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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2015 (08.01.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/002915 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 9/00* (2006.01)
C07D 498/04 (2006.01) *A61P 11/00* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number: PCT/US2014/044988

(22) International Filing Date: 1 July 2014 (01.07.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/842,098 2 July 2013 (02.07.2013) US

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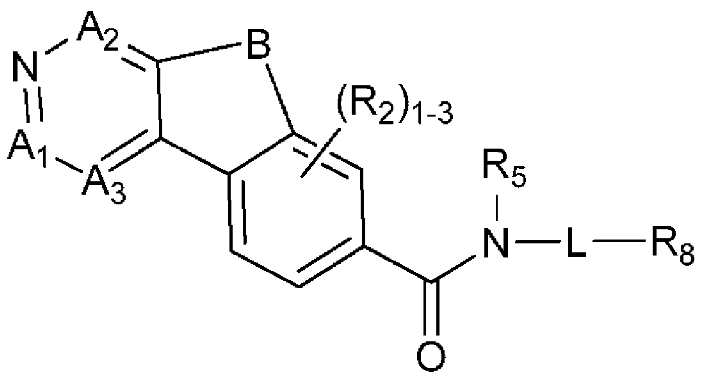
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: TRICYCLIC PYRI DO-CARBOXAM I D E DERIVATIVES AS ROCK INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of Formula (I): or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein all the variables are as defined herein. These compounds are selective ROCK inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds and methods of treating cardiovascular, smooth muscle, oncologic, neuropathologic, autoimmune, fibrotic, and/or inflammatory disorders using the same.

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TRICYCLIC PYRIDO-CARBOXAMID E DERIVATIVES AS ROCK INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. §119(e) to U.S. provisional patent application No. 61/842,098, filed on July 2, 2013, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel tricyclic carboxamide derivatives, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of disorders associated with aberrant Rho kinase activity.

BACKGROUND OF THE INVENTION

Rho-Kinase (ROCK) is a member of the serine-threonine protein kinase family. ROCK exists in two isoforms, ROCK1 and ROCK2 (Ishizaki, T. et al., *EMBO J.*, 15:1885-1893 (1996)). ROCK has been identified as an effector molecule of RhoA, a small GTP-binding protein (G protein) that plays a key role in multiple cellular signaling pathways. ROCK and RhoA are ubiquitously expressed across tissues. The RhoA/ROCK signaling pathway is involved in a number of cellular functions, such as actin organization, cell adhesion, cell migration, and cytokinesis (Riento, K. et al., *Nat. Rev. Mol. Cell Biol.*, 4:446-456 (2003)). It is also directly involved in regulating smooth muscle contraction (Somlyo, A.P., *Nature*, 389:908-911 (1997)). Upon activation of its receptor, RhoA is activated, and, in turn, it activates ROCK. Activated ROCK phosphorylates the myosin-binding subunit of myosin light chain phosphatase, which inhibits activity of the phosphatase and leads to contraction. Contraction of the smooth muscle in the vasculature increases blood pressure, leading to hypertension.

There is considerable evidence in the literature that the RhoA/ROCK signaling pathway plays an important role in signal transduction initiated by several vasoactive factors, for example angiotensin II (Yamakawa, T. et al., *Hypertension*, 35:313-318 (2000)), urotension II (Sauzeau, V. et al., *Circ. Res.*, 88:1102-1104 (2001)), endothelin-1 (Tangkijvanich, P. et al., *Hepatology*, 33:74-80 (2001)), serotonin (Shimokawa, H., *Jpn. Circ. J.*, 64:1-12 (2000)), norepinephrine (Martinez, M.C. et al., *Am. J. Physiol.*, 279:H1228-H1238 (2000)) and platelet-derived growth factor (PDGF) (Kishi, H. et al., *J. Biochem.*, 128:719-722 (2000)). Many of these factors are implicated in the pathogenesis of cardiovascular disease.

Additional studies in the literature, some using the known ROCK inhibitors fasudil (Asano, T. et al., *J. Pharmacol. Exp. Ther.*, 241:1033-1040 (1987)) or Y-27632 (Uehata, M. et al., *Nature*, 389:990-994 (1997)) further illustrate the link between ROCK and cardiovascular disease. For example, ROCK expression and activity have been shown to be elevated in spontaneously hypertensive rats, suggesting a link to the development of hypertension in these animals (Mukai, Y. et al., *FASEB J.*, 15:1062-1064 (2001)). The ROCK inhibitor Y-27632 (Uehata, M. et al., *Nature*, *ibid.*) was shown to significantly decrease blood pressure in three rat models of hypertension, including the spontaneously hypertensive rat, renal hypertensive rat and deoxycortisone acetate salt hypertensive rat models, while having only a minor effect on blood pressure in control rats. This reinforces the link between ROCK and hypertension.

Other studies suggest a link between ROCK and atherosclerosis. For example, gene transfer of a dominant negative form of ROCK suppressed neointimal formation following balloon injury in porcine femoral arteries (Eto, Y. et al., *Am. J. Physiol. Heart Circ. Physiol.*, 278:H1744-H1750 (2000)). In a similar model, ROCK inhibitor Y-27632 also inhibited neointimal formation in rats (Sawada, N. et al., *Circulation*, 101:2030-2033 (2000)). In a porcine model of IL-1 beta-induced coronary stenosis, long term treatment with the ROCK inhibitor fasudil was shown to progressively reduce coronary stenosis, as well as promote a regression of coronary constrictive remodeling (Shimokawa, H. et al., *Cardiovasc. Res.*, 51:169-177 (2001)).

Additional investigations suggest that a ROCK inhibitor would be useful in treating other cardiovascular diseases. For example, in a rat stroke model, fasudil was shown to reduce both the infarct size and neurologic deficit (Toshima, Y., *Stroke*, 31:2245-2250 (2000)). The ROCK inhibitor Y-27632 was shown to improve ventricular hypertrophy, fibrosis and function in a model of congestive heart failure in Dahl salt-sensitive rats (Kobayashi, N. et al., *Cardiovasc. Res.*, 55:757-767 (2002)).

Other animal or clinical studies have implicated ROCK in additional diseases including coronary vasospasm (Shimokawa, H. et al., *Cardiovasc. Res.*, 43:1029-1039 (1999)), cerebral vasospasm (Sato, M. et al., *Circ. Res.*, 87:195-200 (2000)), ischemia/reperfusion injury (Yada, T. et al., *J. Am. Coll. Cardiol.*, 45:599-607 (2005)), pulmonary hypertension (Fukumoto, Y. et al., *Heart*, 91:391-392 (2005)), angina (Shimokawa, H. et al., *J. Cardiovasc. Pharmacol.*, 39:319-327 (2002)), renal disease (Satoh, S. et al., *Eur. J. Pharmacol.*, 455:169-174 (2002)) and erectile dysfunction (Gonzalez-Cadavid, N.F. et al., *Endocrine*, 23:167-176 (2004)).

In another study, it has been demonstrated that inhibition of the RhoA/ROCK signaling pathway allows formation of multiple competing lamellipodia that disrupt the productive migration of monocytes (Worthylake, R.A. et al., *J. Biol. Chem.*, 278:13578-13584 (2003)). It has also been reported that small molecule inhibitors of Rho Kinase are capable of inhibiting MCP-1 mediated chemotaxis *in vitro* (Iijima, H., *Bioorg. Med. Chem.*, 15:1022-1033 (2007)). Due to the dependence of immune cell migration upon the RhoA/ROCK signaling pathway one would anticipate inhibition of Rho Kinase should also provide benefit for diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

The above studies provide evidence for a link between ROCK and cardiovascular diseases including hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, pulmonary hypertension and angina, as well as renal disease and erectile dysfunction. Given the demonstrated effect of ROCK on smooth muscle, ROCK inhibitors may also be useful in other diseases involving smooth muscle hyper-reactivity, including asthma and glaucoma (Shimokawa, H. et al., *Arterioscler. Thromb. Vasc. Biol.*, 25:1767-1775 (2005)). Furthermore, Rho-kinase has been indicated as a drug target for the treatment of various other diseases, including airway inflammation and hyperresponsiveness (Henry, P.J. et al., *Pulm. Pharmacol. Ther.*, 18:67-74 (2005)), cancer (Rattan, R. et al., *J. Neurosci. Res.*, 83:243-255 (2006); Lepley, D. et al., *Cancer Res.*, 65:3788-3795 (2005)), fibrotic diseases (Jiang, C. et al., *Int. J. Mol. Sci.*, 13:8293-8307 (2012); Zhou, L. et al., *Am. J. Nephrol.*, 34:468-475 (2011)), as well as neurological disorders, such as spinal-cord injury, Alzheimer disease, multiple sclerosis, stroke and neuropathic pain (Mueller, B.K. et al., *Nat. Rev. Drug Disc.*, 4:387-398 (2005); Sun, X. et al., *J. Neuroimmunol.*, 180:126-134 (2006)).

There remains an unmet medical need for new drugs to treat cardiovascular disease. In the 2012 update of Heart Disease and Stroke Statistics from the American Heart Association (*Circulation*, 125:e2-e220 (2012)), it was reported that cardiovascular disease accounted for 32.8% of all deaths in the US, with coronary heart disease accounting for ~1 in 6 deaths overall in the US. Contributing to these numbers, it was found that ~33.5% of the adult US population was hypertensive, and it was estimated that in 2010 ~6.6 million US adults would have heart failure. Therefore, despite the number of medications available to treat cardiovascular diseases (CVD), including diuretics, beta blockers, angiotensin converting enzyme inhibitors, angiotensin blockers and calcium channel blockers, CVD remains poorly controlled or resistant to current medication for many patients.

Although there are many reports of ROCK inhibitors under investigation (see, for example, U.S. Publication No. 2008/0275062 A1), fasudil is the only marketed ROCK inhibitor at this time. An i.v. formulation was approved in Japan for treatment of cerebral vasospasm. There remains a need for new therapeutics, including ROCK inhibitors, for the treatment of cardiovascular diseases, cancer, neurological diseases, renal diseases, fibrotic diseases, bronchial asthma, erectile dysfunction, and glaucoma.

SUMMARY OF THE INVENTION

The present invention provides novel tricyclic carboxamide derivatives including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, which are useful as selective inhibitors of Rho kinases.

The present invention also provides processes and intermediates for making the compounds of the present invention.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of conditions associated with aberrant ROCK activity.

The compounds of the present invention may be used in therapy.

The compounds of the present invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of a condition associated with aberrant ROCK activity.

In another aspect, the present invention is directed to a method of treating a cardiovascular or related disease which method comprises administering to a patient in need of such treatment a compound of the present invention as described above. Examples of such diseases that may be treated include, for example, hypertension, atherosclerosis, restenosis, stroke, heart failure, renal failure, coronary artery disease, peripheral artery disease, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, pulmonary hypertension, angina, erectile dysfunction and renal disease.

In another aspect, the present invention is directed to a method of treating diseases involving smooth muscle hyper reactivity including asthma, erectile dysfunction and glaucoma, which method comprises administering to a patient in need of such treatment a compound of the present invention as described above.

In another aspect, the present invention is directed to a method of treating diseases mediated at least partially by Rho kinase including fibrotic diseases, oncology, spinal-cord injury, Alzheimer's disease, multiple sclerosis, stroke, neuropathic pain, rheumatoid arthritis, psoriasis and inflammatory bowel disease, which method comprises administering to a patient in need of such treatment a compound of the present invention as described above.

In yet additional aspects, the present invention is directed at pharmaceutical compositions comprising the above-mentioned compounds, processes for preparing the above-mentioned compounds and intermediates used in these processes.

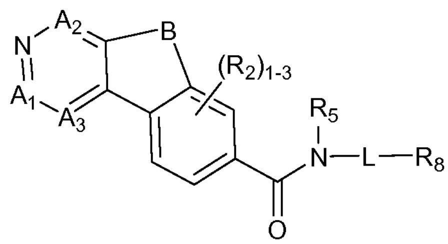
The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s).

These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

In one aspect, the present invention provides, *inter alia*, compounds of Formula (I):



(I)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

A_1, A_2, and A_3 are independently selected from N and CR_1; provided no more than one A_1, A_2, and A_3 is N;

B is independently selected from $-(CR_3R_4)_mCR_3R_4-$, $-(CR_3R_4)_mO(CR_3R_4)_n-$, $-(CR_3R_4)_mNR_a(CR_3R_4)_n-$, $-(CR_3R_4)_mS(O)_p(CR_3R_4)_n-$, $-(CR_3R_4)_mC(O)(CR_3R_4)_n-$, $-(CR_3R_4)_mC(O)O(CR_3R_4)_n-$, $-(CR_3R_4)_mC(O)NR_a(CR_3R_4)_n-$, $-(CR_3R_4)_mOC(O)(CR_3R_4)_n-$, $-(CR_3R_4)_mNR_aC(O)(CR_3R_4)_n-$, $-(CR_3R_4)_mNR_aS(O)_p(CR_3R_4)_n-$, and $-(CR_3R_4)_mS(O)_pNR_a(CR_3R_4)_n-$;

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5(CR_6R_7)_q-$, $-(CR_6R_7)_sO(CR_6R_7)_q-$, and $-(CR_6R_7)_sC(O)(CR_6R_7)_q-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_3 and R_4 are independently selected from H, F, OH, CN, NR_aR_a, C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$,

$-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from C_{3-10} carbocyclyl and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl

substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

m and n, at each occurrence, are independently selected from zero, 1, and 2; provided $m + n \leq 2$;

p, at each occurrence, is independently selected from zero, 1, and 2;

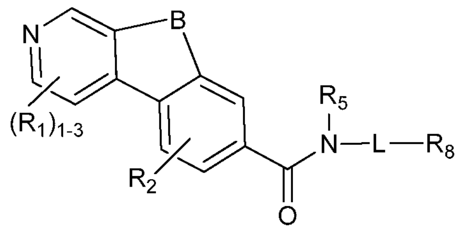
q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4;

s, at each occurrence, is independently selected from 1, and 2; provided when s and q are in the same term, $s + q \leq 3$;

provided when A_1 is CR_1, A_3 is N, and B is $-CH_2C(O)NH-$, R_1 is not -NH-substituted phenyl.

In another aspect, the present invention provides compounds of Formula (II):



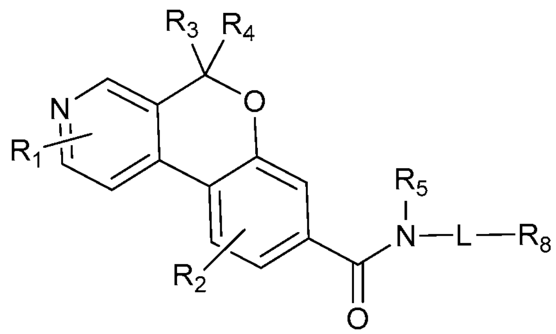
(II)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

B is independently selected from $-(CR_3R_4)_mO(CR_3R_4)_n-$, $-(CR_3R_4)_mNRa(CR_3R_4)_n-$, $-(CR_3R_4)_mS(O)_p(CR_3R_4)_n-$, $-(CR_3R_4)_mC(O)O(CR_3R_4)_n-$, $-(CR_3R_4)_mC(O)NRa(CR_3R_4)_n-$, $-(CR_3R_4)_mOC(O)(CR_3R_4)_n-$, and $-(CR_3R_4)_mNRaC(O)(CR_3R_4)_n-$;

other variables are as defined in Formula (I) above.

In another aspect, the present invention provides compounds of Formula (III):



(III)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q-$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

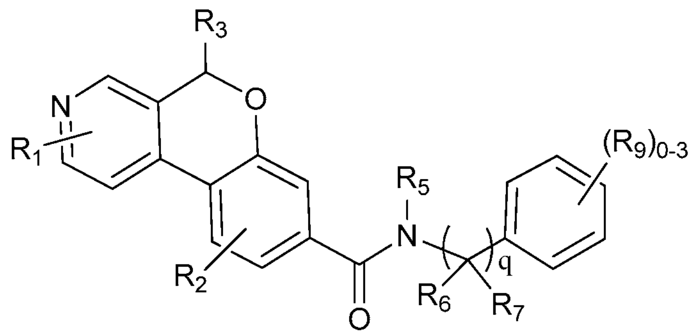
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

In another aspect, the present invention provides compounds of Formula (IV):



(IV)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 and R_2 are independently selected from H, F, Cl, Br, OH, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, and C_{1-4} alkyl substituted with 0-3 R_e;

R_3 is independently selected from H and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, -OR_b, -$S(O)_pR_c$, -$C(=O)R_b$, -NR_aR_a, -$C(=O)NR_aR_a$, -$C(=O)(CH_2)_rNR_aR_a$, CN, -$NR_aC(=O)R_b$, -$NR_aC(=O)OR_b$, -$OC(=O)NR_aR_a$, -$NR_aC(=O)NR_aR_a$, -$C(=O)OR_b$, -$S(O)_pNR_aR_a$, -$NR_aS(O)_pNR_aR_a$, and -$NR_aS(O)_pR_c$, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, -$(CH_2)_rOR_b$, -$(CH_2)_rS(O)_pR_c$, -$(CH_2)_rC(=O)R_b$, -$(CH_2)_rNR_aR_a$, -$(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, -$(CH_2)_rNR_aC(=O)R_b$, -$(CH_2)_rNR_aC(=O)OR_b$, -$(CH_2)_rOC(=O)NR_aR_a$, -$(CH_2)_rNR_aC(=O)NR_aR_a$, -$(CH_2)_rC(=O)OR_b$, -$(CH_2)_rS(O)_pNR_aR_a$, -$(CH_2)_rNR_aS(O)_pNR_aR_a$, -$(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (IV), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 and R_2 are H;

R_3 is independently selected from H and Me;

R_5 is H;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4;

other variables are as defined in Formula (IV) above.

In another aspect, the present invention provides compounds of Formula (IV), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-4 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

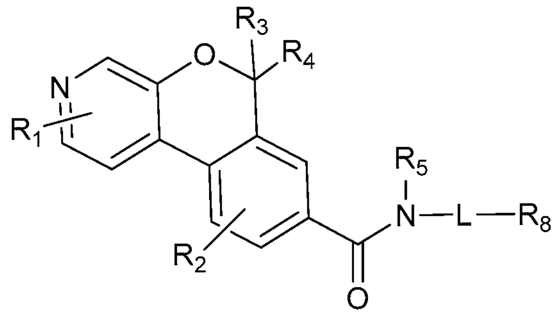
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4;

other variables are as defined in Formula (IV) above.

