = 7.3 Hz, 1 H), 3.91 (dd, *J* = 10.2, 1.9 Hz, 2 H), 2.86 (td, *J* = 12.2, 2.3 Hz, 2 H), 2.51 - 2.59 (m, 1 H), 1.87 (s, 1 H) 2.44 (s, 3 H), 1.84 (d, *J* = 1.5 Hz, 1 H), 1.72 (qd, *J* = 12.7, 3.9 Hz, 2 H)	350.1
302	NA	18.1	 Hexahydro-pyrrolo[1,2-a]pyrazine-2-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, CD_3CN) δ: 8.35 (br s, 1 H), 7.60 (t, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 6.77 (d, J = 7.6 Hz, 1 H), 3.77 (dd, *J* = 10.4, 1.5 Hz, 1 H), 3.77 (dd, *J* = 10.4, 1.5 Hz, 1 H), 3.61 (d, *J* = 4.8 Hz, 4 H), 3.04 (m, 3 H), 2.61 (t, *J* = 10.4 Hz, 1 H), 2.41 (s, 3 H), 2.20-1.97 (m, 3 H), 1.86-1.71 (m, 3 H), 1.41-1.33 (m, 1 H)	297.0
303	7.6	89.3	 3,4-Dihydro-1H-isoquinoline-2-sulfonic acid (6-ethyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ ppm 1.28 (t, *J* = 7.58 Hz, 3 H), 2.70 (q, *J* = 7.58 Hz, 2 H), 2.94 (t, *J* = 5.94 Hz, 2 H), 3.57 (t, *J* = 5.94 Hz, 2 H), 4.48 (s, 2 H), 6.63 (d, *J* = 7.33 Hz, 1 H), 6.96 - 7.00 (m, 1 H), 7.03 (dd, *J* = 5.18, 3.66 Hz, 1 H), 7.07 - 7.11 (m, 1 H), 7.12 - 7.15 (m, 2 H), 7.55 (dd, *J* = 8.46, 7.45 Hz, 1 H)	318.1

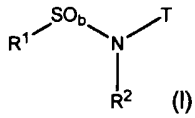
Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
304	20	79.6	 3,4-Dihydro-1H-isoquinoline-2-sulfonic acid (4,6-dimethyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 2.23 (s, 3 H) 2.36 (s, 3 H) 2.92 (t, *J*=5.81 Hz, 2 H) 3.52 (t, *J*=5.94 Hz, 2 H) 4.44 (s, 2 H) 6.34 (s, 1 H) 6.73 (s, 1 H) 7.00 - 7.05 (m, 1 H) 7.07 - 7.11 (m, 1 H) 7.11 - 7.16 (m, 2 H)	318.2
305	NA	1.1	 4-Cyano-4-phenyl-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 10.36 (br s, 1 H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.45–7.28 (m, 5H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.00–3.80 (m, 2 H), 3.30–3.15 (m, 2 H), 2.45 (s, 3 H), 2.20–2.05 (m, 4 H)	357.1379
306	7.4	100	 4-Phenyl-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 9.56 (br s, 1 H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.34–7.24 (m, 2H), 7.24–7.12 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 3.97–3.87 (m, 2 H), 2.93–2.80 (m, 2 H), 2.62–2.50 (m, 1 H), 2.47 (s, 3 H), 1.93–1.83 (m, 2 H), 1.83–1.67 (m, 2 H)	332.1432
307	NA	29.5	 4,4-Diphenyl-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 9.60 (br. s, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.30–7.10 (m, 10 H), 6.99 (d, *J* = 8.0 Hz), 6.63 (d, *J* = 8.0 Hz), 3.40–3.32 (m, 4 H), 2.48–2.41 (m, 4 H), 2.38 (s, 3 H)	408.1739
308	<1	95.7	 4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid quinolin-2-ylamide	AK	(400 MHz, $CDCl_3$) δ: 1.65 - 1.76 (m, 4 H) 2.42 - 2.52 (m, 1 H) 2.64 (td, *J* = 11.56, 3.66 Hz, 2 H) 3.75 (d, *J* = 11.87 Hz, 2 H) 6.68 (d, *J* = 9.35 Hz, 1 H) 7.11 (d, *J* = 8.34 Hz, 2 H) 7.13 - 7.21 (m, 2 H) 7.37 - 7.46 (m, 4 H) 7.67 (d, *J* = 9.60 Hz, 1 H)	393.1
309	7.6	90	 4-(3-Fluoro-phenyl)-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 1.66 - 1.82 (m, 2 H) 1.83 - 1.93 (m, 2 H) 2.45 (s, 3 H) 2.52 - 2.64 (m, 1 H) 2.83 - 2.98 (m, 2 H) 3.88 - 3.97 (m, 2 H) 6.67 (d, *J*=7.07 Hz, 1 H) 6.88 - 7.23 (overlapping m, 5 H), 7.50 - 7.60 (m, 1 H)	350.1
310	18	100	 4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, CD_3CN) δ: 8.91 (br s, 1 H), 8.68 (d, *J* = 8.3 Hz, 2 H), 7.61 (t, *J* = 8.6, 1 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.01 (d, *J* = 8.6 Hz, 1 H), 6.80 (d, *J* = 7.3 Hz, 1 H), 3.87 (dd, *J* = 10.1, 2.1 Hz, 2 H), 2.88 (td, *J* = 12.3, 2.3 Hz, 2 H), 2.42 (s, 3 H), 1.86 (bd, *J* = 12.9 Hz, 2 H), 1.69 (qd, *J* = 12.6, 4 Hz, 2 H)	357.1
311	2.6	100	 4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid (4,6-dimethyl-pyridin-2-yl)-amide	AK	(400 MHz, DMSO-d_6) δ: 7.56 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 6.70 (bs, 1 H), 6.32 (bs, 1 H), 3.51 (d, *J* = 7.6 Hz, 2 H), 2.64-2.42 (m, 3 H), 2.11 (s, 3 H), 2.03 (s, 3 H), 1.61 (d, J = 11.4 Hz, 1 H), 1.49-1.34 (m, 2 H)	371.1

Eg.	Ki app (nM)	% inh @ 0.1 uM	Structure	Mth.	^{1}H NMR	MS (*m/z*)
312	NA	6.9	 3-Methyl-4,5,7,8-tetrahydro-1,2,3a,6-tetraaza-azulene-6-sulfonic acid quinolin-2-ylamide	AK	(400 MHz, $CDCl_3$) δ: 2.42 (s, 3 H) 3.34 (dd, *J*=6.06, 4.04 Hz, 2 H) 3.60 (dt, *J*=5.05, 2.53 Hz, 2 H) 3.72 (dd, *J*=5.94, 2.40 Hz, 2 H) 4.21 (d, *J*=7.07 Hz, 2 H) 6.93 (d, *J*=8.84 Hz, 1 H) 7.32 - 7.41 (m, 2 H) 7.57 - 7.65 (m, 2 H) 7.87 (d, *J*=9.60 Hz, 1 H)	359.1
313	NA	27.2	 3-(4-Fluoro-phenoxy)-azetidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, DMSO-d_6) δ: 7.67 (m, 1 H), 7.04–7.17 (m, 3 H), 6.84 (dd, *J* = 9.1, 4.3 Hz, 2 H), 6.70 (br s, 1 H), 4.89 (m, 1 H), 4.15 (br s, 2 H), 3.82 (br s, 2 H), 2.33 (s, 3 H)	338.0974
314	52	71.8	 4-Phenoxy-piperidine-1-sulfonic acid (6-methyl-pyridin-2-yl)-amide	AK	(400 MHz, $CDCl_3$) δ: 7.61 (dd, *J* = 8.6, 7.6 Hz, 1 H), 7.26 (m, 2 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 6.94 (t, *J* = 7.3 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 2 H), 6.71 (d, *J* = 7.3 Hz, 1 H), 4.45 (m, 1 H), 3.52 (m, 2 H), 3.33 (m, 2 H), 2.48 (s, 3 H), 2.00 (m, 2 H), 1.90 (m, 2 H)	348.1376
315	25	86.1	 4,5,7,8-Tetrahydro-isoxazolo[3,4-d]azepine-6-sulfonic acid quinolin-2-ylamide	AK	(400 MHz, DMSO-d_6) δ: 2.73 - 2.81 (m, 2 H) 3.01 (ddd, *J*=5.37, 2.59, 2.40 Hz, 2 H) 3.46 (s, 2 H) 3.52 (s, 2 H) 7.30 - 7.42 (m, 2 H) 7.57 - 7.67 (m, 2 H) 7.80 (d, *J*=8.08 Hz, 1 H) 8.20 (d, *J*=9.60 Hz, 1 H) 8.60 (s, 1 H)	345.1
316	67	67.4	 3',4',5',6'-Tetrahydro-2'H-[2,4']bipyridinyl-1'-sulfonic acid quinolin-2-ylamide	AK	NA	369.5
317	<1	100	 4-(4-Cyano-phenyl)-piperidine-1-sulfonic acid (6-amino-pyridin-2-yl)-amide	AL	(400 MHz, CD_3OD) δ: 1.67 (qd, *J*=12.59, 3.92 Hz, 2 H) 1.78 - 1.85 (m, 2 H) 2.65 - 2.74 (m, *J*=12.16, 12.16, 3.60, 3.41 Hz, 1 H) 2.91 (td, *J*=12.44, 2.40 Hz, 2 H) 3.85 - 3.93 (m, 2 H) 6.13 (d, *J*=8.08 Hz, 1 H) 6.39 (dd, *J*=8.08, 0.51 Hz, 1 H) 7.35 - 7.40 (m, 3 H) 7.60 - 7.66 (m, 2 H)	356.2

Various embodiments of the present invention have been described above but a person skilled in the art realizes further minor alterations that would fall into the scope of the present invention. The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

We Claim:

1. A compound of formula (I):



(I)

wherein:

R^1 is selected from the group consisting of $(C_1–C_6)$alkyl, $-(CR^3R^4)_t(C_3-C_{12})$cycloalkyl, $-(CR^3R^4)_t(C_6-C_{12})$aryl, and $-(CR^3R^4)_t$(4-10)-membered heterocyclyl;

b and k are each independently selected from 1 and 2;

j is selected from the group consisting of 0, 1, and 2;

t, u, p, q, and v are each independently selected from the group consisting of 0, 1, 2, 3, 4, and 5;