In another aspect, the present invention provides compounds of Formula (V):



(V)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

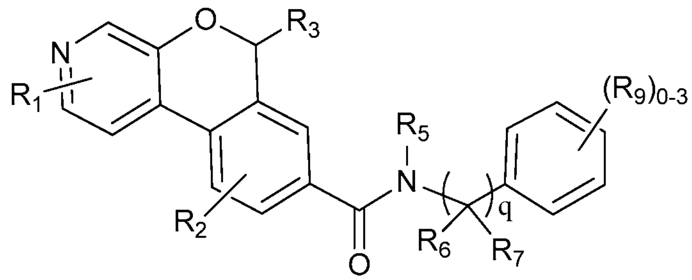
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

In another aspect, the present invention provides compounds of Formula (VI):



(VI)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 and R_2 are independently selected from H, F, Cl, Br, OH, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, and C_{1-4} alkyl substituted with 0-3 R_e;

R_3 is independently selected from H and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$,

$(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl,

$-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

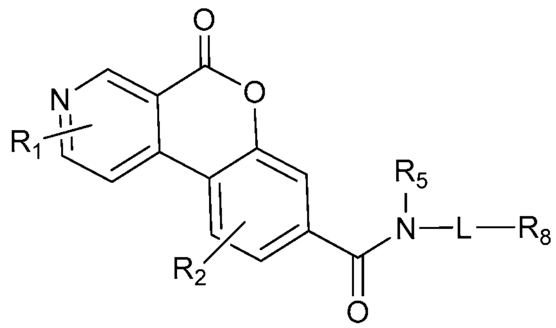
R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (VII):



(VII)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5$-, $-(CR_6R_7)_sO$-, and $-(CR_6R_7)_sC(O)$-;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$,

$-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

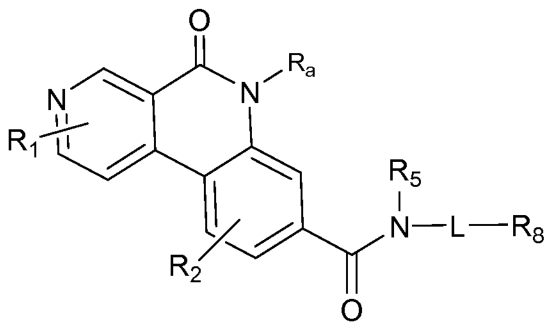
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

In another aspect, the present invention provides compounds of Formula (VIII):



(VIII)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$,

$-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e,

$-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

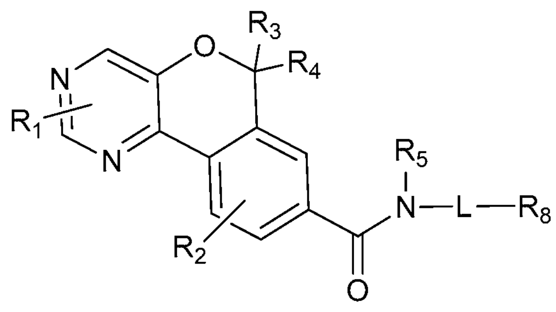
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

In another aspect, the present invention provides compounds of Formula (IX):



(IX)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and -$(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, -OR_b, -$S(O)_pR_c$, -$C(=O)R_b$, -NR_aR_a, -$C(=O)NR_aR_a$, -$C(=O)(CH_2)_rNR_aR_a$, CN, -$NR_aC(=O)R_b$, -$NR_aC(=O)OR_b$, -$OC(=O)NR_aR_a$, -$NR_aC(=O)NR_aR_a$, -$C(=O)OR_b$, -$S(O)_pNR_aR_a$, -$NR_aS(O)_pNR_aR_a$, -$NR_aS(O)_pR_c$, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, -$(CH_2)_rOR_b$, -$(CH_2)_rS(O)_pR_c$, -$(CH_2)_rC(=O)R_b$, -$(CH_2)_rNR_aR_a$, -$(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, -$(CH_2)_rNR_aC(=O)R_b$, -$(CH_2)_rNR_aC(=O)OR_b$, -$(CH_2)_rOC(=O)NR_aR_a$, -$(CH_2)_rNR_aC(=O)NR_aR_a$, -$(CH_2)_rC(=O)OR_b$, -$(CH_2)_rS(O)_pNR_aR_a$, -$(CH_2)_rNR_aS(O)_pNR_aR_a$, -$(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

In another aspect, the present invention provides compounds of Formula (IX), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is $-(CR_6R_7)_q$;

R_1 and R_2 are H;

R_3 and R_4 are independently selected from H, F, and C_{1-4}alkyl substituted with 0-3 R_e;

R_5 is H;

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-3 R_e;

R_8 is selected from aryl and heterocyclyl, each substituted with 0-5 R_9; and

R_9 is independently selected from F, Cl, Br, CN, C_{1-4}alkyl, OH, OC_{1-4} alkyl, $-C(=O)OC_{1-4}$ alkyl, $-C(=O)NH_2$, $-C(=O)NHC_{1-4}$ alkyl, $-C(=O)NHC_{3-6}$ cycloalkyl, C_{3-6}cycloalkyl, heterocyclyl, aryl, and heteroaryl;

other variables are as defined in Formula (IX) above.

In another aspect, the present invention provides compounds of Formula (I), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

A_1 and A_2 are CR_1;

A_3 is independently selected from N and CR_1;

B is independently selected from -O-, $-CR_3R_4O-$, $-OCR_3R_4-$, $-NR_a-$, -C(O)O-, -OC(O)-, $-C(O)NR_a-$, $-NR_aC(O)-$, and -S-;

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5(CR_6R_7)_q-$, $-(CR_6R_7)_sO(CR_6R_7)_q-$, and $-(CR_6R_7)_sC(O)(CR_6R_7)_q-$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, NR_aR_a, C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$,

$-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from C_{3-10} carbocyclyl and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e,

$-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4;

s, at each occurrence, is independently selected from 1, and 2; provided when s and q are in the same term, $s + q \leq 3$.

In another aspect, the present invention provides compounds of Formula (II), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

B is independently selected from -O- and $-NR_a-$;

L is $-(CR_6R_7)_q$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and -$(CH_2)_rOR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and -$(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, and -$(CH_2)_rC(=O)OR_b$;

R_8 is selected from phenyl, C_{3-6} cycloalkyl and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, C_{1-4}alkyl substituted with 0-5 R_e, -$NR_aS(O)_pC_{1-4}$ alkyl, -OR_b, and -CN;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H and C_{1-6} alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), F, Cl, Br, CN, NO_2, -$(CH_2)_rOC_{1-5}$ alkyl, and -$(CH_2)_rOH$;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (III), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from -$(CR_6R_7)_q$-, -$(CR_6R_7)_sNR_5$-, -$(CR_6R_7)_sO$-, and -$(CR_6R_7)_sC(O)$-;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, -$(CH_2)_rOR_b$, -$NR_aC(=O)R_b$, and -$NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and -$(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

In another aspect, the present invention provides compounds of Formula (IV), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NR_aC(=O)R_b$, and $-NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, and NR_aR_a;

R_3 is independently selected from H and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (IV), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 and R_2 are H;

R_3 is independently selected from H and Me;

R_5 is H;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e,

$-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

other variables are as defined in Formula (IV) above.

In another aspect, the present invention provides compounds of Formula (IV), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-4 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

other variables are as defined in Formula (IV) above.

In another aspect, the present invention provides compounds of Formula (V), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NR_aC(=O)R_b$, and $-NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, Cl, Br, OH, CN, C_{1-4} alkyl substituted with 0-3 R_e, and C_{3-6} carbocyclyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro,

$-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

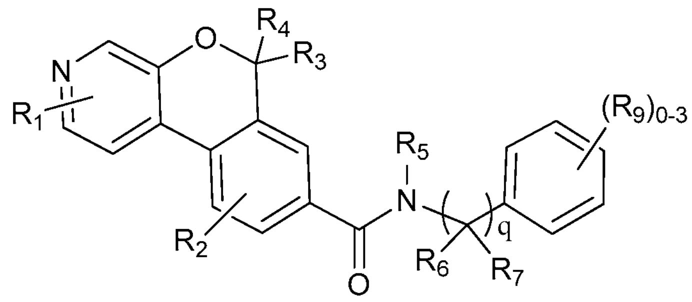
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

In another aspect, the present invention provides compounds of Formula (VIa):



(VIa)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NHC(=O)R_b$, and $-NHC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, OH, CN, and NR_aR_a;

R_3 and R_4 are independently selected from H, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl,

-$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

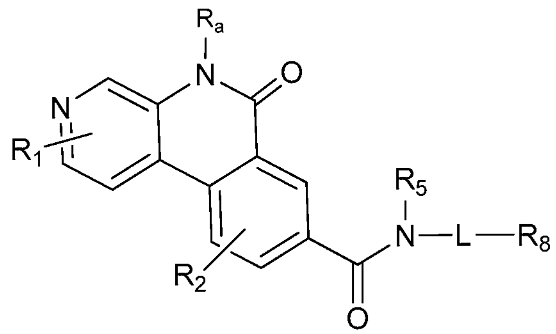
R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides compounds of Formula (X):



(X)

or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is -$(CR_6R_7)_q$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, -OC_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and -$(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl;

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-4 R_e;

R_8 is aryl substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl,

$-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In another aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another aspect, the present invention provides a compound selected from any subset list of compounds within the scope of the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a group of compounds having ROCK2 IC_{50} values ≤ 10 μM.

In another embodiment, the present invention provides a group of compounds having ROCK2 IC_{50} values ≤ 1 μM.

In another embodiment, the present invention provides a group of compounds having ROCK2 IC_{50} values ≤ 0.1 μM.

In another embodiment, the present invention provides a group of compounds having ROCK2 IC_{50} values ≤ 0.05 μM.

In another embodiment, the present invention provides a group of compounds having ROCK2 IC_{50} values ≤ 0.01 μM.

II. OTHER EMBODIMENTS OF THE INVENTION

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate, thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention.

In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s).

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of a condition associated with aberrant ROCK activity comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof. As used herein, the term "patient" encompasses all mammalian species.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state.

As used herein, "prophylaxis" or "prevention" covers the preventive treatment of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a patient that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state. In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. *Cis*- and *trans*- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are examples of stereoisomers. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superimposable. The term "diastereomer" refers to stereoisomers that are not mirror images. The term "racemate" or "racemic mixture" refers to a composition composed of equimolar quantities of two enantiomeric species, wherein the composition is devoid of optical activity.

The symbols "R" and "S" represent the configuration of substituents around a chiral carbon atom(s). The isomeric descriptors "R" and "S" are used as described herein for indicating atom configuration(s) relative to a core molecule and are intended to be used as defined in the literature (IUPAC Recommendations 1996, *Pure and Applied Chemistry*, 68:2193-2222 (1996)).

The term "chiral" refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image. The term "homochiral" refers to a state of enantiomeric purity. The term "optical activity" refers to the degree to which a homochiral molecule or nonracemic mixture of chiral molecules rotates a plane of polarized light.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1 to C_{10} alkyl" or "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl).

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

"Halo" or "halogen" includes fluoro (F), chloro (Cl), bromo (Br), and iodo (I). "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_1 to C_6 haloalkoxy" or "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. "C_3 to C_7 cycloalkyl" or "C_{3-7} cycloalkyl" is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl".

As used herein, "carbocycle", "carbocyclyl" or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and indanyl. When the term "carbocyclyl" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "bicyclic carbocyclyl" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

"Aryl" groups refer to monocyclic or polycyclic aromatic hydrocarbons, including, for example, phenyl, naphthyl, and phenanthranyl. Aryl moieties are well known and described, for example, in Lewis, R.J., ed., *Hawley's Condensed Chemical Dictionary*, 13th Edition, John Wiley & Sons, Inc., New York (1997). "C_6 or C_{10} aryl" or "C_{6-10} aryl" refers to phenyl and naphthyl. Unless otherwise specified, "aryl", "C_6 or C_{10} aryl" or "C_{6-10} aryl" or "aromatic residue" may be unsubstituted or substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group, wherein said phenyl group may optionally be substituted with 1 to 5 groups, preferably 1 to 3 groups, OH, OCH_3, Cl, F, Br, I, CN, NO_2, NH_2, $N(CH_3)H$, $N(CH_3)_2$, CF_3, OCF_3, $C(=O)CH_3$, SCH_3, $S(=O)CH_3$, $S(=O)_2CH_3$, CH_3, CH_2CH_3, CO_2H, and CO_2CH_3.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic ring" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1H-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "counterion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (*e.g.*, carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (*i.e.*, within) of the ring. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide ($N\rightarrow O$) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by reference.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula

I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", *A Textbook of Drug Design and Development*, pp. 113-191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988); and

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984).

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (1994); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, Academic Press, San Diego, CA (1999).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Deuterium has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium can be represented by symbols such as "^{2}H" or "D". The term "deuterated" herein, by itself or used to modify a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. Isotopes of carbon include ^{13}C and ^{14}C.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that compounds of the present invention do not contain a N-halo, $S(O)_2H$, or $S(O)H$ group.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "saturated" for saturated, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	Methyl
Et	Ethyl
Pr	Propyl
i-Pr	Isopropyl
Bu	Butyl
i-Bu	Isobutyl
t-Bu	*tert*-butyl
Ph	Phenyl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
AcOH or HOAc	acetic acid
$AlCl_3$	aluminum chloride
AIBN	Azobisisobutyronitrile
BBr_3	boron tribromide
BCl_3	boron trichloride
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

BOP reagent	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	1-methoxy-N-triethylammoniosulfonyl-methanimidate
CBz	Carbobenzyloxy
CH_2Cl_2	Dichloromethane
CH_3CN or ACN	Acetonitrile
$CDCl_3$	deutero-chloroform
$CHCl_3$	Chloroform
mCPBA or m-CPBA	*meta*-chloroperbenzoic acid
Cs_2CO_3	cesium carbonate
$Cu(OAc)_2$	copper (II) acetate
Cy_2NMe	N-cyclohexyl-N-methylcyclohexanamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2 dichloroethane
DCM	dichloromethane
DEA	diethylamine
Dess-Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-beniziodoxol-3-(1H)-one
DIC or DIPCDI	diisopropylcarbodiimide
DIEA, DIPEA or Hunig's base	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
cDNA	complimentary DNA
Dppp	(*R*)-(+)-1,2-bis(diphenylphosphino)propane
DuPhos	(+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene
EDC	*N*-(3-dimthylaminopropyl)-*N*′-ethylcarbodiimide
EDCI	*N*-(3-dimthylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
(*S,S*)-EtDuPhosRh(I)	(+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate

Et_3N or TEA	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	Ethanol
GMF	glass microfiber filter
Grubbs (II)	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(triycyclohexylphosphine)ruthenium
HCl	hydrochloric acid
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HEPES	4-(2-hydroxyethyl)piperaxine-1-ethanesulfonic acid
Hex	Hexane
HOBt or HOBT	1-hydroxybenzotriazole
H_2SO_4	sulfuric acid
K_2CO_3	potassium carbonate
KOAc	potassium acetate
K_3PO_4	potassium phosphate
LAH	lithium aluminum hydride
LG	leaving group
LiOH	lithium hydroxide
MeOH	Methanol
$MgSO_4$	magnesium sulfate
MsOH or MSA	methylsulfonic acid
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
Na_2CO_3	sodium carbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide

NH_3	Ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
OTf	triflate or trifluoromethanesulfonate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	palladium(II) acetate
Pd/C	palladium on carbon
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
Ph_3PCl_2	triphenylphosphine dichloride
PG	protecting group
$POCl_3$	phosphorus oxychloride
i-PrOH or IPA	isopropanol
PS	polystyrene
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
SEM-Cl	2-(trimethysilyl)ethoxymethyl chloride
SiO_2	silica oxide
$SnCl_2$	tin(II) chloride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
$TMSCHN_2$	trimethylsilyldiazomethane
T_3P	propane phosphonic acid anhydride
TRIS	tris (hydroxymethyl) aminomethane

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis.

IV. BIOLOGY

In vitro Assays

The effectiveness of compounds of the present invention as ROCK inhibitors can be determined in a 30 µL assay containing 20 mM HEPES, pH 7.5, 20 mM $MgCl_2$, 0.015% Brij-35, 4 mM DTT, 5 µM ATP and 1.5 µM peptide substrate (FITC-AHA-AKRRRLSSLRA-OH). Compounds were dissolved in DMSO so that the final concentration of DMSO was < 2%, and the reaction was initiated with Rho kinase variants. After incubation, the reaction was terminated by the addition of EDTA and the phosphorylated and non-phosphorylated peptides separated using a LABCHIP® 3000 Reader (Caliper Life Sciences). Controls consisted of assays that did not contain compound, and backgrounds consisted of assays that contained enzyme and substrate but had EDTA from the beginning of the reaction to inhibit kinase activity. Compounds were tested in dose-response format, and the inhibition of kinase activity was calculated at each concentration of compound. The inhibition data were fit using a curve-fitting program to determine the IC_{50}; *i.e.*, the concentration of compound required to inhibit 50% of kinase activity.

Representative Examples were tested in the ROCK assay described above and found having ROCK inhibitory activity. A range of ROCK inhibitory activity (IC_{50} values) of ≤ 50 µM (50000 nM) was observed. Table A below lists the ROCK2 IC_{50} values measured for the following Examples.

Table A

Example No.	ROCK2 IC_{50} (nM)
I-1	0.51
I-2	9.59
I-3	5.52
I-4	49.1
I-5	238
I-6	17.0
I-7	367
I-8	5490
I-9	486
I-10	30.4
I-11	242

Example No.	ROCK2 IC_{50} (nM)
I-12	664
I-13	979
I-14	149
I-15	7440
I-16	3920
I-17	165
I-18	37.2
I-19	75.0
I-20	199
I-21	177
I-22	29.4
I-23	158
I-24	50.7
I-25	41.3
I-26	300
I-27	6.32
I-28	59.8
I-29	1640
I-30	349
I-31	2100
I-32	55.5
I-33	291
I-34	1040
I-35	602
I-36	282
I-37	198
I-38	404
I-39	1370
I-40	7090
I-41	38.0

Example No.	ROCK2 IC_{50} (nM)
I-42	537
I-43	643
I-44	1790
I-45	258
I-46	233
I-47	55.5
I-48	3170
I-49	717
I-50	38.1
I-51	3.23
I-52	1640
I-53	318
I-54	137
I-55	174
I-56	19.9
I-57	4910
I-58	95.9
I-59	113
I-60	36.7
I-61	98.3
I-62	7610
I-63	63.2
I-64	2150
I-65	198
I-66	92.3
I-67	54.5
I-68	37.6
I-69	75.5
I-70	0.81
I-71	12.3

Example No.	ROCK2 IC_{50} (nM)
I-72	224
I-73	5980
I-74	24.8
I-75	159
I-76	493
I-77	17.5
I-78	4440
I-79	184
I-80	81.4
I-81	4180
I-82	2410
I-83	7.69
I-84	4.95
I-85	25.2
I-86	471
I-87	4340
I-88	4080
I-89	5650
I-90	49.7
I-91	607
I-92	682
I-93	315
I-94	260
I-95	31.9
I-96	2970
I-97	2210
I-98	1200
I-99	657
I-100	695
I-101	1320

Example No.	ROCK2 IC_{50} (nM)
I-102	1170
I-103	1620
I-104	4460
I-105	62.1
I-106	10.6
I-107	429
I-108	8.54
I-109	131
I-110	218
I-111	3.62
I-112	615
I-113	1340
I-114	106
I-115	3210
I-116	1080
I-117	368
I-118	15.1
I-119	845
I-120	2280
I-121	973
I-122	2780
I-123	688
I-124	7.28
I-125	9.52
I-126	16.8
I-127	27.7
I-128	141
I-129	6310
I-130	170
I-131	411

Example No.	ROCK2 IC_{50} (nM)
I-132	3780
I-133	1990
I-134	5320
I-135	1980
I-136	6580
I-137	4470
I-138	176
I-139	24.5
I-140	1620
I-141	6270
I-142	550
I-143	5090
I-144	9920
I-145	3420
I-146	106
I-147	835
I-148	640
I-149	593
I-150	589
I-151	458
I-152	8190
I-153	7070
I-154	378
I-155	8640
I-156	1210
I-157	810
I-158	6.18
I-159	194
I-160	3.68
I-161	875

Example No.	ROCK2 IC_{50} (nM)
I-162	22.4
I-163	32.5
I-164	14.0
I-165	5.14
I-166	1490
II-1	15.5
II-2	16.2
II-3	25.4
II-4	55.1
II-5	458
II-6	9070
II-7	51.2
II-8	6070
II-9	42.6
II-10	6930
II-11	541
II-12	516
II-13	382
II-14	36.0
II-15	756
II-16	35.2
III-1	2.51
III-2	25.5
III-3	1.70
III-4	2.24
III-5	2.54
III-6	281
III-7	120
III-8	33.8
III-9	497

Example No.	ROCK2 IC_{50} (nM)
III-10	684
III-11	583
III-12	429
III-13	2.58
III-14	18.8
III-15	191
III-16	66.9
III-17	377
III-18	18.2
III-19	15.5
IV-1	107
IV-2	72.5
IV-3	321
IV-4	276
IV-5	1590
IV-6	44.5
IV-7	111
IV-8	1220
IV-9	12.4
IV-10	30.2
IV-11	108
IV-12	12.8
IV-13	35.2
IV-14	77.9
IV-15	74.3
IV-16	371
IV-17	52.5
IV-18	370
IV-19	187
V-1	30.2

Example No.	ROCK2 IC_{50} (nM)
V-2	169
V-3	23.1
V-4	664
V-5	4.71
V-6	15.9
V-7	24.3
V-8	42.4
V-9	8.97
V-10	53.9
V-11	80.3
V-12	3.90
VI-1	1.05
VI-2	2.78
VI-3	6.23
VI-4	6.36
VI-5	2.80
VI-6	1.32
VI-7	0.35
VI-8	19.9
VI-9	11.4
VI-10	7.31
VI-11	5.66
VI-12	56.0
VII-1	1.29
VII-2	2.87
VII-3	2.25
VII-4	3.73
VII-5	0.80
VII-6	1.34
VII-7	1.50

Example No.	ROCK2 IC_{50} (nM)
VII-8	2.54
VII-9	0.78
VII-10	12.6
VII-11	1.14
VII-12	1.82
VIII-1	0.59
VIII-2	4.09
VIII-3	1.99
VIII-4	0.34
VIII-5	0.85
VIII-6	0.85
VIII-7	0.85
VIII-8	0.85
VIII-9	2.55
VIII-10	6.35
VIII-11	2.54
VIII-12	0.85
VIII-13	0.85
VIII-14	0.79
VIII-15	0.56
VIII-16	0.60
VIII-17	13.8
VIII-18	5.16
VIII-19	4.10
VIII-20	14.3
VIII-21	11.2
VIII-22	18.8
VIII-23	0.72
VIII-24	12.4
VIII-25	4.18

Example No.	ROCK2 IC_{50} (nM)
VIII-26	13.1
VIII-27	11.9
VIII-28	4.74
VIII-29	41.5
VIII-30	13.2
VIII-31	11.0
VIII-32	12.8
VIII-33	4.38
VIII-34	4.37
VIII-35	18.6
VIII-36	1.70
VIII-37	9.03
IX-1	9.66
IX-2	3.74
IX-3	2.39
IX-4	20.9
IX-5	18.7
IX-6	17.7
IX-7	231
IX-8	27.6
IX-9	46.3
X-1	90.2
X-2	138
X-3	13.3
X-4	2.71
X-5	104
XI-1	452
XI-2	19.3
XI-3	25.2
XI-4	10.3

Example No.	ROCK2 IC_{50} (nM)
XI-1	452
XI-2	19.3
XI-3	25.2
XI-4	10.3
XI-5	33.1
XI-6	637
XI-7	17.1
XI-8	61.4
XI-9	122.6
XI-10	73.8
XI-11	93.1
XI-12	12.6
XI-13	9.03
XI-14	32.6
XI-15	1112
XI-16	0.52
XI-17	0.18
XI-18	176
XI-19	3.79
XI-20	1.81
XI-21	0.65
XI-22	7.34
XI-23	2.95
XI-24	20.4
XI-25	4.69
XI-26	9.28
XI-27	3.94
XI-28	239
XI-29	362
XI-30	15.9

Example No.	ROCK2 IC_{50} (nM)
XI-31	1.44
XI-32	935
XI-33	51.7
XI-34	472
XI-35	229
XI-36	265
XI-37	494
XI-38	130
XII-1	1480
XII-2	1750
XII-3	957
XII-4	782
XII-5	49.3
XII-6	620
XIII-1	68.9
XIII-2	882
XIII-3	337
XIII-4	781
XIII-5	792
XIII-6	47.9
XIII-7	583
XIII-8	68.9
XIII-9	1840
XIII-10	175
XIV-1	3.91
XIV-2	16.3
XIV-3	13.7
XIV-4	1.29
XIV-5	89.6
XIV-6	6.98

Example No.	ROCK2 IC_{50} (nM)
XIV-7	13.7
XIV-8	13.5
XIV-9	2.32
XIV-10	12.2
XIV-11	7.16
XIV-12	1020
XIV-13	43.2
XIV-14	48.8
XIV-15	33.6
XIV-16	3.69
XIV-17	15.2
XIV-18	45.9
XIV-19	80.8
XIV-20	1.01
XIV-21	15.0
XIV-22	27.7
XIV-23	8.09
XIV-24	25.3
XIV-25	38.8
XIV-26	144
XIV-27	34.2
XIV-28	46.6
XIV-29	1490
XIV-30	213
XIV31	1.16
XIV-32	5.70
XIV-33	7.43
XIV-34	66.3
XIV-35	33.1
XIV-36	2.66

Example No.	ROCK2 IC_{50} (nM)
XIV-37	297
XV-1	2.85
XV-2	49.4
XV-3	44.2
XV-4	49.2
XV-5	460
XV-6	552
XV-7	1140
XV-8	606
XV-9	161
XV-10	77.8
XV-11	965
XV-12	28.6
XV-13	81.0
XV-14	26.4
XV-15	224
XV-16	1070
XVI-1	20.3
XVI-2	36.9
XVI-3	7.40
XVI-4	2230
XVI-5	61.5
XVI-6	34.3

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the patient to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 18th Edition (1990).

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can also be administered by parenteral administration (*e.g.*, intra-venous, intra-arterial, intramuscularly, or subcutaneously. When administered intra-venous or intra-arterial, the dose can be given continuously or intermittent. Furthermore, formulation can be developed for intramuscularly and subcutaneous delivery that ensure a gradual release of the active pharmaceutical ingredient.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 1000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of ROCK. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving ROCK. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a cardiovascular and/or inflammatory disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat cardiovascular and/or inflammatory disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof. The following Examples have been prepared, isolated and characterized using the methods disclosed herein.

VI. GENERAL SYNTHESIS INCLUDING SCHEMES

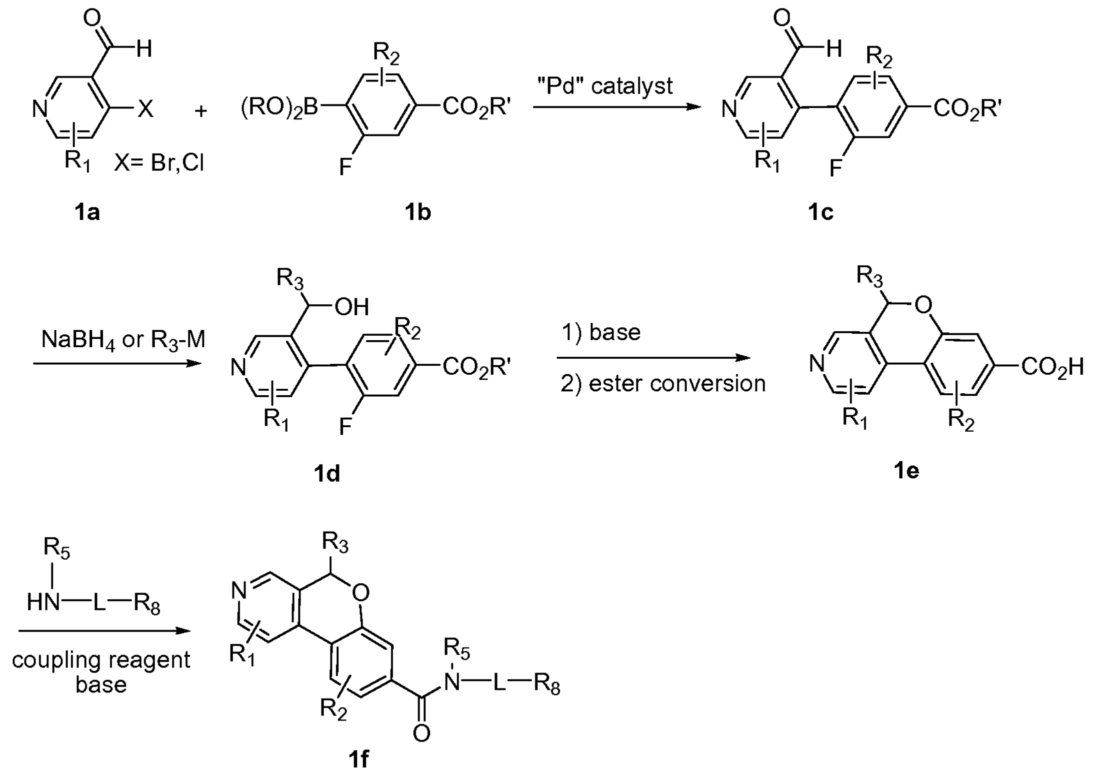
The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry (Maffrand, J.P. et al., *Heterocycles*, 16(1):35-37 (1981)). General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds.

Examples of compounds of the present invention prepared by methods described in the general schemes are given in the intermediates and examples section set out hereinafter. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates which serve to control the diastereoselectivity of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary.

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being affected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

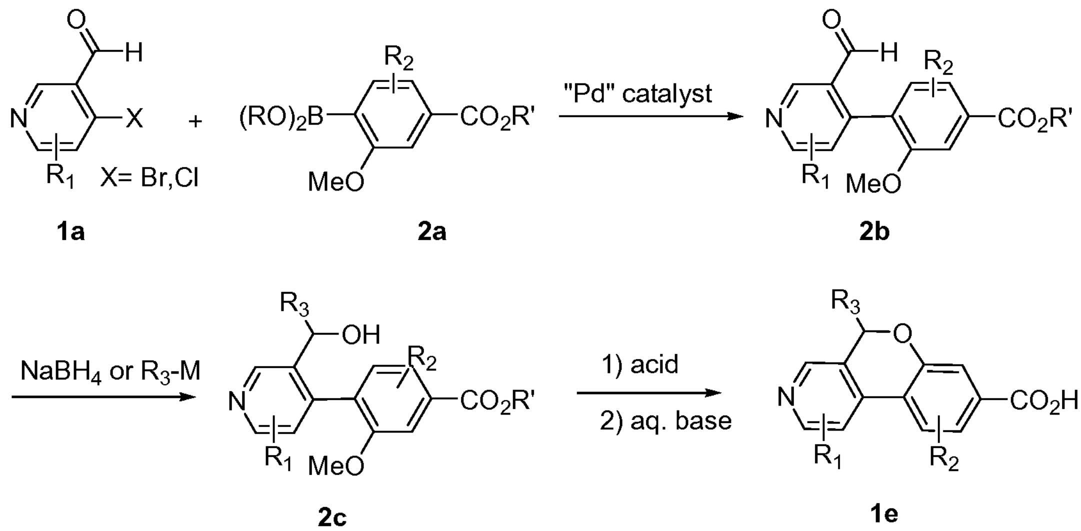
It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, 4th Edition, Wiley-Interscience (2006)).

Scheme 1



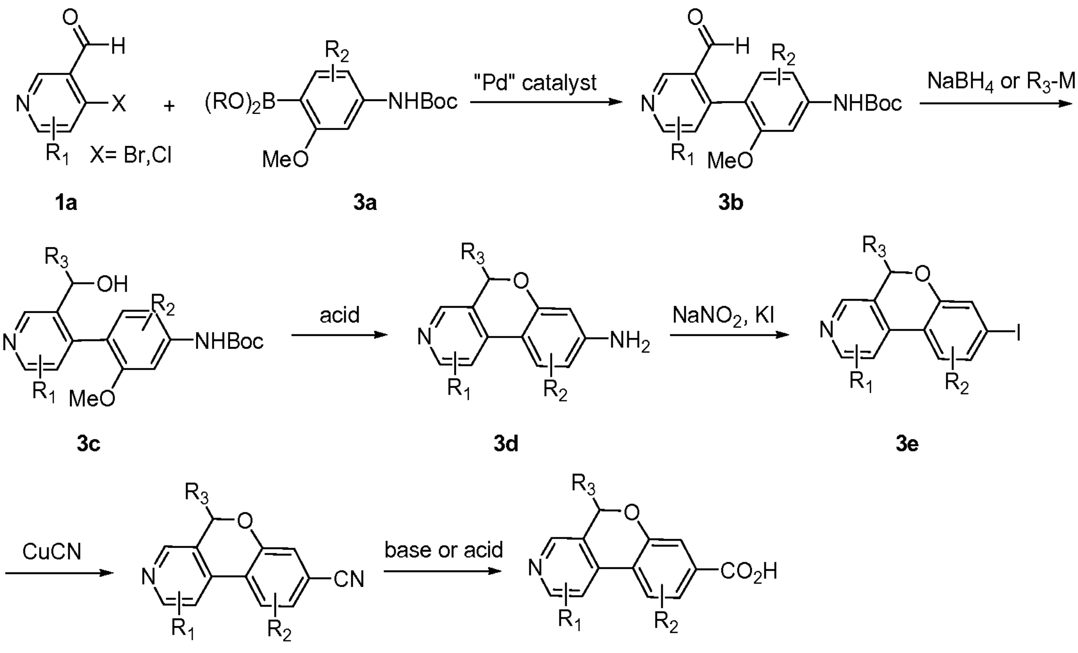
Compounds of this invention with the structure of **1f** could be prepared as shown in Scheme 1. Suzuki-Miyaura coupling between 4-halopyridine derivative **1a** and fluorophenyl boronic acid or boronate **1b**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $PdCl_2$(dppf), affords intermediate **1c**. Aldehyde **1c** is either reduced using a reducing reagent such as $NaBH_4$, or treated with an alkyl metal reagent such as a Grignard's reagent, to afford alcohol **1d**. Ring closure of **1d** by treatment with a base, such as NaH, Cs_2CO_3, etc, followed by aqueous basic workup to afford the tricyclic acid common intermediate **1e**. Amide formation affords target **1f** by coupling intermediate **1e** with an appropriate amine in the presence of a coupling reagent, such as HATU or EDC, and a base such as DIEA.

Scheme 2



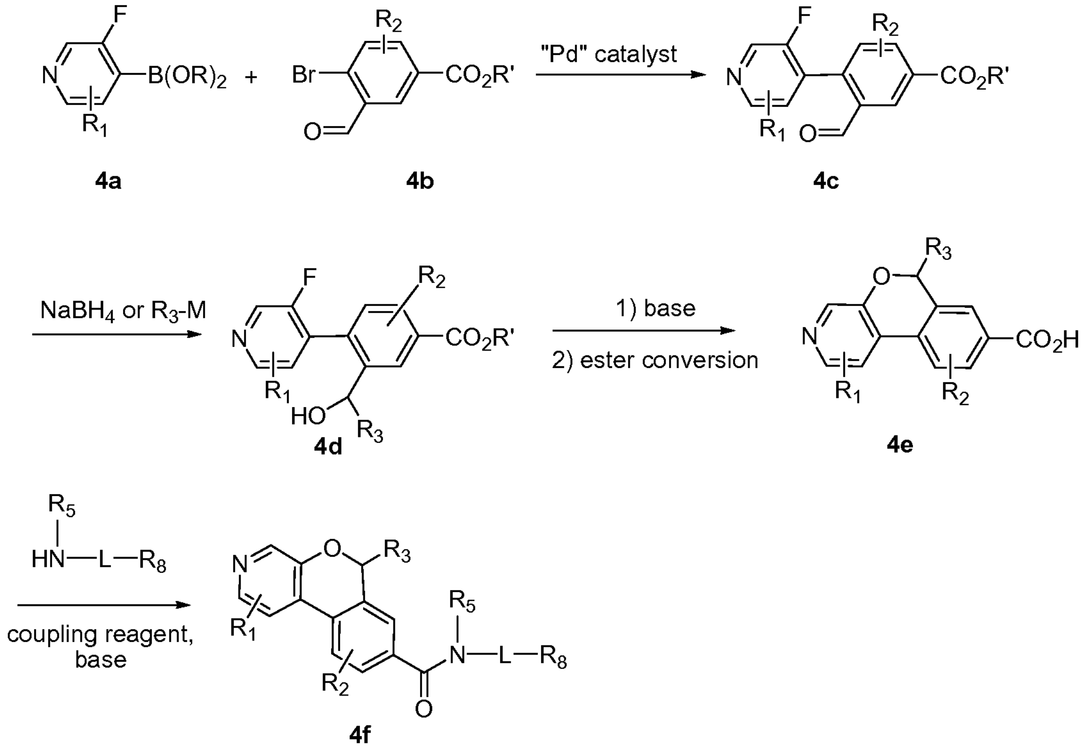
Alternatively, the common intermediate **1e** can be prepared as shown in Scheme 2. Suzuki-Miyaura coupling between 4-halopyridine derivative **1a** and methoxyphenyl boronic acid or boronate **2a**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $PdCl_2$(dppf), affords intermediate **2b**. Aldehyde **2b** is either reduced using a reducing reagent such as $NaBH_4$, or treated with an alkyl metal reagent such as a Grignard's reagent, to afford alcohol **2c**. Ring closure of **2c** by treatment with a strong acid, such as HBr, followed by aqueous basic workup to afford the tricyclic acid **1e**.