T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom;

R^2 is selected from the group consisting of H, $(C_1–C_6)$alkyl, $-(CR^3R^4)_t(C_3-C_{12})$cycloalkyl, $-(CR^3R^4)_t(C_6-C_{12})$aryl, and $-(CR^3R^4)_t$(4-10)-membered heterocyclyl;

each R^3 and R^4 is independently selected from H and (C_1-C_6)alkyl;

the carbon atoms of T, R^1, R^2, R^3 and R^4 may each be optionally substituted by 1 to 5 R^5 groups;

each R^5 group is independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(C=O)-R^6$, $-(C=O)-O-R^6$, $-O-(C=O)-R^7$, $-O-(C=O)-NR^7$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-S(O)_kNR^8R^9$, $-S(O)_j(C_1-C_6)$alkyl, $-O-SO_2-R^9$, $-NR^8-S(O)_k-R^9$, $-(CR^{10}R^{11})_v(C_6-C_{12}$ aryl), $-(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_q(C=O)(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q(C_6-C_{12})$aryl, $-(CR^{10}R^{11})_vO(CR^{10}R^{11})_q$(4-10)-membered heterocyclyl, $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v(C_6-C_{12})$aryl, and $-(CR^{10}R^{11})_qS(O)_j(CR^{10}R^{11})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl of the foregoing R^6 groups are optionally substituted with an oxo (=O);

any carbon atom of any (C_1-C_6)alkyl, any (C_6-C_{12})aryl, and any (4-10)-membered heterocyclyl of the foregoing R^5 groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$, trifluoromethoxy, azido, $-OR^{12}$, $-(C=O)-R^{12}$, $-(C=O)-O-R^{13}$, $-O-(C=O)-R^{13}$, $-NR^{13}(C=O)-R^{14}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{17}R^{18}$, $-NR^{14}OR^{15}$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(CR^{16}R^{17})_u(C_6-C_{12})$aryl, and $-(CR^{16}R^{17})_u$(4-10)-membered heterocyclyl;

each R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} group is independently selected from the group consisting of H, (C_1-C_6)alkyl, $-(C=O)N(C_1–C_6)$alkyl, $-(CR^{18}R^{19})_p(C_6-C_{12})$aryl, and $-(CR^{18}R^{19})_p$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of each said R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} group is optionally substituted with an oxo (=O);

any carbon atom of any $(C_1$-$C_6)$alkyl, any $(C_6$-$C_{12})$aryl, and any (4-10)-membered heterocyclyl of the foregoing R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-NR^{21}R^{22}$, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, and $(C_1$-$C_6)$ alkoxy;

each R^{18}, R^{19}, R^{20}, R^{21} and R^{22} group is independently selected from H and $(C_1$-$C_6)$alkyl;

and wherein any of the above-mentioned substituents comprising a $-CH_3$ (methyl), $-CH_2$ (methylene), or -CH (methine) group which is not attached to a halo, -SO or $-SO_2$ group or to a N, O or S atom optionally bears on said group a substituent independently selected from the group consisting of hydroxy, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $-NH_2$, $-NH(C_1$-$C_6)$(alkyl) and $-N((C_1$-$C_6)$(alkyl))$_2$;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1, wherein b is 2.

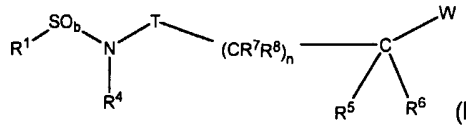
3. The compound according to claim 1, wherein T is a 6-membered heterocyclyl containing at least one nitrogen atom.

4. The compound according to claim 1 wherein each R^1 is selected from the group consisting of phenyl, biphenyl, benzothiophenyl, and napthyl and may optionally be substituted by 1 to 5 R^6 groups;

wherein:

each R^6 group is independently selected from the group consisting of halo, cyano, $-CF_3$, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$–$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $-(CR^{10}R^{11})_p$(4-10)-membered heterocyclyl, $-(C=O)-R^6$, $-(C=O)-O-R^6$, $-O-(C=O)-R^7$, $-NR^8(C=O)-R^9$, $-(C=O)-NR^8R^9$, $-NR^8R^9$, $-NR^8OR^9$, $-(CR^{10}R^{11})-O-(CR^{10}R^{11})_p(C_6$-$C_{12})$aryl, and $-(CR^{10}R^{11})_p-O-(CR^{10}R^{11})_p$(4-10)-membered heterocyclyl.