Scheme 3



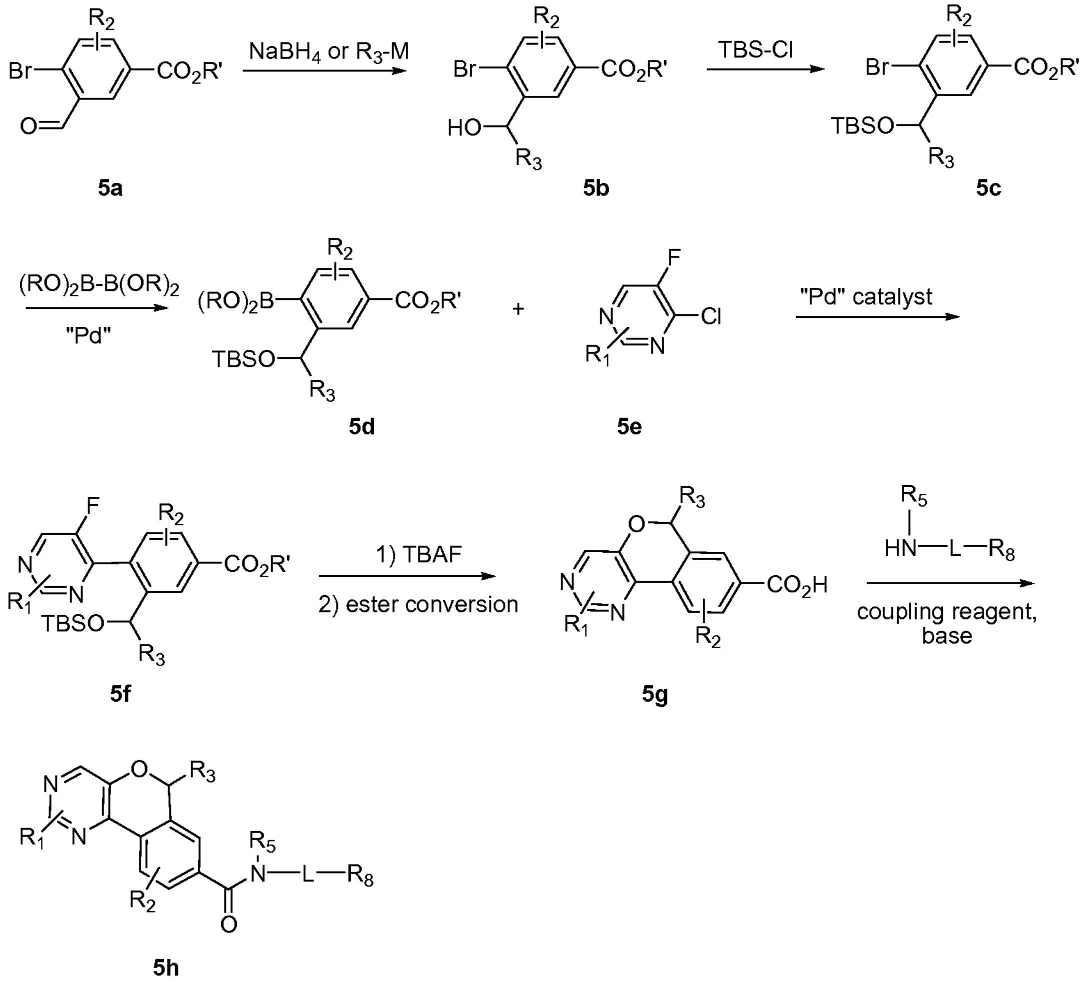
Alternatively, intermediate **1e** can be prepared as shown in Scheme 3. Suzuki-Miyaura coupling between 4-halopyridine derivative **1a** and methoxy aniline boronic acid or boronate **3a**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $PdCl_2$(dppf), affords intermediate **3b**. Aldehyde **3b** is either reduced using a reducing reagent such as $NaBH_4$, or treated with an alkyl metal reagent such as a Grignard's reagent, to afford alcohol **3c**. Ring closure of **3c** by treatment with a strong acid, such as HBr, to afford tricyclic aniline **3d**. Conversion of the amino group of **3c** to iodide in **3e**, followed by cyanization provides **3f**. The cyano group is hydrolyzed to the acid by treating **3f** with an aqueous base such NaOH, or an aqueous acid such as HCl, to give the tricyclic acid **1e**.

Scheme 4



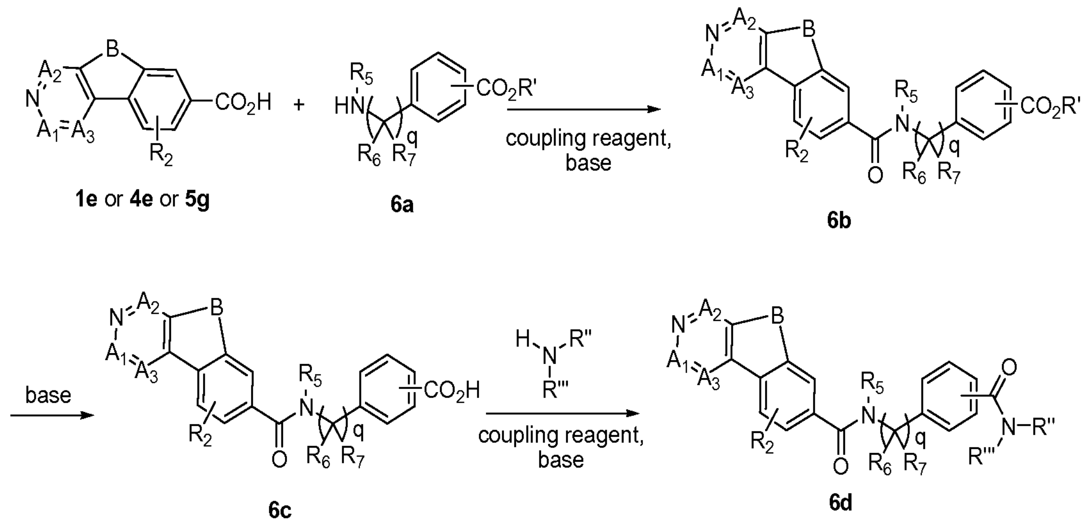
Compounds of this invention with the structure of **4f** could be prepared as shown in Scheme 4. Suzuki-Miyaura coupling between 4-pyridine boronic acid or boronate derivative **4a** and bromobenzaldehyde derivative **4b**, or other appropriate Suzuki coupling partners, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $PdCl_2$(dppf), affords intermediate **4c**. Aldehyde **4c** is either reduced using a reducing reagent such as $NaBH_4$, or treated with an alkyl metal reagent such as a Grignard's reagent, to afford alcohol **4d**. Ring closure of **4d** by treatment with a base, such as NaH, Cs_2CO_3, etc, followed by aqueous basic workup to afford the tricyclic acid common intermediate **4e**. Amide formation affords target **4f** by coupling intermediate **4e** with an appropriate amine in the presence of a coupling reagent, such as HATU or EDC, and a base such as DIEA.

Scheme 5



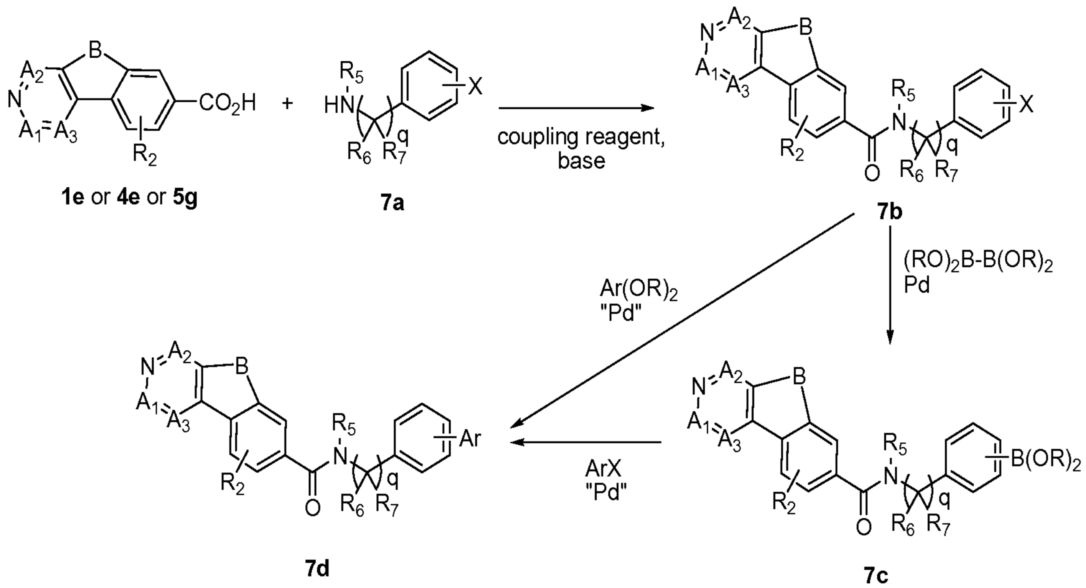
Compounds of this invention with the structure of **5h** could be prepared as shown in Scheme 5. Aldehyde **5a** is either reduced using a reducing reagent such as $NaBH_4$, or treated with an alkyl metal reagent such as a Grignard's reagent, to afford alcohol **5b**. The alcohol is protected using a protecting group such as TBS to give **5c**, which is then converted to boronic acid or boronate **5d** under Miyaura condition. Suzuki-Miyaura coupling between **5d** and chloropyrimidine derivative **5e**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $Pd(PPh_3)_4$, affords intermediate **5f**. Removal of the TBS protecting group and closure of the ring by treating **5f** with TBAF followed by ester conversion by treating with an aqueous base such as LiOH, affords common intermediate **5g**. Amide formation affords target **5h** by coupling intermediate **5g** with an appropriate amine in the presence of a coupling reagent, such as HATU or EDC, and a base such as DIEA.

Scheme 6



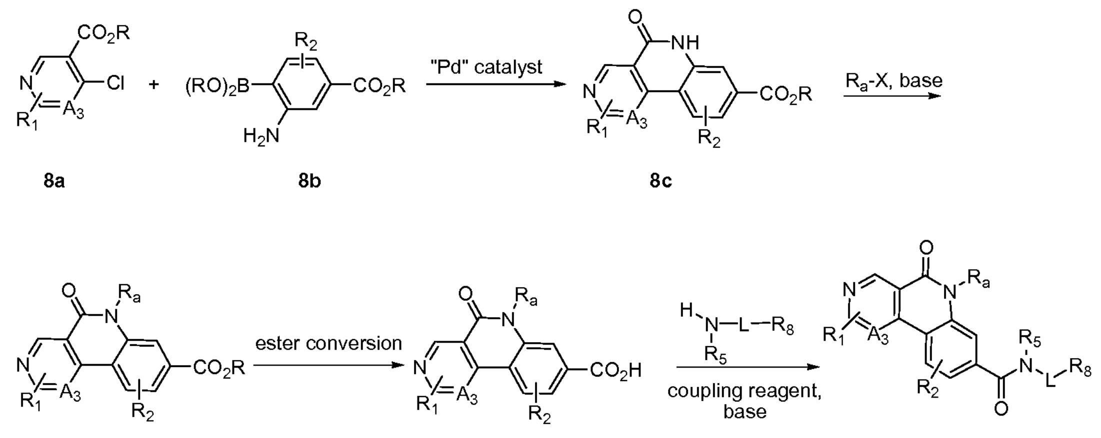
Compounds of this invention with the structure of **6d** could be prepared as shown in Scheme 6. Amide formation provides compound **6b** by coupling intermediate **1e** or **4e** or **5g** with amino ester **6a** in the presence of a coupling reagent, such as HATU or EDC, and a base such as DIEA. Ester **6b** is converted to acid **6c** when treated with a base such as LiOH. Target **6d** is afforded by coupling **6c** with an appropriate amine using a coupling reagent, such as HATU or EDC, and a base such as DIEA.

Scheme 7



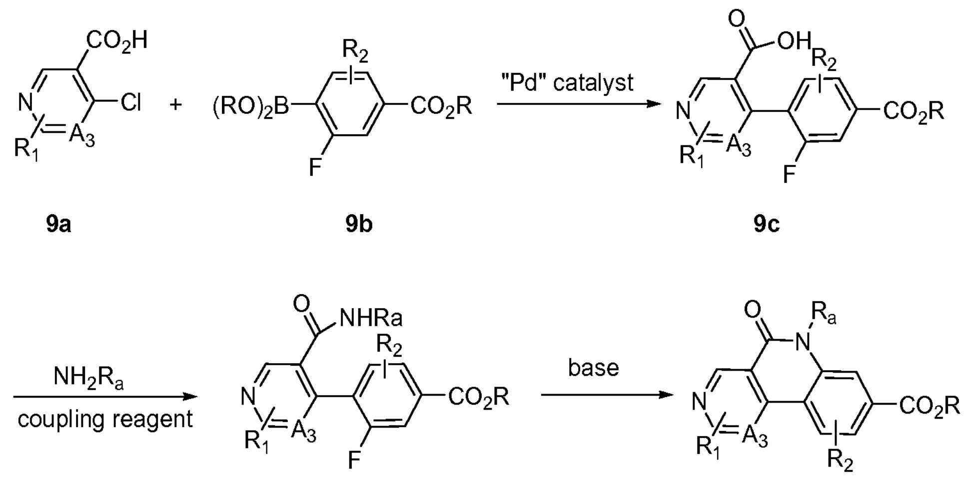
Compounds of this invention with the structure of **7d** could be prepared as shown in Scheme 7. Amide formation of intermediate **1e**, or **4e**, or **5g** with **7a** provides intermediate **7b**. Suzuki-Miyaura coupling between **7b** and an appropriate aromatic boronic acid or boronate derivative, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $PdCl_2$(dppf), affords **7d**. Alternatively, **7b** can be converted to boronic acid or boronate **7c**. Then **7c** can couple with aromatic halides following Suzuki-Miyaura coupling condition to afford target **7d**.

Scheme 8



Compounds of this invention with the structure of **8f** could be prepared as shown in Scheme 8. Suzuki-Miyaura coupling between **8a** and **8b**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $Pd(PPh_3)_4$, affords intermediate **8c**. Substitution of the lactam by treating **8c** with an appropriate alkylating reagent at the presence of a base such as NaH, affords **8d**. Ester conversion by treatment with an aqueous base such as LiOH, affords common intermediate **8e**. Amide formation affords target **8f** by coupling intermediate **8e** with an appropriate amine in the presence of a coupling reagent, such as HATU or EDC, and a base such as DIEA.

Scheme 9



9a **9b** **9c**

9d **8d**

Alternatively, intermediate **8d** could be prepared as shown in Scheme 9. Suzuki-Miyaura coupling between **9a** and **9b**, in the presence of a base such as K_3PO_4, and a Pd catalyst such as $Pd(PPh_3)_4$, affords intermediate **9c**. Amide formation affords **9d** by coupling intermediate **7c** with an appropriate amine in the presence of a coupling reagent, such as HATU, EDC or T_3P, and a base such as DIEA. Ring closure by treating **9d** with a base such as NaH, followed by aqueous base treatment of the ester, affords **8d**.

Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out using prepacked SiO_2 cartridges eluting with either gradients of hexanes and EtOAc or DCM and MeOH, or DCM and EtOAc unless otherwise indicated. Reverse phase preparative HPLC was carried out using C18 columns eluting with gradients of Solvent A (90% H_2O, 10% MeOH, 0.1% TFA) and Solvent B (10% H_2O, 90% MeOH, 0.1% TFA, UV 220 nm) or with gradients of Solvent A (90% H_2O, 10% ACN, 0.1% TFA) and Solvent B (10% H_2O, 90% ACN, 0.1% TFA, UV 220 nm) or with gradients of Solvent A (98% H_2O, 2% ACN, 0.05% TFA) and Solvent B (98% ACN, 2% H_2O, 0.05% TFA, UV 220 nm) (or) SunFire Prep C18 OBD 5μ 30x100mm, 25 min gradient from 0-100% B. A = H_2O/ACN/TFA 90:10:0.1. B = ACN/H_2O/TFA 90:10:0.1 (or) Waters XBridge C18, 19 x 200 mm, 5-μm particles; Guard Column: Waters XBridge C18, 19 x 10 mm, 5-μm particles; Solvent A: water with 20-mM ammonium acetate; Solvent B: 95:5 acetonitrile:water with 20-mM ammonium acetate; Gradient: 25-65% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min or with gradients of Solvent A (5:95 acetonitrile:water with 0.1% formic acid) and Solvent B (95:5 acetonitrile:water with 0.1% formic acid).

Unless otherwise stated, analysis of final products was carried out by reverse phase analytical HPLC.

Method A: SunFire C18 column (3.5 μm C18, 3.0 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 10 min and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 254 nm).

Method B: XBridge Phenyl column (3.5 μm C18, 3.0 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 10 min and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 254 nm).

Method C: Waters BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 40 °C; Gradient: 0.5 min hold at 0%B, 0-100% B over 4 minutes, then a 0.5-minute hold at 100% B; Flow: 1 mL/min.

Method C-1: Waters BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile:water with 0.05% TFA; Temperature: 40 °C; Gradient: 0.5 min hold at 0%B, 0-100% B over 4 minutes, then a 0.5-minute hold at 100% B; Flow: 1 mL/min.

Method D: Waters BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 methanol:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 methanol:water with 10 mM ammonium acetate; Temperature: 40 °C; Gradient: 0.5 min hold at 0%B, 0-100% B over 4 minutes, then a 0.5-minute hold at 100% B; Flow: 0.5 mL/min.

Method E: Waters BEH C18, 2.1 x 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile:water with 0.05% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes; Flow: 1.11 mL/min.

Method F: Waters BEH C18, 2.1 x 50 mm, 1.7-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 ºC; Gradient: 0-100% B over 3 minutes; Flow: 1.11 mL/min.

Method G: SunFire C18 column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 18 min and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

Method H: XBridge Phenyl column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 18 min and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

Method I: SunFire C18 column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 12 min and then 100% Solvent B for 3 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

Method J: XBridge Phenyl column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 10-100% Solvent B over 12 min and then 100% Solvent B for 3 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

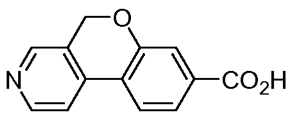
Method K: SunFire C18 column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 0-50% Solvent B over 15 min, 50-100% Solvent B over 3 min, and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

Method L: XBridge Phenyl column (3.5 µm, 4.6 × 150 mm). Gradient elution (1.0 mL/min) from 0-50% Solvent B over 15 min, 50-100% Solvent B over 3 min, and then 100% Solvent B for 5 min was used. Solvent A is (95% water, 5% acetonitrile, 0.05% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.05% TFA, UV 220 nm).

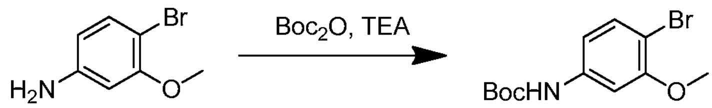
Method M: Ascentis Express C18 (2.7 µm, 4.6 × 50 mm). Gradient elution (4.0 mL/min) from 0-100% Solvent B over 4 min. Solvent A is (95% water, 5% acetonitrile, 0.1% TFA) and Solvent B is (5% water, 95% acetonitrile, 0.1% TFA, UV 220 nm).

Method N: Ascentis Express C18 (2.7 µm, 4.6 × 50 mm). Gradient elution (4.0 mL/min) from 0-100% Solvent B over 4 min. Solvent A is (95% water, 5% acetonitrile, 10 mM NH_4OAc) and Solvent B is (5% water, 95% acetonitrile, 10 mM NH_4OAc, UV 220 nm).

Intermediate 1: 5H-Chromeno[3,4-c]pyridine-8-carboxylic acid

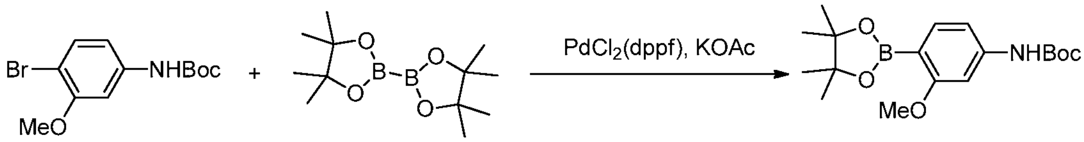


Intermediate 1a: *tert*-Butyl (4-bromo-3-methoxyphenyl)carbamate



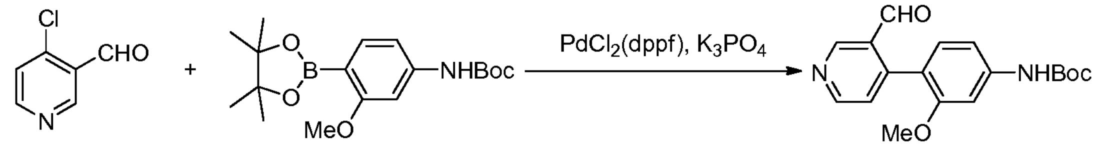
To a stirred solution of 4-bromo-3-methoxyaniline (50 g, 247 mmol) in THF (1.5 L) were added Boc_2O (69 mL, 297 mmol) and TEA (45 mL, 322 mmol). The reaction mixture was refluxed for 12 h. The solvent was removed and the residue was taken in ethyl acetate. It was washed with water and brine, and then dried over sodium sulfate and concentrated. The crude mixture was purified by normal phase chromatography to give Intermediate 1a as white solid (60.0 g, 78%). LC-MS (ESI) *m/z*: 302.0 $[M+H]^-$; ^1H NMR (400MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.37 (d, *J*=2.0 Hz, 1H), 6.96 (dd, *J*=8.4, 2.0 Hz, 1H), 3.79 (s, 3H), 1.48 (s, 9H).

Intermediate 1b: *tert*-Butyl (3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate



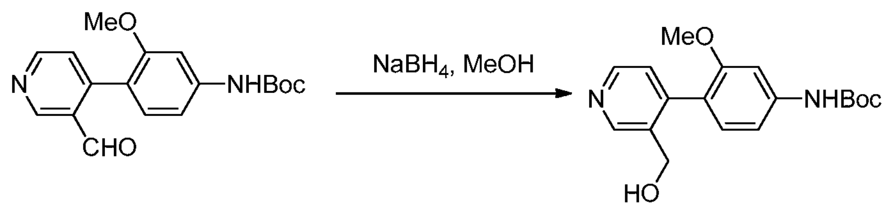
To a stirred solution of 1a (25 g, 83 mmol) in DMF (750 mL) were added KOAc (24.36 g, 248 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (31.5 g, 124 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (6.76 g, 8.27 mmol). The reaction was heated at 100 °C for 12 h. The DMF was removed and the residue was taken in ethyl acetate. It was washed with water and brine, dried over sodium sulfate and concentrated. The crude mixture was purified by normal phase chromatography to provide Intermediate 1b as white solid (15.0 g, 48%). ^{1}H NMR (400MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.41 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=1.6 Hz, 1H), 7.00 (dd, *J*=8.0, 1.6 Hz, 1H), 3.68 (s, 3H), 1.48 (s, 9H), 1.24 (s, 12H).

Intermediate 1c: *tert*-Butyl (4-(3-formylpyridin-4-yl)-3-methoxyphenyl)carbamate



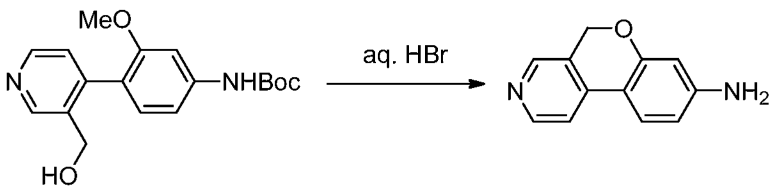
To a stirred solution of 1b (15.54 g, 44.5 mmol) in 1,4-dioxane (450 mL) and H_2O (75mL) were added 4-chloronicotinaldehyde (6.0 g, 42.4 mmol), K_3PO_4 (36.0 g, 170 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (2.77 g, 3.39 mmol). The reaction mixture was heated at 100 °C for 1 h under nitrogen. The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate and then concentrated. Purification by normal phase chromatography provided Intermediate 1c as yellow solid (12.0 g, 84%). LC-MS (ESI) *m/z*: 329.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 9.75 (d, *J*=0.4 Hz, 1H), 9.63 (s, 1H), 8.89 (s, 1H), 8,79 (d, *J*=6.8 Hz, 1H), 7.43-7.40 (m, 2H), 7.29 (d, *J*=11.2 Hz, 1H), 7.20 (dd, *J*=11.2, 2.4 Hz, 1H), 3.67 (s, 3H), 1.50 (s, 9H).

Intermediate 1d: *tert*-Butyl (4-(3-(hydroxymethyl)pyridin-4-yl)-3-methoxyphenyl) carbamate



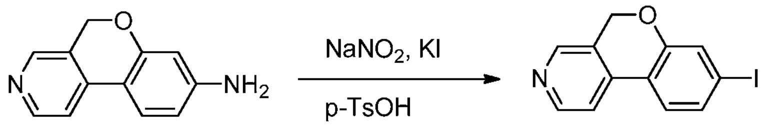
To a stirred solution of 1c (30 g, 91 mmol) in MeOH (500 mL) was added $NaBH_4$ (4.15 g, 110 mmol) at 0 °C under N_2. The reaction was stirred at rt for 1 h. The reaction was quenched with water (150mL) and methanol was removed. The residue was extracted with ethyl acetate (2x200 mL). The combined organic phase was washed with water and brine, dried over sodium sulfate and concentrated. The crude solid was further washed with hot 50% ethyl acetate in petroleum ether (50 mL) to provide Intermediate 1d as off-white solid (30 g, 98%). LC-MS (ESI) *m/z*: 329.2 $[M-H]^-$; ^{1}H NMR (400MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.67 (d, *J*=0.4 Hz, 1H), 8.43 (d, *J*=6.4 Hz, 1H), 7.38 (d, *J*=1.6 Hz, 1H), 7.12-7.03 (m, 3H), 5.14 (t, *J*=7.2 Hz, 1H), 4.03 (d, *J*=7.6 Hz, 1H), 3.68 (s, 3H), 1.50 (s, 9H).

Intermediate 1e: 5H-Chromeno[3,4-c]pyridin-8-amine



A suspension of 1d (30 g, 91 mmol) in HBr (63% in water, 8.0 mL, 91 mmol) was heated at 100 °C overnight. The reaction mixture was concentrated. The residue was dissolved in water and it was basified with sodium hydroxide solution and then extracted with DCM (2x300 mL). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated. The crude solid was washed with 20% of ethyl acetate in petroleum ether and then dried to give Intermediate 1e as yellow solid (15 g, 83%). LC-MS (ESI) *m/z*: 199.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.40 (d, *J*=6.8 Hz, 1H), 8.31 (m, 1H), 7.57 (d, *J*=11.2 Hz, 1H), 7.50 (d, *J*=6.8 Hz, 1H), 6.33 (dd, *J*=11.2, 2.8 Hz, 1H), 6.14 (d, *J*=2.8 Hz, 1H), 5.72 (s, 2H), 5.06 (s, 2H).

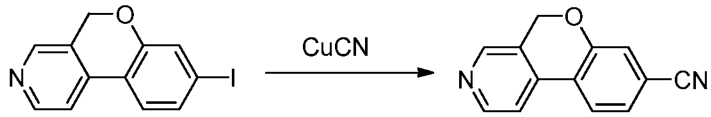
Intermediate 1f: 8-Iodo-5H-chromeno[3,4-c]pyridine



To a stirred solution of 1e (15 g, 76 mmol) in acetonitrile (150 mL) was added p-toluenesulfonic acid monohydrate (43.2 g, 227 mmol) at rt. After stirred for 10 min, an aqueous solution of $NaNO_2$ (13.05 g, 189 mmol) and KI (25.1 g, 151 mmol) was added slowly. After the addition was completed, the reaction was stirred at rt for 1 h. The reaction was basified with saturated sodium carbonate solution and then it was extracted with EtOAc (2x50 mL). The combined organic layer was washed with saturated sodium thiosulfate solution, water and brine, dried over sodium sulfate and concentrated. Purification by normal phase chromatography provided 1f as off-white solid (17.5 g, 74%). LC-MS (ESI) *m/z*: 310.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.59 (d, *J*=5.2

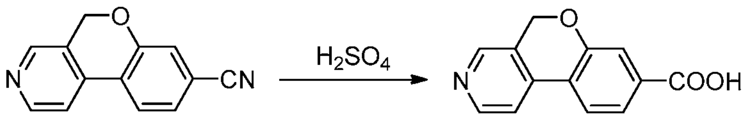
Hz, 1H), 8.50 (s, 1H), 7.81 (d, *J*=5.2 Hz, 1H), 7.76 (d, *J*=8.4 Hz, 1H), 7.50 (dd, *J*=8.0,1.6 Hz, 1H), 7.44 (s, 1H), 5.23 (s, 1H).

Intermediate 1g: 5H-Chromeno[3,4-c]pyridine-8-carbonitrile



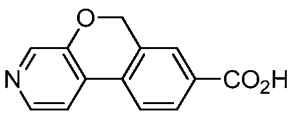
To a stirred solution of 1f (17 g, 55.0 mmol) in dry DMF (160 mL) was added CuCN (7.39 g, 82 mmol) as a single portion at rt under nitrogen. The reaction was heated at 150 ºC overnight. The reaction was cooled to rt and then quenched with saturated aqueous ammonia solution (500 mL). The solid formed was collected by filtration and it was washed with water and then dried to afford 1g (9.0 g, 78%). LC-MS (ESI) *m/z*: 209.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.65 (d, *J*=4.8 Hz, 1H), 8.56 (s, 1H), 8.18 (d, *J*=8.0 Hz, 1H), 8.18 (d, *J*=4.8 Hz, 1H), 7.59-7.56 (m, 2H), 5.32 (s, 2H).

Intermediate 1:

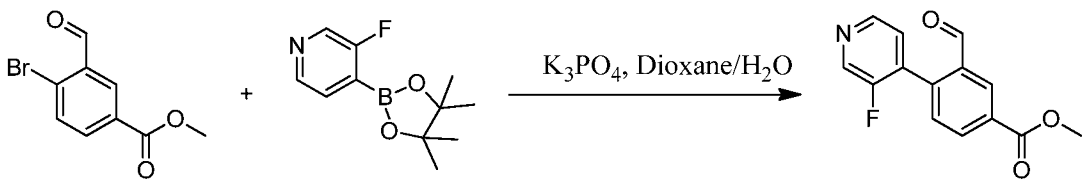


To a stirred solution of 1g (8.5 g, 40.8 mmol) in H_2O (80 mL) was added H_2SO_4 (80 mL) as a single lot and the reaction was heated at 80 ºC overnight. The reaction mixture was diluted with water (200 mL). The solid formed was collected by filtration, washed with water and dried. The crude solid was triturated with methanol at 50 ºC and then cooled to rt. The solid was filtered and dried to give Intermediate 1 as light yellow solid (8.2 g, 86%). LC-MS (ESI) *m/z*: 228.1 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.78 (d, *J*=5.6 Hz, 1H), 8.71 (s, 1H), 8.22-8.18 (m, 2H), 7.70 (dd, *J*=8.0, 1.6 Hz, 1H), 7.53 (d, *J*=1.6 Hz, 1H), 5.37(s, 2H).

Intermediate 2: 6H-Isochromeno[3,4-c]pyridine-8-carboxylic acid

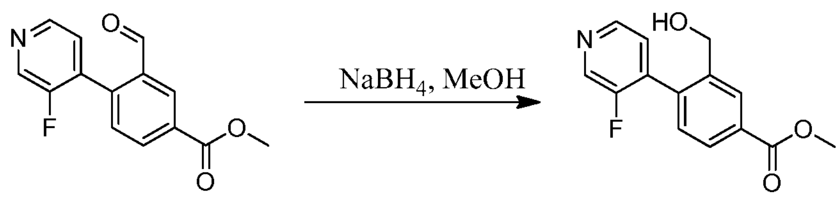


Intermediate 2a: Methyl 4-(3-fluoropyridin-4-yl)-3-formylbenzoate



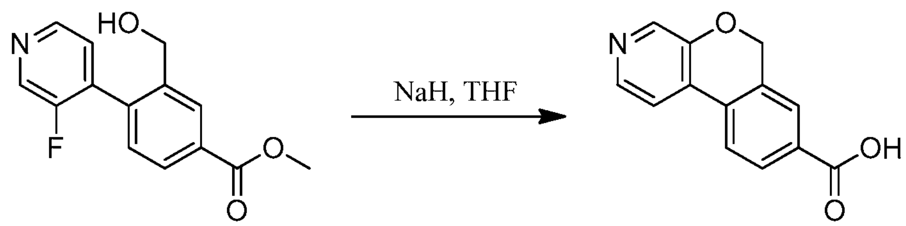
To a solution of methyl 4-bromo-3-formylbenzoate (500 mg, 2.057 mmol) in dioxane (15 mL) were added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (551 mg, 2.469 mmol), K_3PO_4 (6.17 mL, 6.17 mmol), and XPhos-G2-PreCat (81 mg, 0.103 mmol) at rt. The reaction was stirred under argon at 80 ºC for 2 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to provide Intermediate 2a as pale solid (362 mg, 68%). LCMS (ESI) *m/z*: 260.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 9.96 (d, *J*=2.4 Hz, 1H), 8.68 (d, *J*=1.5 Hz, 1H), 8.60 (d, *J*=1.3 Hz, 1H), 8.57 (dd, *J*=4.8, 0.9 Hz, 1H), 8.36 (dd, *J*=7.9, 1.8 Hz, 1H), 7.51 (d, *J*=8.1 Hz, 1H), 7.31 (dd, *J*=6.1, 5.0 Hz, 1H), 4.00 (s, 3H); ^{19}F NMR (376MHz, $CDCl_3$) δ -129.71 (s, 1F).

Intermediate 2b: Methyl 4-(3-fluoropyridin-4-yl)-3-(hydroxymethyl)benzoate



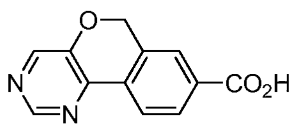
To a solution of Intermediate 2a (1.57g, 6.06 mmol) in MeOH (15 mL) was added $NaBH_4$ (0.229 g, 6.06 mmol) at 0 ºC. The reaction was stirred under argon at 0 ºC for 30 min. LCMS showed the reaction was completed. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give Intermediate 2b as clear colorless oil (0.82 g, 52%). LCMS (ESI) *m/z*: 262.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.57 (d, *J*=1.3 Hz, 1H), 8.51 (dd, *J*=4.8, 0.9 Hz, 1H), 8.33 (d, *J*=1.1 Hz, 1H), 8.07 (dd, *J*=7.9, 1.8 Hz, 1H), 7.35 (d, *J*=7.9 Hz, 1H), 7.30 (dd, *J*=6.1, 5.0 Hz, 1H), 4.60 (d, *J*=5.1 Hz, 2H), 3.97 (s, 3H), 1.98 (t, *J*=5.6 Hz, 1H).

Intermediate 2:

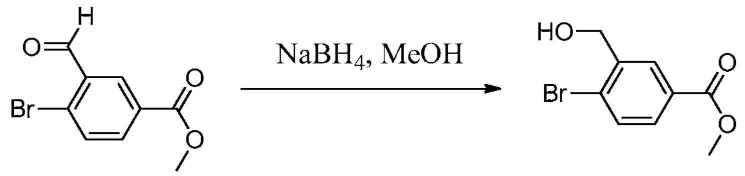


To a solution of Intermediate 2b (0.82 g, 3.14 mmol) in THF (10 mL) was added NaH (0.251 g, 6.28 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 1 hr. Then it was stirred at rt overnight. Water (5 mL) was added carefully to quench the reaction and stirred for another hour at RT. The solvent was removed. The crude product was purified by reverse phase chromatography to provide Intermediate 2 as light brown solid (770 mg, 77%). LCMS (ESI) *m/z*: 228.0 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.24 (d, *J*=5.1 Hz, 1H), 7.92 - 7.87 (m, 1H), 7.85 - 7.80 (m, 2H), 7.75 (d, *J*=0.9 Hz, 1H), 5.24 (s, 2H).

Intermediate 3: 6H-Isochromeno[3,4-c]pyridine-8-carboxylic acid

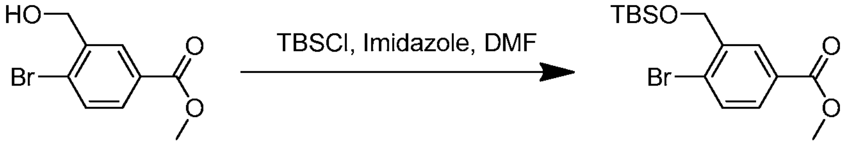


Intermediate 3a: Methyl 4-bromo-3-(hydroxymethyl)benzoate



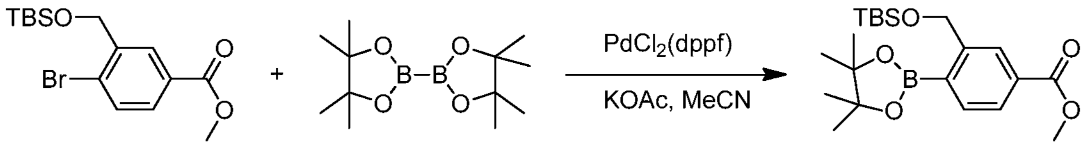
To a solution of methyl 4-bromo-3-formylbenzoate (1.53 g, 6.29 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.238 g, 6.29 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 30 min. LCMS showed the reaction was completed. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to give Intermediate 3a as clear colorless oil (1.50 g, 97%). LCMS (ESI) *m/z*: 244.9/246.9 $[M+H]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.17 (d, *J*=2.0 Hz, 1H), 7.82 (dd, *J*=8.4, 2.2 Hz, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 4.79 (s, 2H), 3.93 (s, 3H).

Intermediate 3b: Methyl 4-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)benzoate



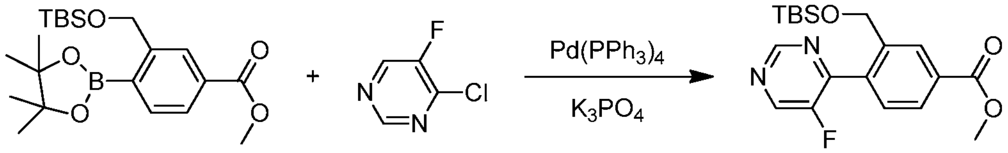
To a solution of Intermediate 3a (1.49 g, 6.08 mmol) in DMF (10 mL) were added imidazole (0.621 g, 9.12 mmol) and TBS-Cl (1.100 g, 7.30 mmol) at 0 °C. The reaction was stirred under argon at rt overnight. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give 3b (1.89 g, 87%). LCMS (ESI) *m/z*: 359.0/360.9 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.26 - 8.21 (m, 1H), 7.79 (dd, *J*=8.4, 2.2 Hz, 1H), 7.58 (d, *J*=8.1 Hz, 1H), 4.76 (s, 2H), 3.93 (s, 3H), 1.00 (s, 9H), 0.16 (s, 6H).

Intermediate 3c: Methyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate



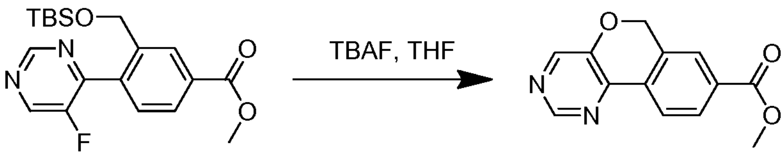
To a solution of Intermediate 3b (1.41 g, 3.92 mmol) in acetonitrile (15 mL) were added 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (1.196 g, 4.71 mmol), KOAc (0.770 g, 7.85 mmol), and $PdCl_2(dppf)$ (0.144 g, 0.196 mmol) at rt. The reaction was stirred under argon at 90 °C for 5 h. The solvent was removed. The crude product was purified by normal phase chromatography to afford Intermediate 3c as clear colorless oil (1.18 g, 74%). LCMS (ESI) *m/z*: 407.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.14 (d, *J*=0.9 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.74 - 7.68 (m, 1H), 4.91 (s, 2H), 3.81 (s, 3H), 1.24 (s, 12H), 0.86 (s, 9H), 0.00 (s, 6H).