5. A compound of formula (II):



(II)

wherein:

R^1 is $(C_1$–$C_6)$alkyl, $-(CR^7R^8)_t(C_3$-$C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6$-$C_{10})$aryl, or $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

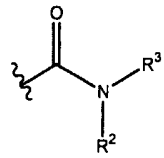
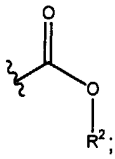
b and k are each independently selected from 1 and 2;

n and j are each independently selected from the group consisting of 0, 1, and 2;

t, u, p, q and v are each independently selected from the group consisting of 0, 1, 2, 3, 4, and 5;

T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom;

W is selected from the group consisting of:

 ;  ; (C_1-C_6) alkyl; and a 5-membered heterocyclyl;

each R^2, R^3, and R^4 are independently selected from the group consisting of H, (C_1-C_6)alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, and $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

each R^2 and R^3 may optionally be taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl;

each R^5 and R^6 are independently selected from the group consisting of H, (C_1-C_6) alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, and $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

or R^5 and R^6 may optionally be taken together with the carbon to which they are attached to form a (C_3-C_6)cycloalkyl or a (3-7)-membered heterocyclyl;

each R^7 and R^8 are independently selected from H and (C_1-C_6)alkyl;

the carbon atoms of T, R^1, R^2, R^3, R^4 , R^5, R^6, R^7, R^8 , and said W 5-membered heterocyclyl are optionally substituted by 1 to 5 R^9 groups;

each R^9 group is independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(C=O)-R^{10}$, $-(C=O)-O-R^{11}$, $-O-(C=O)-R^{11}$, $-NR^{11}(C=O)-R^{12}$, $-(C=O)-NR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}OR^{12}$, $-S(O)_kNR^{11}R^{12}$, $-S(O)_j(C_1-C_6)$alkyl, $-O-SO_2-R^{10}$, $-NR^{11}-S(O)_k-R^{12}$, $-(CR^{13}R^{14})_v(C_6-C_{10}$ aryl), $-(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v(C_6-C_{10})$aryl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_vO(CR^{13}R^{14})_q(C_6-C_{10})$aryl, $-(CR^{13}R^{14})_vO(CR^{13}R^{14})_q$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_qS(O)_j(CR^{13}R^{14})_v(C_6-C_{10})$aryl, and $-(CR^{13}R^{14})_qS(O)_j(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with an oxo (=O);

any carbon atom of any (C_1-C_6)alkyl, any (C_6-C_{10})aryl and any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CFH_2$, $-CF_2H$, trifluoromethoxy, azido, $-OR^{15}$, $-(C=O)-R^{15}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(CR^{17}R^{18})_u(C_6-C_{10})$aryl, and $-(CR^{17}R^{18})_u$(4-10)-membered heterocyclyl;

each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is independently selected from the group consisting of H, (C_1-C_6)alkyl, $-(CR^{19}R^{20})_p(C_6-C_{10})$aryl, and $-(CR^{19}R^{20})_p$(4-10)-membered heterocyclyl;

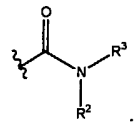
any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of said each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is optionally substituted with an oxo (=O);

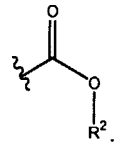
any carbon atom of any $(C_1\text{-}C_6)$alkyl, any $(C_6\text{-}C_{10})$aryl and any (4-10)-membered heterocyclyl of the foregoing R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, nitro, $-NR^{21}R^{22}$, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, and $(C_1\text{-}C_6)$ alkoxy;

each R^{19}, R^{20}, R^{21}, and R^{22} group is independently selected from H and $(C_1\text{-}C_6)$alkyl;

and wherein any of the above-mentioned substituents comprising a $-CH_3$ (methyl), $-CH_2$ (methylene), or -CH (methine) group which is not attached to a halo, -SO or $-SO_2$ group or to a N, O or S atom optionally bears on said group a substituent independently selected from the group consisting of hydroxy, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, amino, $-NH(C_1\text{-}C_6)$(alkyl) and $-N(C_1\text{-}C_6)$(alkyl)$(C_1\text{-}C_6)$ alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

6. The compound according to claim 5, wherein W is  .

7. The compound according to claim 5, wherein W is  .

8. The compound according to claim 5, wherein W is a 5-membered heterocyclyl.

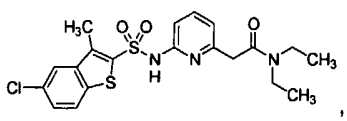
9. The compound according to claim 8, wherein said 5-membered heterocyclyl is selected from the group consisting of oxazolyl, thiazolyl, pyrazolyl, triazolyl, and oxadiazolyl.

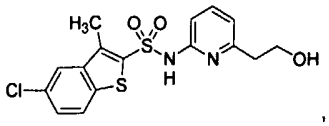
10. The compound according to claim 5, wherein b is 2.

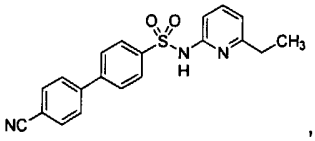
11. The compound according to claim 5, wherein T is a 6-membered heterocyclyl containing at least one nitrogen atom.

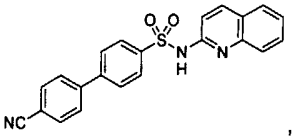
12. The compound according to claim 6, wherein R^2 and R^3 are taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl.