Intermediate 3d: Methyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(5-fluoropyrimidin-4-yl)benzoate



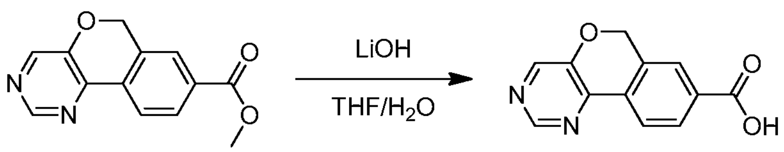
To a solution of Intermediate 3c (285 mg, 0.701 mmol) in dioxane (2 mL) were added 4-chloro-5-fluoropyrimidine (93 mg, 0.701 mmol), K_3PO_4 (447 mg, 2.104 mmol) and $Pd(Ph_3P)_4$ (81 mg, 0.070 mmol) at rt. The reaction was stirred under argon at 90 °C for 3 h. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give Intermediate 3d as clear colorless oil (225 mg, 85%). LCMS (ESI) *m/z*: 377.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 9.14 (d, *J*=2.9 Hz, 1H), 8.71 (d, *J*=2.0 Hz, 1H), 8.33 (d, *J*=1.1 Hz, 1H), 8.09 (dd, *J*=7.9, 1.8 Hz, 1H), 7.55 (dd, *J*=8.0, 1.4 Hz, 1H), 4.87 (s, 2H), 3.99 (s, 3H), 0.85 (s, 9H), 0.00 (s, 6H).

Intermediate 3e: Methyl 6H-isochromeno[4,3-d]pyrimidine-8-carboxylate



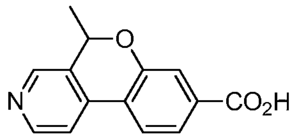
To a solution of Intermediate 3d (225 mg, 0.598 mmol) in THF (3 mL) was added TBAF (1 M in THF, 2.99 ml, 2.99 mmol) at rt. The reaction was stirred under argon at rt for 30 min. LCMS showed the reaction was completed. The solvent was removed. The crude product was purified by normal phase chromatography to afford Intermediate 3e as white solid (142 mg, 98%). LCMS (ESI) *m/z*: 243.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.44 (s, 1H), 8.33 (d, *J*=8.1 Hz, 1H), 8.14 (dd, *J*=8.0, 1.7 Hz, 1H), 7.87 (d, *J*=0.9 Hz, 1H), 5.37 (s, 2H), 3.97 (s, 3H).

Intermediate 3:

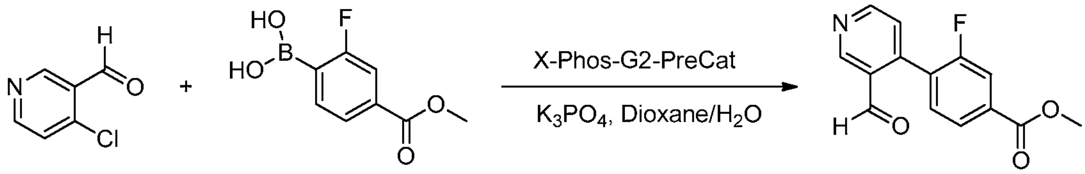


To a solution of Intermediate 3e (142 mg, 0.586 mmol) in THF (6 mL) and H_2O (2 mL) was added LiOH (70.2 mg, 2.93 mmol) at RT. The reaction was stirred under argon at rt for 2 h. The solvent was removed to give Intermediate 3 as white solid (134 mg, 100%). LCMS (ESI) *m/z*: 229.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.46 (s, 1H), 8.04 (d, *J*=8.1 Hz, 1H), 7.95 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=1.0 Hz, 1H), 5.39 (s, 2H)

Intermediate 4: 5-Methyl-5H-chromeno[3,4-c]pyridine-8-carboxylic acid, TFA salt

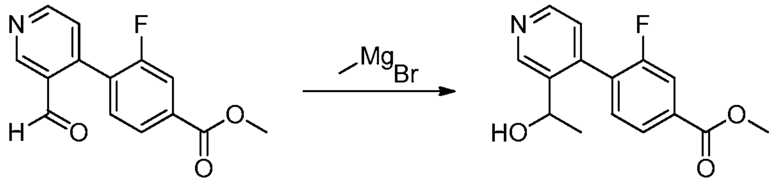


Intermediate 4a: Methyl 3-fluoro-4-(3-formylpyridin-4-yl)benzoate



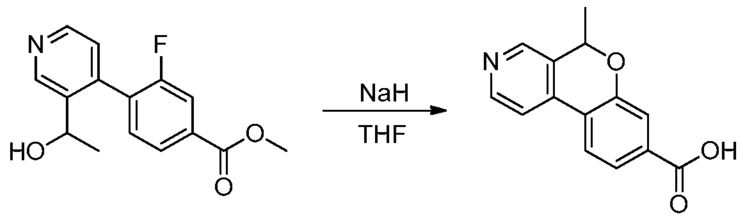
To a solution of (2-fluoro-4-(methoxycarbonyl)phenyl)boronic acid (441 mg, 2.225 mmol) in dioxane (6 mL) and H_2O (1.6 mL) were added 4-chloronicotinaldehyde (300 mg, 2.119 mmol), K_3PO_4 (990 mg, 4.66 mmol), and XPhos-G2-PreCat (66.8 mg, 0.085 mmol) at rt. The reaction was heated at 140 °C with microwave for 10 min. The reaction was diluted with EtOAc and the organic layer was separated and concentrated. Purification by normal phase chromatography gave Intermediate 4a as tan oil (320 mg, 58.2%). LC-MS (ESI) *m/z*: 260.0$[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.99 (d, *J*=2.2 Hz, 1H), 9.13 (s, 1H), 8.94 (d, *J*=5.1 Hz, 1H), 7.94 (dd, *J*=7.9, 1.5 Hz, 1H), 7.84 (dd, *J*=10.3, 1.5 Hz, 1H), 7.68 (t, *J*=7.6 Hz, 1H), 7.59 (d, *J*=5.1 Hz, 1H), 3.92 (s, 3H).

Intermediate 4b: Methyl 3-fluoro-4-(3-(1-hydroxyethyl)pyridin-4-yl)benzoate



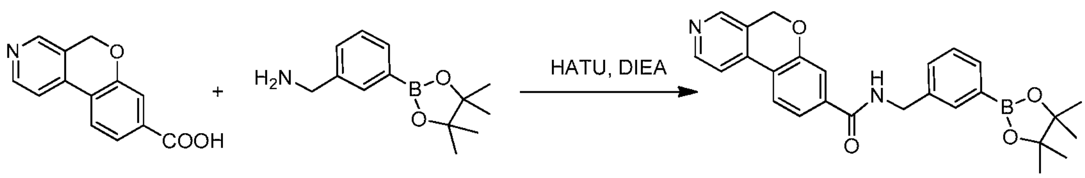
To a solution of 4a (320 mg, 1.234 mmol) in THF (10 mL) was added methyl magnesium bromide (0.970 mL, 1.358 mmol, 1.4 M in toluene/THF) dropwise over 30 min. The resulted mixture was stirred at rt for 20 min. The reaction was cooled to 0 °C and quenched with sat. NH_4Cl solution. The reaction mixture was extracted with EtOAc. The organic layer was concentrated and then purified by normal phase chromatography to give Intermediate 4b as oil (258 mg, 68.3%). LC-MS (ESI) *m/z*: 276.0[M+H]$^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.48 (d, *J*=5.1 Hz, 1H), 7.90 (dd, *J*=7.9, 1.3 Hz, 1H), 7.81 (dd, *J*=9.9, 1.3 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 7.08 (d, *J*=5.1 Hz, 1H), 4.81 (q, *J*=5.9 Hz, 1H), 3.95 (s, 3H), 1.39 (d, *J*=6.2 Hz, 3H).

Intermediate 4:



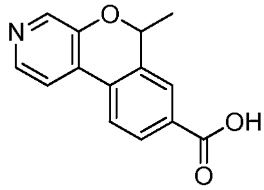
To a solution of Intermediate 4b (258 mg, 0.937 mmol) in THF (5 mL) was added NaH (75.0 mg, 1.874 mmol) at 0 ºC. The reaction was stirred under argon at 0 ºC for 1 h and then at rt for 2 h. Water was added carefully to quench the reaction. The pH was adjusted to ~8 with 4 N HCl. The solvent was removed. Purification by reverse phase chromatography provided Intermediate 4 as white solid (195 mg, 55.6%). LC-MS (ESI) *m/z*: 242.0 M+H]$^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.91 - 8.63 (m, 1H), 8.38 (d, *J*=6.2 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.81 (dd, *J*=8.3, 1.7 Hz, 1H), 7.67 (d, *J*=1.5 Hz, 1H), 5.60 (q, *J*=6.5 Hz, 1H), 1.74 (d, *J*=6.6 Hz, 3H).

Intermediate 5: N-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide

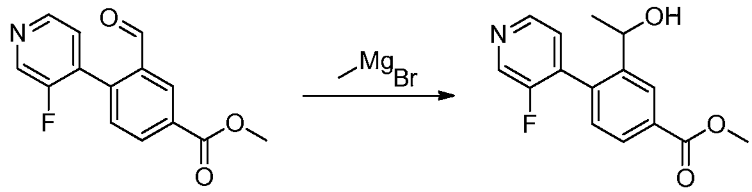


To a suspension of Intermediate 1 (792 mg, 3.49 mmol) in DMF (12 mL) were added (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine,HCl salt (940 mg, 3.49 mmol), DIEA (2.436 mL, 13.95 mmol) and HATU (1856 mg, 4.88 mmol) at rt. The reaction was stirred under argon at rt overnight. The reaction was diluted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. Purification by normal phase chromatography gave Intermediate 5 as white solid (910 mg, 41%). LC-MS (ESI) *m/z*: 443.2[M+H]$^+$.

Intermediate 6: 6-Methyl-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

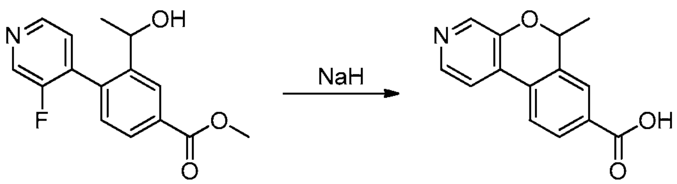


Intermediate 6a: Methyl 4-(3-fluoropyridin-4-yl)-3-(1-hydroxyethyl)benzoate



To a solution of Intermediate 2a (368 mg, 1.420 mmol) in THF (14 mL) was added methyl magnesium bromide (1.014 mL, 1.420 mmol, 1.4 M in toluene/THF) dropwise over 40 min. The resulted reaction mixture was stirred at rt for 30 min. It was then cooled to 0 °C and quenched with sat. NH_4Cl solution. The reaction mixture was extracted with EtOAc (3x). Organic phase was dried over Na_2SO_4 and concentrated. Purification by normal phase chromatography gave Intermediate 6a as oil (280 mg, 72%). LC-MS (ESI) *m/z*: 276.0$[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.57 (d, *J*=1.1 Hz, 1H), 8.49 (d, *J*=4.8 Hz, 1H), 8.40 (d, *J*=1.8 Hz, 1H), 8.00 (dd, *J*=8.1, 1.8 Hz, 1H), 7.42 (dd, *J*=6.2, 5.3 Hz, 1H), 7.32 (d, *J*=8.1 Hz, 1H), 4.72 (q, *J*=6.2 Hz, 1H), 3.95 (s, 3H), 1.31 (d, *J*=6.4 Hz, 3H).

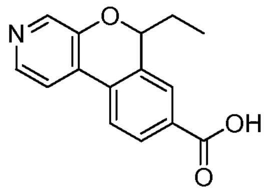
Intermediate 6:



To a solution of methyl 4-(3-fluoropyridin-4-yl)-3-(1-hydroxyethyl)benzoate (280 mg, 1.017 mmol) in THF (5 mL) was added NaH (60%, 102 mg, 2.54 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 20 min and then at rt overnight. Water was added carefully to quench the reaction and then 4 N HCl was added to adjust the pH to

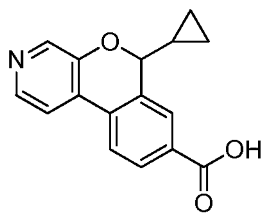
~8. The solvent was removed. Purification by reverse phase chromatography provided Intermediate 6 as white solid (195 mg, 51%). LC-MS (ESI) *m/z*: 242.0$[M+H]^+$.

Intermediate 7: 6-Ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid



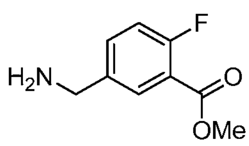
Intermediate 7 was prepared by following a similar procedure as described in Intermediate 6 by replacing methyl magnesium bromide with ethyl magnesium bromide in step 6a. LC-MS (ESI) *m/z*: 256.0$[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.36 (d, *J*=5.1 Hz, 1H), 8.15 (d, *J*=8.1 Hz, 1H), 8.07 - 7.98 (m, 2H), 7.91 (s, 1H), 5.47 (dd, *J*=8.6, 4.8 Hz, 1H), 1.91 - 1.61 (m, 2H), 0.98 (t, *J*=7.4 Hz, 3H).

Intermediate 8: 6-Cyclopropyl-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

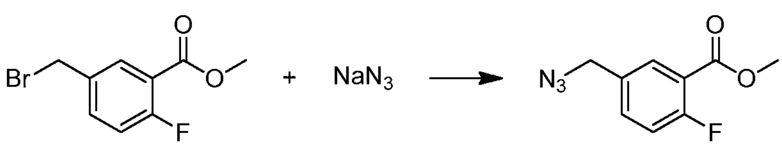


Intermediate 8 was prepared by following a similar procedure as described in Intermediate 6 by replacing methyl magnesium bromide with cyclopropyl magnesium bromide in step 6a. LC-MS (ESI) *m/z*: 268.0$[M+H]^+$.

Intermediate 9: Methyl 5-(aminomethyl)-2-fluorobenzoate

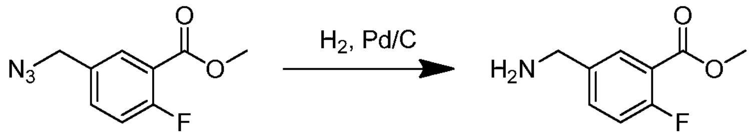


Intermediate 9a: Methyl 5-(azidomethyl)-2-fluorobenzoate



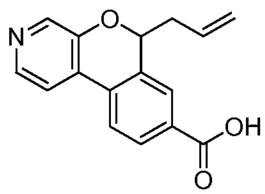
To a solution of methyl 5-(bromomethyl)-2-fluorobenzoate (500 mg, 2.024 mmol) in DMF (4 mL) was added NaN_3 (395 mg, 6.07 mmol) at rt. The reaction was stirred under argon at 60 °C overnight. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. Purification by normal phase chromatography afforded Intermediate 9a as colorless oil (415 mg, 98%). LC-MS (ESI) *m/z*: 210.0$[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.91 (dd, *J*=6.8, 2.2 Hz, 1H), 7.49 (ddd, *J*=8.5, 4.5, 2.4 Hz, 1H), 7.17 (dd, *J*=10.3, 8.6 Hz, 1H), 4.38 (s, 2H), 3.95 (s, 3H).

Intermediate 9:



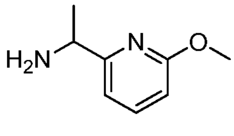
To a solution of Intermediate 9a (415 mg, 1.984 mmol) in MeOH (10 mL) was added catalytic amount of 5% Pd/C. The reaction was stirred under a hydrogen balloon at rt for 5 h. The catalyst was filtered off and the solvent was removed to afford Intermediate 9 as white solid (342 mg, 94%). LC-MS (ESI) *m/z*: 184.0$[M+H]^+$.

Intermediate 10: 6-Allyl-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

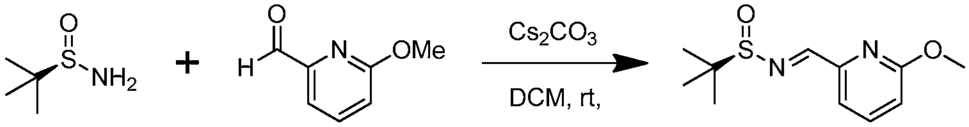


Intermediate 10 was prepared by following a similar procedure as described in Intermediate 6 by replacing methyl magnesium bromide with allyl magnesium bromide in step 6a. LC-MS (ESI) *m/z*: 268.0$[M+H]^+$.

Intermediate 11: 1-(6-Methoxypyridin-2-yl)ethanamine HCl salt

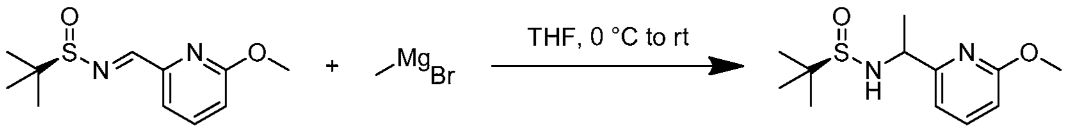


Intermediate 11A: (R)-N-((6-Methoxypyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide



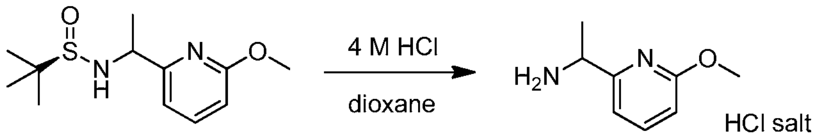
To a stirred suspension of (R)-2-methylpropane-2-sulfinamide (1.0 g, 8.3 mmol) and Cs_2CO_3 (4.0 g, 12 mmol) in DCM (15 mL), was added a solution of 6-methoxypicolinaldehyde in DCM (1.1 mL, 9.1 mmol, in 3 mL DCM) dropwise. The solution was then stirred at rt for 5 h. The solid was filtered off, and the solvent was removed. The crude product was purified by normal phase chromatography to afford Intermediate 11A (1.9 g, 96%) as a clear colorless oil. LC-MS (ESI) *m/z*: 241.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.72 - 7.58 (m, 2H), 6.85 (dd, *J* = 7.9, 1.1 Hz, 1H), 3.99 (s, 3H), 1.29 (s, 9H).

Intermediate 11B: (R)-N-(1-(6-Methoxypyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide



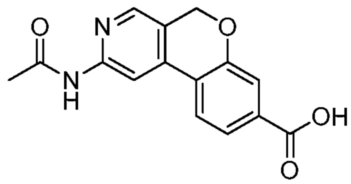
To a solution of Intermediate 11A (0.65 g, 2.7 mmol) in THF (6 mL), was added methylmagnesium bromide (1.4 M in toluene/THF, 2.9 mL, 4.1 mmol) at 0 ºC. The reaction was stirred under argon from 0 ºC to rt for 2 h. It was cooled to 0 ºC, and NH_4Cl solution was carefully added. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 11B (0.58 g, 83%) as a mixture of two diastereomers as a clear colorless oil. LC-MS (ESI) *m/z*: 257.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.53 (dt, *J* = 8.3, 7.1 Hz, 2H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 2H), 4.83 (br. d, *J* = 4.6 Hz, NH) 4.59 - 4.44 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 6H), 1.21 (s, 6H).

Intermediate 11:

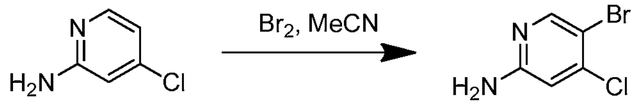


To a solution of Intermediate 11B (0.58, 2.3 mmol) in MeOH (5 mL), was added HCl (4 M in dioxane, 2.8 ml, 11 mmol) at rt. The reaction was stirred under argon at rt for 2 h. The solvent was removed to give Intermediate 11 (0.52 g, 100%) as white solid. LC-MS (ESI) *m/z*: 153.0 $[M+H]^+$.

Intermediate 12: 2-Acetamido-5H-chromeno[3,4-c]pyridine-8-carboxylic acid

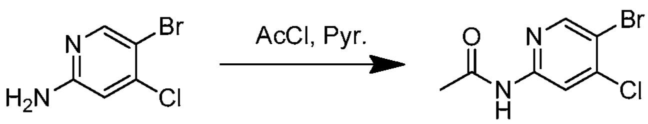


Intermediate 12A: 5-Bromo-4-chloropyridin-2-amine



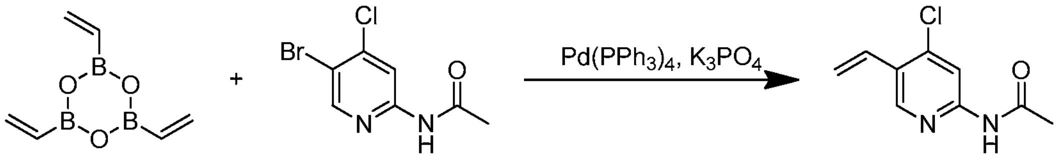
To a solution of 4-chloropyridin-2-amine (5.0 g, 39 mmol) in MeCN (200 mL) at 0 °C was added Br_2 (2.2 mL, 43 mmol) in portions over a period of 30 min. The reaction was warmed to rt and stirred overnight. The solid was filtered, washed with hexane (3x), and dried to afford Intermediate 12A (9.1 g, 81%) as an off-white solid. LC-MS (ESI) *m/z*: 206.9/208.9 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.02 (s, 1H).

Intermediate 12B: N-(5-Bromo-4-chloropyridin-2-yl)acetamide



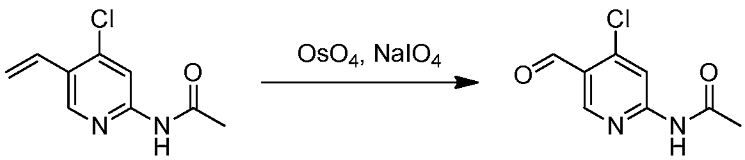
To a solution of Intermediate 12A (5.0 g, 17 mmol) in pyridine (40 mL) at 0 °C, was added acetyl chloride (3.5 mL, 49 mmol) dropwise over 30 min. The reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C, and it was added acetyl chloride (6.2 mL, 87 mmol) dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. It was diluted with DCM, and the solid was filtered off. The filtrate was concentrated. The residue was dissolved in EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 12B (3.6 g, 82%) as an off-white solid. LC-MS (ESI) *m/z*: 248.9/250.9 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.40 - 8.28 (m, 2H), 2.23 (s, 3H).

Intermediate 12C: N-(4-Chloro-5-vinylpyridin-2-yl)acetamide



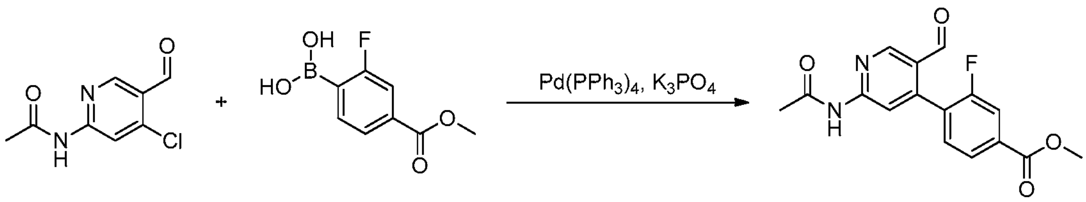
To a solution of Intermediate 12B (1.4 g, 5.4 mmol) in dioxane (12 mL) and water (2.2 mL), were added 2,4,6-trivinyl-1,3,5,2,4,6-trioxatriborinane pyridine complex (0.79 g, 4.9 mmol) and K_3PO_4 (2.3 g, 11 mmol). The reaction mixture was bubbled with argon for 10 min. Then $Pd(PPh_3)_4$ (0.44 g, 0.38 mmol) was added, and the mixture was again bubbled with argon for 5 min. The reaction was heated at 150 °C in a microwave reactor for 5 min. It was filtered through CELITE® and was washed with EtOAc (50 ml). The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 12C (0.73 g, 69%) as a yellowish solid. LC-MS (ESI) *m/z*: 197.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.29 (s, 1H), 7.95 (br. s., 1H), 6.94 (dd, J = 17.7, 11.6 Hz, 1H), 5.77 (dd, J = 17.6, 0.7 Hz, 1H), 5.42 (dd, J = 11.2, 0.9 Hz, 1H), 2.22 (s, 3H).

Intermediate 12D: N-(4-Chloro-5-formylpyridin-2-yl)acetamide



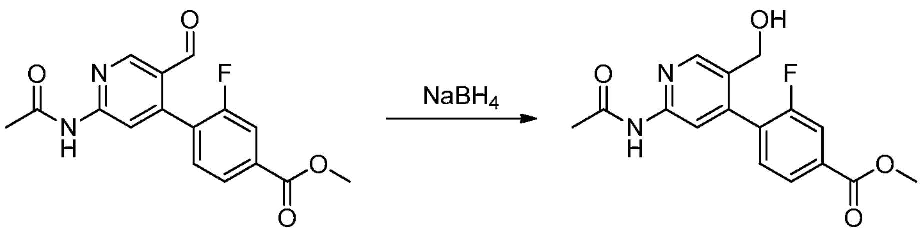
To a solution of Intermediate 12C (1.5 g, 7.8 mmol) and 2,6-lutidine (1.8 mL, 16 mmol) in dioxane (25 mL) and water (1.7 mL), was added sodium periodate (5.0 g, 23 mmol) at 0 °C, followed by the addition of osmium tetroxide (2.5% in *t*-butanol,2.4 mL, 0.21 mmol) over 10 min. The reaction was allowed to warm to rt and stirred overnight. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 12D (1.0 g, 66%) as a white solid. LC-MS (ESI) *m/z*: 199.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.76 (s, 1H), 8.39 (s, 1H), 8.19 (br. s., 1H), 2.27 (s, 3H).

Intermediate 12E: Methyl 4-(2-acetamido-5-formylpyridin-4-yl)-3-fluorobenzoate



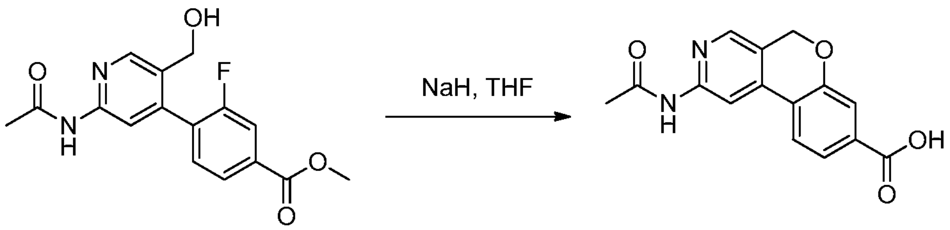
Intermediate 12D (0.92 g, 4.6 mmol), (2-fluoro-4-(methoxycarbonyl)phenyl) boronic acid (1.7 g, 8.3 mmol), K_3PO_4 (2.3 g, 11 mmol), dioxane (12 mL) and water (2 mL) were placed in a 20 mL microwave vial. The mixture was bubbled with argon for 10 min. $Pd(PPh_3)_4$ (0.32 g, 0.28 mmol) was added, and the mixture was again bubbled with argon for 7 min. The reaction was heated at 145 °C in a microwave reactor for 7 min. The reaction mixture was filtered through CELITE®, and was washed with EtOAc (55 ml). The solvent was removed under reduced pressure. The crude product was purified by normal phase chromatography to afford Intermediate 12E (1.4 g, 86%) as an off-white solid. LC-MS (ESI) *m/z*: 317.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 9.87 (d, *J* = 2.9 Hz, 1H), 8.89 (s, 1H), 8.28 (s, 1H), 8.24 (br. s., 1H), 7.98 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.86 (dd, *J* = 10.0, 1.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 3.99 (s, 3H), 2.28 (s, 3H).

Intermediate 12F: Methyl 4-(2-acetamido-5-(hydroxymethyl)pyridin-4-yl)-3-fluorobenzoate



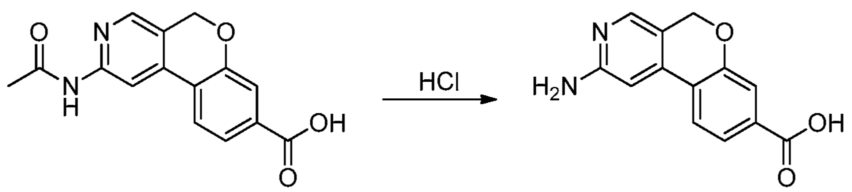
A suspension of Intermediate 12E (430 mg, 1.4 mmol) in ethanol (12 mL) was cooled to 0 °C. To the reaction was added sodium borohydride (51 mg, 1.4 mmol) portionwise. The reaction mixture was stirred for 20 min at 0 °C. Excess ethanol was removed under reduced pressure. Water was added to the mixture. The solid was filtered, washed with water, and dried to afford Intermediate 12F (380 mg, 87%) as a solid. LC-MS (ESI) *m/z*: 319.0 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.46 (s, 1H), 7.99 (s, 1H), 7.90 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.83 (dd, *J* = 10.3, 1.3 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 5.16 (br. s., 1H), 4.32 (d, *J* = 3.1 Hz, 2H), 3.91 (s, 3H), 2.10 (s, 3H).

Intermediate 12:



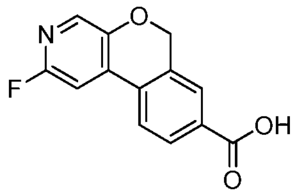
To a cooled a solution (-10 °C) of Intermediate 12F (370 mg, 1.2 mmol) in THF (10 mL) was added NaH (93 mg, 2.3 mmol) portionwise. The reaction was stirred at -10 °C for 50 min, then it was warmed to rt and stirred overnight. The reaction mixture was cooled to 0 °C, and EtOAc was added. The reaction was quenched with aq. NH_4Cl. The two layers were separated. The aqueous layer was concentrated. The crude product was purified by reverse phase chromatography to afford Intermediate 12 (15 mg, 4.5%) as an off-white solid. LC-MS (ESI) *m/z*: 285.0 $[M+H]^+$.

Intermediate 13: 2-Amino-5H-chromeno[3,4-c]pyridine-8-carboxylic acid

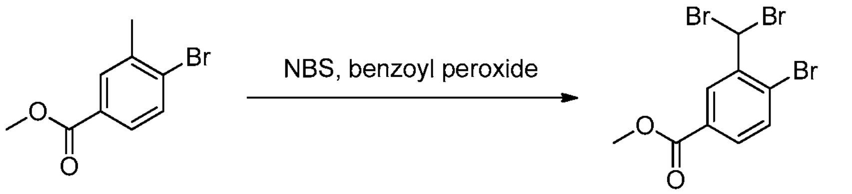


A suspension of Intermediate 12 (8.0 mg, 0.028 mmol) in concentrated HCl (160 µl, 2.0 mmol) in a sealed vial was heated at 100 °C for 70 min. The solvent was removed, and the residue was dried to afford Intermediate 13 (7.0 mg, 90%) as a yellow solid. LC-MS (ESI) *m/z*: 243.0 $[M+H]^+$.

Intermediate 14: 2-Fluoro-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

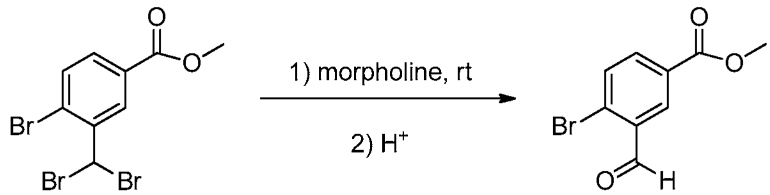


Intermediate 14A: Methyl 4-bromo-3-(dibromomethyl)benzoate



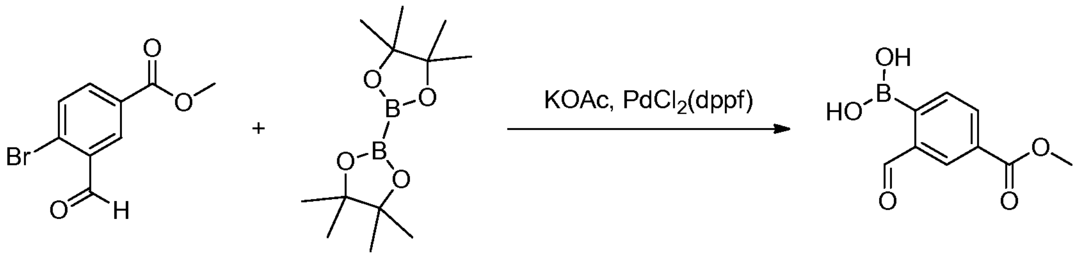
To a solution of methyl 4-bromo-3-methylbenzoate (5.8 g, 25 mmol) in CCl_4 (70 mL), was added NBS (15 g, 84 mmol), followed by addition of benzoyl peroxide (0.61 g, 2.5 mmol). The mixture was heated at reflux for 8 h. The mixture was cooled to rt, and was allowed to stir overnight. The solvent was removed under reduced pressure. Purification by normal phase chromatography afforded Intermediate 14A (9.7 g, 89%) as an off-white solid. LC-MS (ESI) *m/z*: 386.8/388.8 $[M+H]^+$.; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.0 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 3.97 (s, 3H).

Intermediate 14B: Methyl 4-bromo-3-formylbenzoate



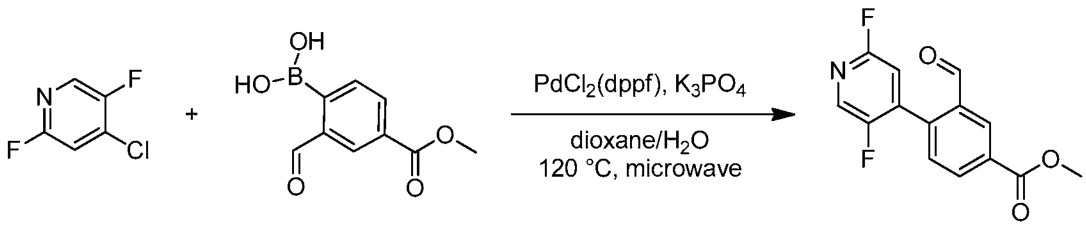
Intermediate 14A (9.7 g, 23 mmol) was suspended in morpholine (22 ml, 170 mmol), and the mixture was stirred at rt for 2 days. The reaction mixture was diluted with EtOAc, and was stirred at rt for 30 min. The solid was removed by filtration and washed with EtOAc. The filtrate was transferred to a separatory funnel and was washed with 5% aq. citric acid (3x), water and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 14B (5.6 g, 92%) as a white solid. LC-MS (ESI) *m/z*: 243.0/245.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.54 (d, *J* = 2.2 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H).

Intermediate 14C: (2-Formyl-4-(methoxycarbonyl)phenyl)boronic acid



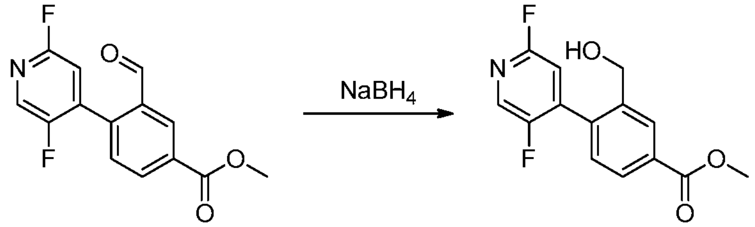
A mixture of Intermediate 12B (2.3 g, 9.5 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (3.4 g, 13 mmol), $PdCl_2$(dppf).CH_2Cl_2 adduct (0.69 g, 0.95 mmol) and potassium acetate (2.8 g, 28 mmol) in dioxane (30 mL) was heated in an oil-bath at 95 °C for 2 h. The reaction was diluted with EtOAc, filtered through CELITE®. The solution was concentrated, and the crude product was purified by normal phase chromatography to afford Intermediate 14C (3.0 g, 91%) as a brown oil. LC-MS (ESI) *m/z*: 191.0 $[M+H-18]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.43 (d, *J* = 1.3 Hz, 1H), 8.35 (br. s., 2H), 8.16 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 3.91 (s, 3H).

Intermediate 14D: Methyl 4-(2,5-difluoropyridin-4-yl)-3-formylbenzoate



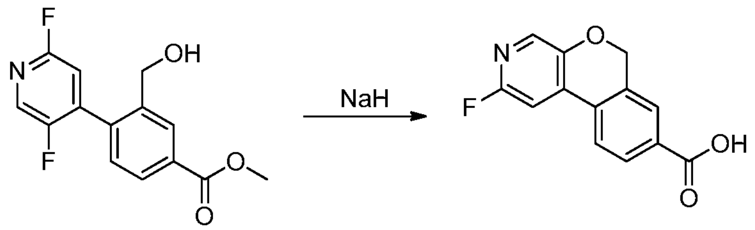
To a microwave vial containing solution of 4-chloro-2,5-difluoropyridine (0.40 g, 2.7 mmol) in dioxane (7 mL), were added Intermediate 14C (1100 mg, 3.2 mmol), K_3PO_4 (1.30 g, 6.2 mmol), water (1.4 mL) and $PdCl_2$(dppf)CH_2Cl_2 adduct (0.17 g, 0.21 mmol) at rt. The mixture was purged with nitrogen, and then was heated in a microwave reactor at 120 °C for 6 min. The reaction mixture was cooled to rt. The aqueous layer was removed with a pipette. The organic phase was concentrated and was purified by normal phase chromatography to afford Intermediate 14D (350 mg, 47%) as a tan solid. LC-MS (ESI) *m/z*: 278.0 $[M+H]^+$.

Intermediate 14E: Methyl 4-(2,5-difluoropyridin-4-yl)-3-(hydroxymethyl)benzoate



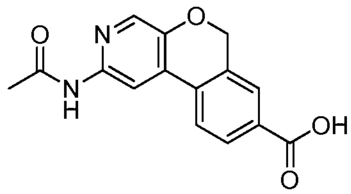
A suspension of Intermediate 14D (390 mg, 1.4 mmol) in ethanol (10 mL) was cooled to 0 ºC. Then sodium borohydride (64 mg, 1.7 mmol) was added portionwise. The reaction mixture was stirred for 20 min at 0 ºC. It was concentrated. The residue was dissolved in EtOAc (30 mL), and was washed with water and brine, dried over sodium sulfate, filtered and concentrated to afford Intermediate 14E (390 mg, 95%) as an oil. LC-MS (ESI) *m/z*: 280.0 [M+H]+;^{1}H NMR (400MHz, CD3OD) δ 8.31 (s, 1H), 8.20 (s, 1H), 8.05 (dd, J = 7.9, 1.5 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 4.6, 2.6 Hz, 1H), 4.53 (s, 2H), 3.96 (s, 3H).