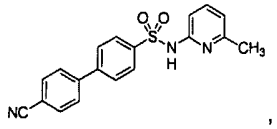
13. A compound selected from the group consisting of:

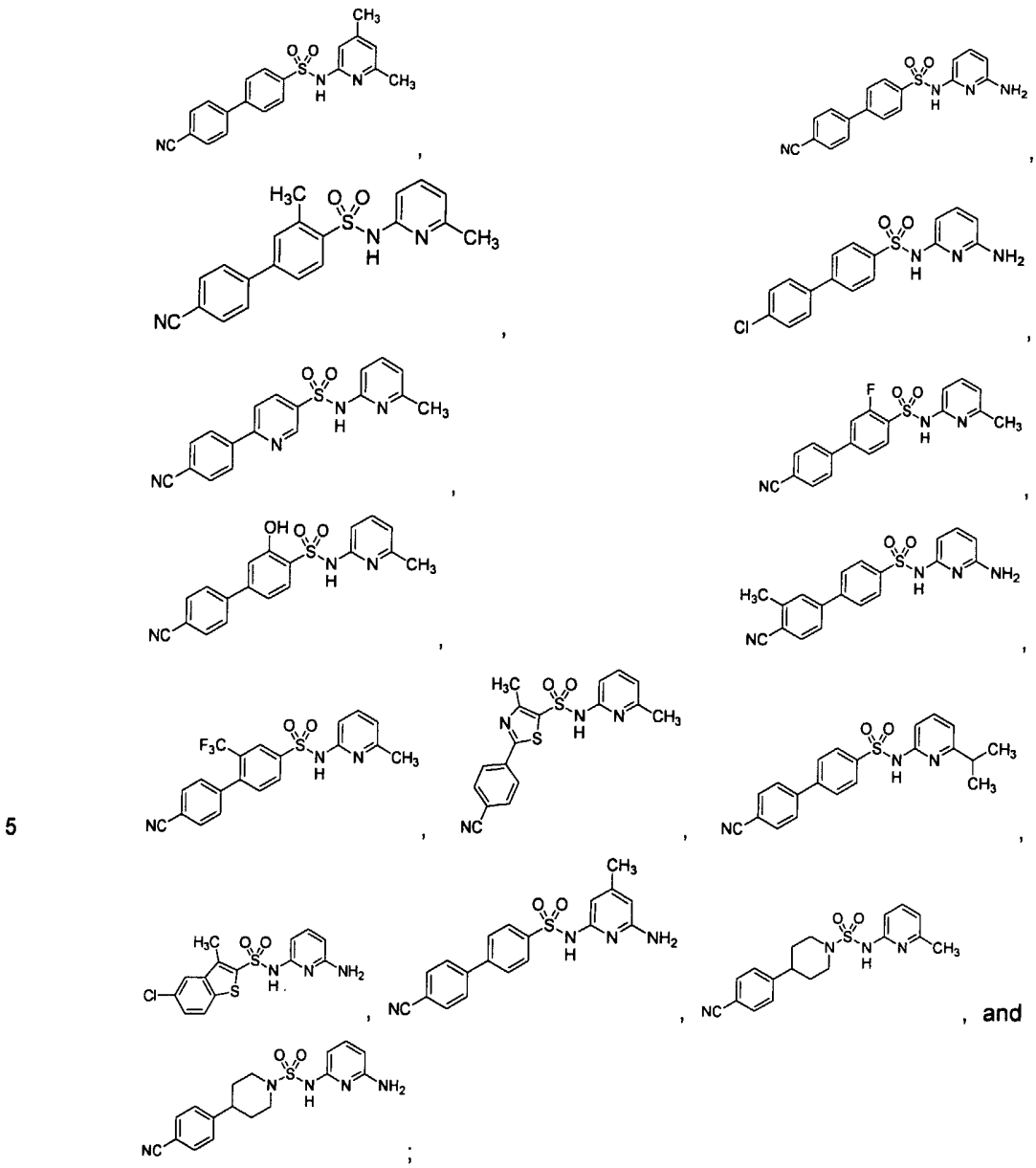
 ,

 ,

 ,

 ,

 ,



or a pharmaceutically acceptable salt or solvate thereof.

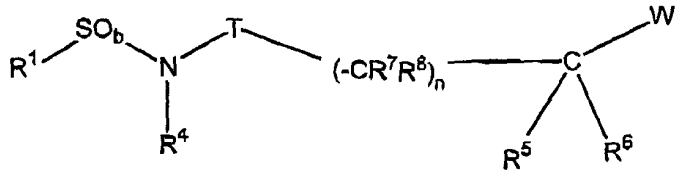
14. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or claim 5, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

15. A method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, virus diseases, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound according to claim 1 or claim 5 or a pharmaceutically acceptable salt or solvate thereof.

AMENDED CLAIMS

[received by the International Bureau on May 13th, 2005 (13.05.05); original claims 1-15 replaced by new claims 1-19]

1. A compound of formula (I):



or a pharmaceutically acceptable salt or solvate thereof, wherein;

R^1 is (C_1-C_6)alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, or $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

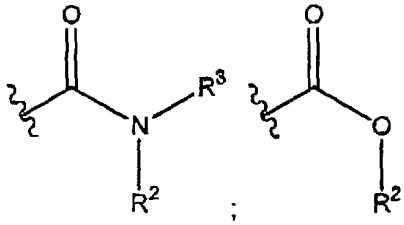
b and k are each independently 1 or 2;

n and j are each independently 0, 1, or 2;

t, u, p, q and v are each independently 0, 1, 2, 3, 4, or 5;

T is a (6-10)-membered heterocyclyl containing at least one nitrogen atom;

W is selected from the group consisting of:



; (C_1-C_6) alkyl; and a 5-membered heterocyclyl;

R^2, R^3, and R^4 are independently H, (C_1-C_6)alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, or $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

R^2 and R^3 may optionally be taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl;

R^5 and R^6 are independently H, (C_1-C_6) alkyl, $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl, $-(CR^7R^8)_t(C_6-C_{10})$aryl, or $-(CR^7R^8)_t$(4-10)-membered heterocyclyl;

or R^5 and R^6 may optionally be taken together with the carbon to which they are attached to form a (C_3-C_6)cycloalkyl or a (3-7)-membered heterocyclyl;

R^7 and R^8 are each independently H and (C_1-C_6)alkyl;

the carbon atoms of T, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and said W 5-membered heterocyclyl are optionally substituted by 1 to 5 R^9 groups;

each R^9 group is independently selected from the group consisting of halo, cyano, nitro, $-CF_3$, $-CHF_2$, $-CH_2F$, trifluoromethoxy, azido, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, $-(C=O)-R^{10}$, $-(C=O)-O-R^{11}$, $-O-(C=O)-R^{11}$, $-NR^{11}(C=O)-R^{12}$, $-(C=O)-NR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}OR^{12}$, $-S(O)_kNR^{11}R^{12}$, $-S(O)_j(C_1-C_6)$alkyl, $-O-SO_2-R^{10}$, $-NR^{11}-S(O)_k-R^{12}$, $-(CR^{13}R^{14})_v(C_6-C_{10}$ aryl), $-(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v(C_6-C_{10})$aryl, $-(CR^{13}R^{14})_q(C=O)(CR^{13}R^{14})_v$(4-10)-membered

heterocyclyl, -$(CR^{13}R^{14})_vO(CR^{13}R^{14})_q(C_6$-$C_{10})$aryl, -$(CR^{13}R^{14})_vO(CR^{13}R^{14})_q$(4-10)-membered heterocyclyl, -$(CR^{13}R^{14})_qS(O)_j$ $(CR^{13}R^{14})_v(C_6$-$C_{10})$aryl, and -$(CR^{13}R^{14})_qS(O)_j$ $(CR^{13}R^{14})_v$(4-10)-membered heterocyclyl;

any 1 or 2 carbon atoms of any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with an oxo (=O);

any carbon atom of a $(C_1$-$C_6)$alkyl, any $(C_6$-$C_{10})$aryl and any (4-10)-membered heterocyclyl of the foregoing R^9 groups are optionally substituted with 1 to 3 substituents independently halo, cyano, nitro, CF_3, CFH_2, CF_2H, trifluoromethoxy, azido, -OR^{15}, -(C=O)-R^{15}, -(C=O)-O-R^{15}, -O-(C=O)-R^{15}, -NR^{15}(C=O)-R^{16}, -(C=O)-$NR^{15}R^{16}$, -$NR^{15}R^{16}$, -$NR^{15}OR^{16}$, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, -$(CR^{17}R^{18})_u(C_6$-$C_{10})$aryl, or -$(CR^{17}R^{18})_u$(4-10)-membered heterocyclyl;

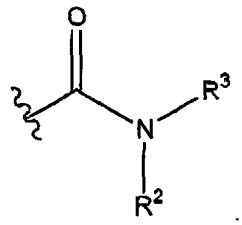
each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is independently H, $(C_1$-$C_6)$alkyl, -$(CR^{19}R^{20})_p(C_6$-$C_{10})$aryl, or -$(CR^{19}R^{20})_p$(4-10)-membered heterocyclyl;

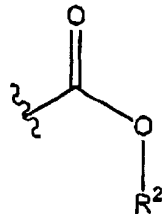
any 1 or 2 carbon atoms of the (4-10)-membered heterocyclyl of said each R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} group is optionally substituted with an oxo (=O);

any carbon atoms of the $(C_1$-$C_6)$alkyl, the $(C_6$-$C_{10})$aryl and the (4-10)-membered heterocyclyl of the foregoing R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, -$NR^{21}R^{22}$, -CF_3, -CHF_2, -CH_2F, trifluoromethoxy, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy, or $(C_1$-$C_6)$ alkoxy;

each R^{19}, R^{20}, R^{21}, and R^{22} group is independently selected from H and $(C_1$-$C_6)$alkyl;

and wherein any of the above-mentioned substituents comprising a -CH_3 (methyl), -CH_2 (methylene), or -CH (methine) group which is not attached to a halo, -SO or -SO_2 group or to a N, O or S atom optionally bears on said group a substituent independently hydroxy, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, amino, -$NH(C_1$-$C_6)$(alkyl) or -$N(C_1$-$C_6)$ (alkyl)$(C_1$-$C_6)$ alkyl.

2. The compound according to claim 1, wherein W is  .

3. The compound according to claim 1, wherein W is  .

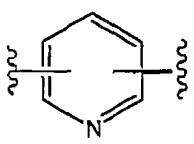
4. The compound according to claim 1, wherein W is a 5-membered heterocyclyl.

5. The compound according to claim 4, wherein said 5-membered heterocyclyl is selected from the group consisting of oxazolyl, thiazolyl, pyrazolyl, triazolyl, and oxadiazolyl.

6. The compound according to claim 1, wherein b is 2.

7. The compound according to claim 1, wherein T is a 6-membered heterocyclyl containing at least one nitrogen atom.

8. The compound according to claim 7, wherein said 6-membered heterocyclyl is selected from the group consisting of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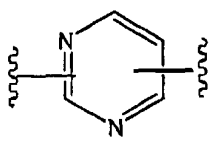
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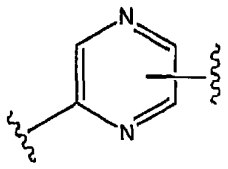
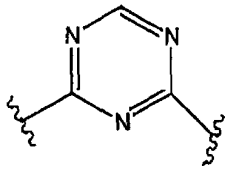
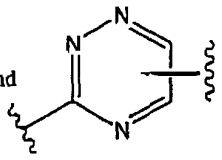

;


; and

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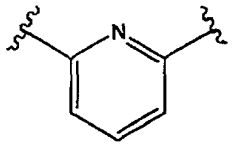
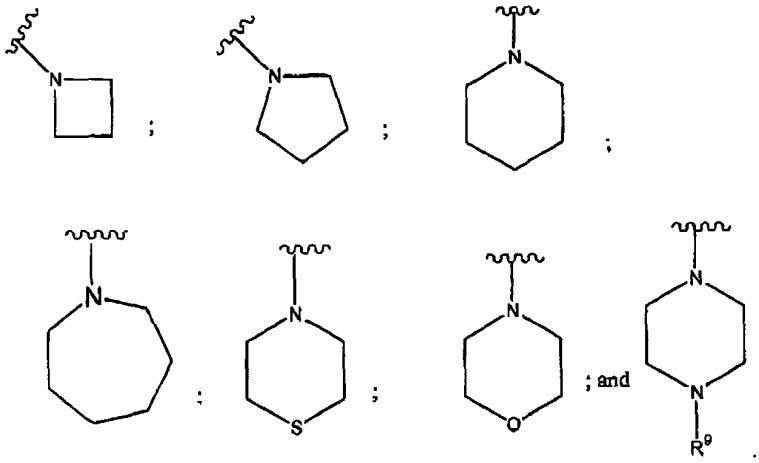
9. The compound according to claim 1 wherein T is

.

10. The compound according to claim 1 wherein R^1 is a phenyl or napthyl substituted by 1 to 5 R^9 groups; wherein each R^9 is independently selected from the group consisting of halo, cyano, $-CF_3$, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, $-(C=O)-R^{10}$, $-(C=O)-O-R^{11}$, $-O-(C=O)-R^{11}$, $-NR^{11}(C=O)-R^{12}$, $-(C=O)-NR^{11}R^{12}$, $-NR^{11}R^{12}$, and $-NR^{11}OR^{12}$.

11. The compound according to claim 2, wherein R^2 and R^3 are each independently H, (C_1-C_6)alkyl, wherein said (C_1-C_6) alkyl is optionally substituted by (C_2-C_6) alkenyl, or $-(CR^7R^8)_t(C_3-C_{10})$cycloalkyl.

12. The compound according to claim 2, wherein R^2 and R^3 are taken together with the nitrogen to which they are attached to form a (4-10)-membered heterocyclyl.

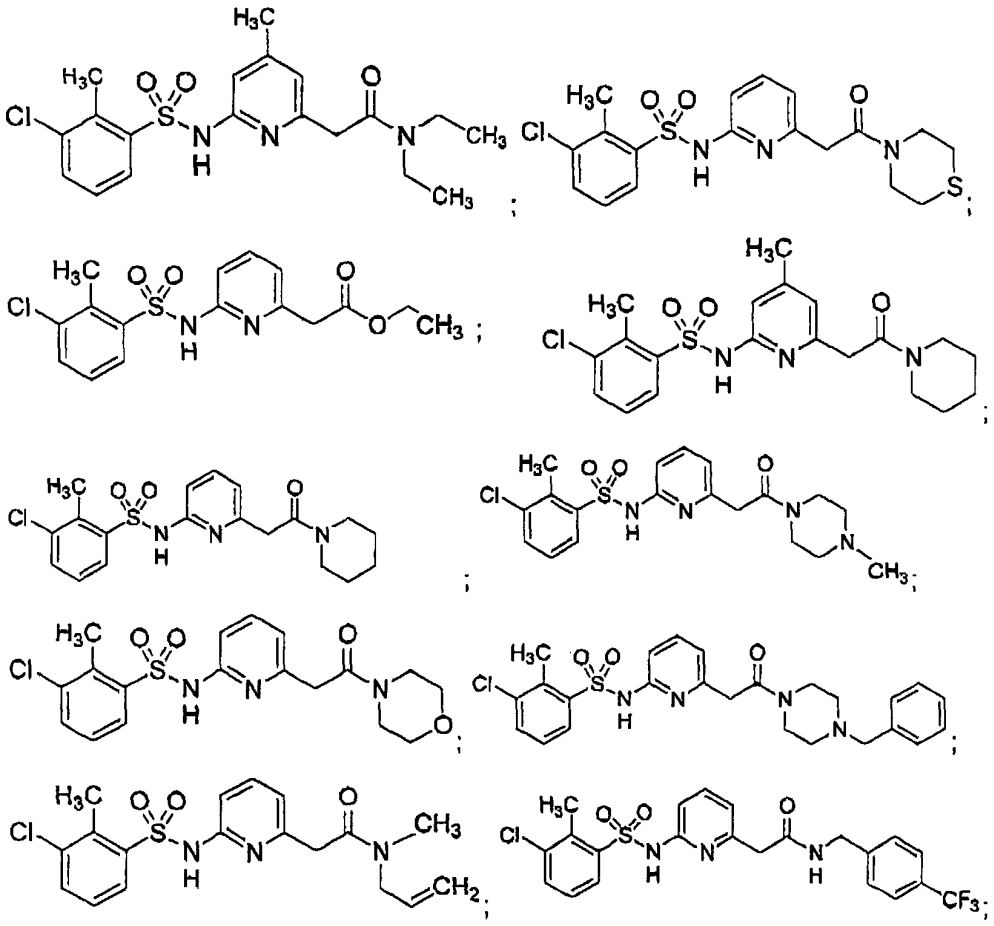
13. The compound according to claim 12, wherein said (4-10)-membered heterocyclyl is selected from the group consisting of:

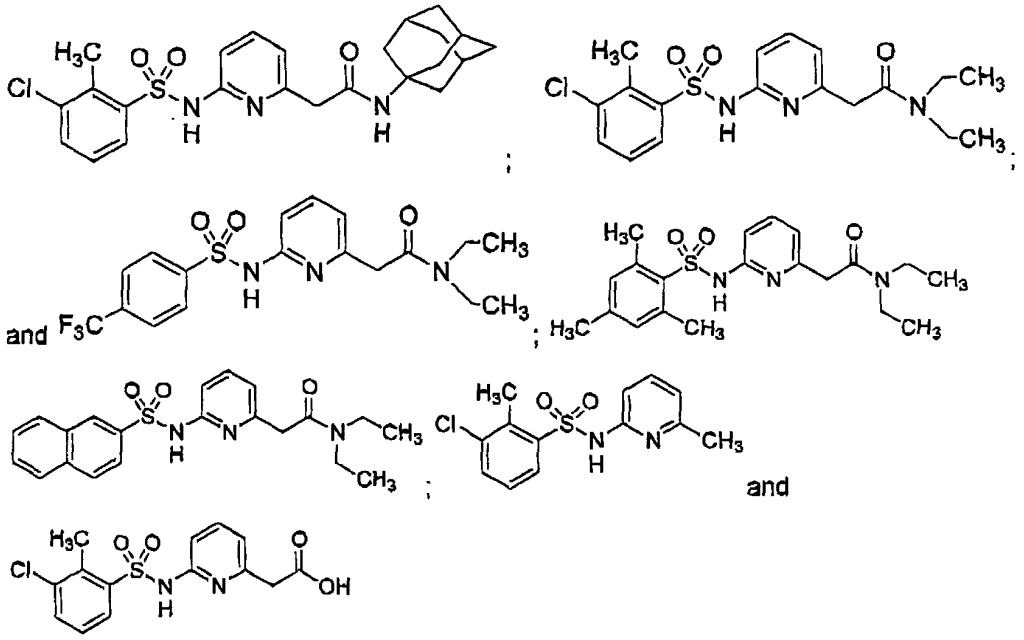


14. The compound according to claim 3, wherein R^2 is $(C_1–C_6)$alkyl.

15. The compound according to claim 1, wherein n is 0 and at least one of R^5 and R^6 is H.

16. A compound selected from the group consisting of:





or a pharmaceutically acceptable salt or solvate thereof.

17. A pharmaceutical composition comprising an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

18. A method of treating a condition that is mediated by the modulation of 11-β-hsd-1, the method comprising administering to a mammal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof.

19. A method of treating diabetes, metabolic syndrome, insulin resistance syndrome, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, atherosclerosis, dementia, depression, virus diseases, inflammatory disorders, or diseases in which the liver is a target organ, the method comprising administering to a mammal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Inte ial Application No
PCT/IB2004/004056

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/4436 C07D213/76 C07D409/12 C07D401/12
C07D417/12 C07C311/37 C07C311/36 A61P3/10 A61P3/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D C07C A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/099773 A (MILLENNIUM PHARMACEUTICALS) 4 December 2003 (2003-12-04) the whole document	1-15
X	WO 01/17955 A (ASTRAZENECA) 15 March 2001 (2001-03-15) the whole document	1-15
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2005	14/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, J

INTERNATIONAL SEARCH REPORT

Inter al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 93/10094 A (KABI PHARMACIA AB) 27 May 1993 (1993-05-27) the whole document	1-15
X	WO 03/043999 A (BIOVITRUM AB) 30 May 2003 (2003-05-30) the whole document	1-15
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P,X	WO 2004/056744 A (JANSSEN PHARMACEUTICA NV) 8 July 2004 (2004-07-08) the whole document	1-15

INTERNATIONAL SEARCH REPORT

Ir ional application No.
PCT/IB2004/004056

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

rmation on patent family members

Inter l Application No
PCT/IB2004/004056

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PCT/IB2004/004056

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