Intermediate 14:

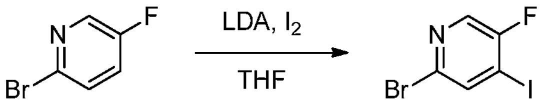


To a solution of Intermediate 14E (390 mg, 1.4 mmol) in THF (7 mL) was added NaH (180 mg, 4.6 mmol) at rt portionwise. The reaction mixture was stirred under argon at rt overnight. Water was added carefully to quench the reaction. Aqueous HCl (4 N) was added to adjust the pH to ~8. The solvent was removed. The residue was dissolved in MeOH-DMSO, filtered and purified by reverse phase chromatography to afford Intermediate 14 (50 mg, 6.0%) as an off-white solid. LC-MS (ESI) *m/z*: 246.0 $[M+H]^{+}$.

Intermediate 15: 2-Acetamido-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

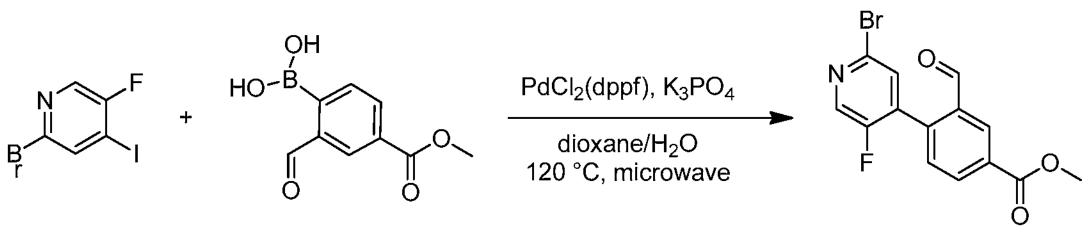


Intermediate 15A: 2-Bromo-5-fluoro-4-iodopyridine



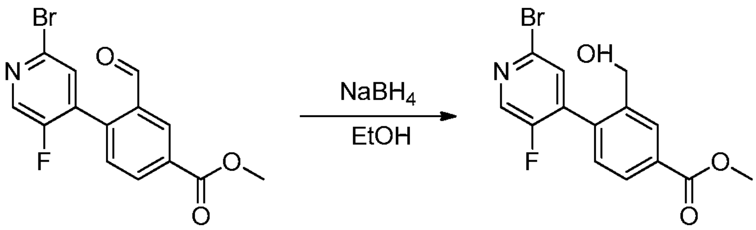
A solution of 2-bromo-5-fluoropyridine (2.0 g, 11 mmol) in THF (30 mL) was cooled to -78 °C. LDA (2 M in THF, 6.3 mL, 13 mmol) was added slowly, and the mixture was stirred for 20 min. To this mixture was added a solution of iodine (3.5 g, 14 mmol) in THF (7 mL), dropwise. The reaction mixture was warmed up and stirred at 0 °C for 30 min. It was quenched with 10% aq. $Na_2S_2O_3$ solution and was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford Intermediate 15A (2.5 g, 72%) as a brown solid. LC-MS (ESI) *m/z*: 301.8/303.8 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92 (d, *J* = 4.4 Hz, 1H).

Intermediate 15B: Methyl 4-(2-bromo-5-fluoropyridin-4-yl)-3-formylbenzoate



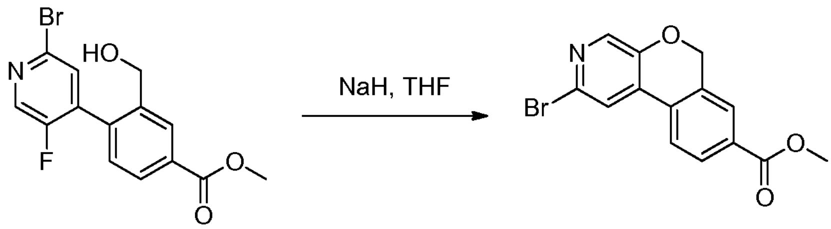
To a microwave vial containing a solution of Intermediate 15A (1.10 g, 3.3 mmol) in dioxane (10 mL), were added Intermediate 14C (0.90 g, 3.9 mmol), K_3PO_4 (1.60 g, 7.5 mmol), water (1.7 mL) and $PdCl_2(dppf)$ CH_2Cl_2 adduct (0.21 g, 0.26 mmol). The mixture was purged with nitrogen, and then was heated with microwave at 120 °C for 5 min. The organic phase was separated and concentrated. Purification by normal phase chromatography afforded Intermediate 15B (0.62 g, 56%) as an off-white solid. LC-MS (ESI) *m/z*: 337.9/339.9 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 10.00 (d, *J* = 2.2 Hz, 1H), 8.67 (d, *J* = 1.8 Hz, 1H), 8.43 - 8.28 (m, 2H), 7.54 - 7.41 (m, 2H), 4.02 (s, 3H).

Intermediate 15C: Methyl 4-(2-bromo-5-fluoropyridin-4-yl)-3-(hydroxymethyl)benzoate



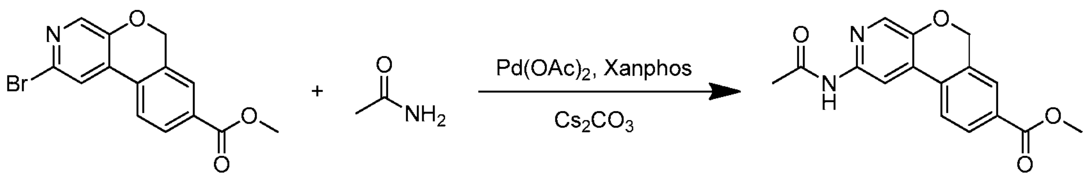
To a suspension of Intermediate 15B (610 mg, 1.8 mmol) in ethanol (10 mL) at 0 °C, was added Sodium borohydride (69 mg, 1.8 mmol), portionwise. The reaction mixture was stirred at 0 °C for 20 min, and then was concentrated. The residue was dissolved in EtOAc, washed with water and brine, dried over sodium sulfate, filtered and concentrated to afford Intermediate 15C (610 mg, 67%) as a foam. LC-MS (ESI) *m/z*: 340.0/342.0 $[M+H]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.24 (s, 1H), 8.03 - 7.96 (m, 1H), 7.42 (d, *J* = 5.5 Hz, 1H), 8.25-7.20 (m, 1H), 4.54 (d, *J* = 4.2 Hz, 2H), 3.93 - 3.87 (s, 3H).

Intermediate 15D: Methyl 2-bromo-6H-isochromeno[3,4-c]pyridine-8-carboxylate



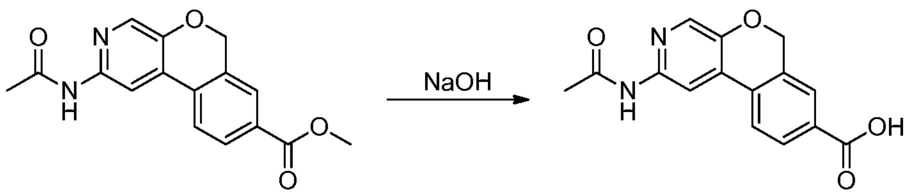
To a solution of Intermediate 15C (550 mg, 1.6 mmol) in THF (10 mL) at -10 °C, was added NaH (110 mg, 2.8 mmol), portionwise. The reaction mixture was stirred at -10 °C for 50 min. It was quenched with aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and purified by normal phase chromatography to afford Intermediate 15D (220 mg, 43%) as an off-white solid. LC-MS (ESI) *m/z*: 319.9/321.9 $[M+H+MeOH]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.09 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.80 - 7.74 (m, 2H), 5.24 (s, 2H), 3.96 (s, 3H).

Intermediate 15E: Methyl 2-acetamido-6H-isochromeno[3,4-c]pyridine-8-carboxylate



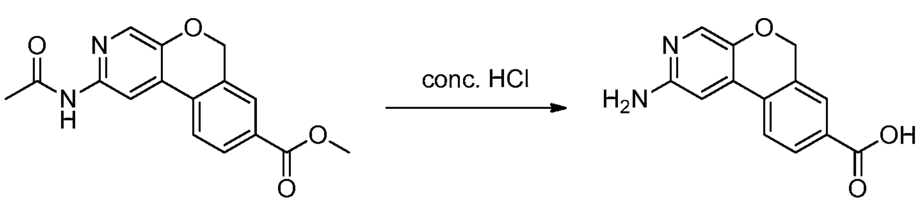
Intermediate 15D (22 mg, 0.70 mmol), Xantphos (41 mg, 0.070 mmol), $Pd(OAc)_2$ (7.9 mg, 0.035 mmol),Cs_2CO_3 (680 mg, 2.1 mmol), 1,4-dioxane (4 mL), and acetamide (62 mg, 1.1 mmol) were placed in a sealed vial. The mixture was degassed by flushing with argon for 20 min. It was heated at 70 ºC for 4.5 h. The mixture was cooled, and was water (8 mL) added. After stirring for 10 min, the resultant precipitate was filtered, washed with ether, and suction-dried to afford Intermediate 15E (210 mg, 90%) as a tan solid. LC-MS (ESI) *m/z*: 299.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.51 (s, 1H), 8.11 (s, 1H), 8.08 - 8.02 (m, 1H), 7.95 (d, *J* = 1.3 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 5.28 (s, 2H), 3.88 (s, 3H), 2.10 (s, 3H).

Intermediate 15: 2-Acetamido-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid



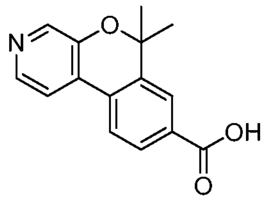
To a suspension of Intermediate 15E (8.7 mg, 0.020 mmol) in EtOH (1 mL), was added NaOH (1 N, 0.16 mL, 0.16 mmol) at rt. The reaction was stirred under argon at rt for 90 min, then HCl (3.7 N, 0.039 mL, 0.14 mmol) was added to adjust the pH to ~8. It was diluted with MeOH. The solid was collected by filtration and dried to afford Intermediate 15 (5.0 mg, 88%). LC-MS (ESI) *m/z*: 285.0 $[M+H]^+$.

Intermediate 16: 2-Amino-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

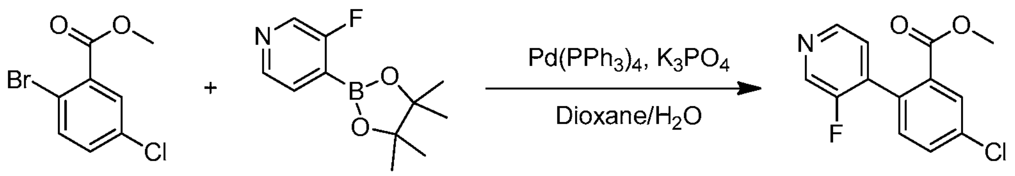


A suspension of Intermediate 15 (180 mg, 0.62 mmol) in concentrated HCl (23 µl, 28 mmol) in a sealed vial was heated 100 ºC for 30 min. The reaction mixture was cooled to rt. It was diluted with water, and the solid was collected by filtration. The solid was washed with water and suction-dried to afford Intermediate 16 (130 mg, 77%) as a yellowish solid. LC-MS (ESI) *m/z*: 243.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.12 - 8.07 (m, 1H), 8.03 - 7.95 (m, 2H), 7.89 (s, 1H), 7.48 (s, 1H), 5.28 (s, 2H).

Intermediate 17: 6,6-Dimethyl-6H-isochromeno[3,4-c]pyridine-8-carboxylic acid

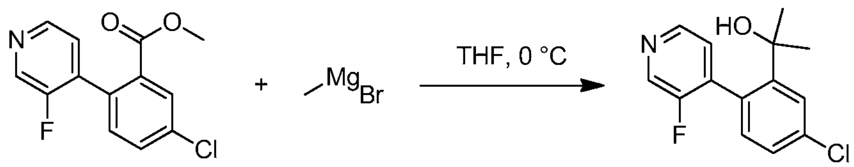


Intermediate 17A: Methyl 5-chloro-2-(3-fluoropyridin-4-yl)benzoate



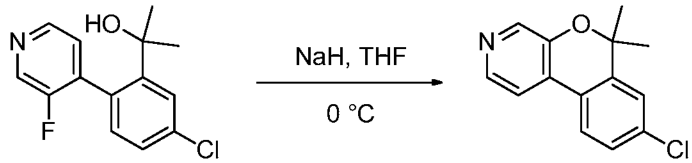
To a solution of methyl 2-bromo-5-chlorobenzoate (1.15g, 4.61 mmol) in dioxane (2 mL), were added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.234 g, 5.53 mmol), K_3PO_4 (2.446 g, 11.52 mmol) and $Pd(Ph_3P)_4$ (0.266 g, 0.230 mmol) at rt. The reaction was stirred under argon at 80 °C for 2 h. The reaction was cooled to rt. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to afford Intermediate 17A as a clear colorless oil (0.50 g, 41%). LC-MS (ESI) *m/z*: 266.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.53 - 8.44 (m, 2H), 8.04 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 8.1, 2.2 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.22 (dd, J = 6.3, 5.0 Hz, 1H), 3.74 (s, 3H).

Intermediate 17B : 2-(5-Chloro-2-(3-fluoropyridin-4-yl)phenyl)propan-2-ol



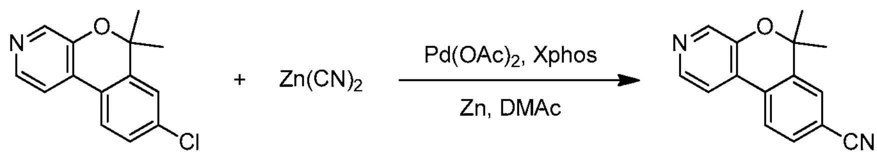
To a solution of Intermediate 17A (0.36 g, 1.4 mmol) in THF (10 mL), was added methylmagnesium bromide (3 M in ether, 1.0 mL, 3.0 mmol) at 0 °C. The reaction was stirred under argon at 0 ºC for 2 h. Aq. NH_4Cl was added to quench the reaction. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give Intermediate 17B as a white solid (259 mg, 72%). LC-MS (ESI) *m/z*: 266.0/268.0[M+H]$^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.36 (d, *J* = 4.8 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.19 (dd, *J* = 6.2, 5.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 2.03 (s, 1H), 1.53 (s, 3H), 1.46 (s, 3H).

Intermediate 17C: 8-Chloro-6,6-dimethyl-6H-isochromeno[3,4-c]pyridine



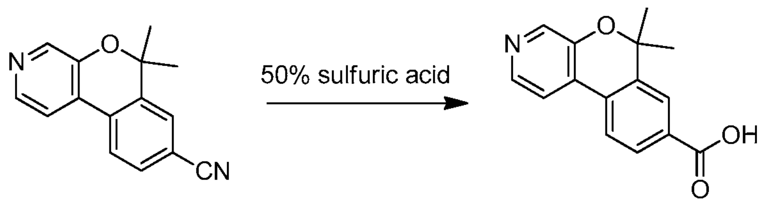
To a solution of Intermediate 17B (200 mg, 0.75 mmol) in THF (3 mL), was added NaH (90 mg, 2.3 mmol) at 0 ºC. The reaction was stirred under argon from 0 ºC to rt overnight. The reaction was quenched with NH_4Cl solution. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography to give Intermediate 17C as a white solid (170 mg, 92%). LC-MS (ESI) *m/z*: 246.1 [M+H]$^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.26 (d, *J* = 1.8 Hz, 1H), 1.65 (s, 6H).

Intermediate 17D: 6,6-Dimethyl-6H-isochromeno[3,4-c]pyridine-8-carbonitrile



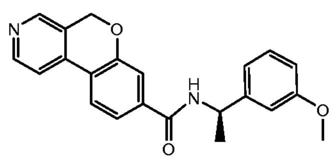
To a solution of Intermediate 17C (170 mg, 0.69 mmol) in DMAc (8 mL), were added $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), XPhos (33 mg, 0.069 mmol), zinc powder (4.5 mg, 0.069 mmol), one drop of sulfuric acid and dicyanozinc (81 mg, 0.69 mmol) at rt. The reaction mixture was purged with argon before heated under argon at 120 ºC for 5 h. The reaction was cooled to rt and then filtered. The crude product was purified by reverse phase chromatography to afford Intermediate 17D as a white solid (185 mg, 76%). LC-MS (ESI) *m/z*: 237.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3/CD_3OD$ mixture) δ 8.27 (s, 1H), 8.23 (d, J = 5.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 5.3 Hz, 1H), 7.66 (dd, J = 7.9, 1.5 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 1.63 (d, *J* = 3.5 Hz, 6H).

Intermediate 17:



A solution of Intermediate 17D (100 mg, 0.42 mmol) in 50% H_2SO_4 solution was heated in a microwave reactor at 160 °C for 15 min. The reaction was diluted with water. The aqueous solution was purified by reverse phase chromatography to give Intermediate 17 as a white solid (92 mg, 85%). LC-MS (ESI) *m/z*: 256.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.34 (d, *J* = 5.3 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.05 - 7.98 (m, 2H), 7.95 (d, *J* = 1.3 Hz, 1H), 1.67 (s, 6H).

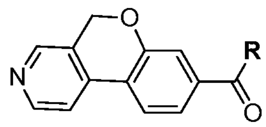
Example I-1: (R)-N-(1-(3-Methoxyphenyl)ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide

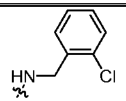
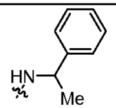


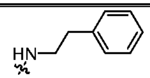
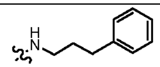
To a solution of Intermediate 1 (33 mg, 0.145 mmol) in DMF (1 mL) were added (R)-1-(3-methoxyphenyl)ethanamine (26.4 mg, 0.174 mmol), DIEA (0.178 mL, 1.017 mmol), and HATU (94 mg, 0.247 mmol) at RT. The reaction was stirred under argon at rt overnight. Purification by reverse phase chromatography afforded Example I-1 as white solid (25.2 mg, 47%). LC-MS (ESI) *m/z*: 361.1$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 8.86 (d, *J*=8.0 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.86 (d, *J*=4.7 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.54 (s, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 6.96 (br. s., 2H), 6.80 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 5.13 (quin, *J*=6.9 Hz, 1H), 3.74 (s, 3H), 1.47 (d, *J*=6.9 Hz, 3H). Analytical HPLC RT E: 1.62 min, F: 1.30 min.

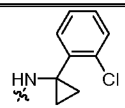
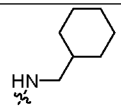
The compounds listed in Table I were prepared by following the similar procedure as described in Example I-1 via reactions of Intermediate 1 with the appropriate amines.

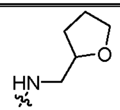
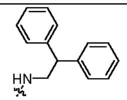
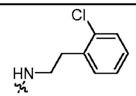
Table I

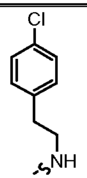
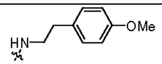
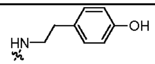


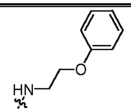
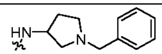
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-2		N-(2-chlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	351.1	E:1.18 F:1.52	(500MHz, CD_3OD) 8.53 (d, *J*=5.2 Hz, 1H), 8.39 (s, 1H), 7.89 (d, *J*=8.3 Hz, 1H), 7.70 (d, *J*=5.2 Hz, 1H), 7.63 - 7.54 (m, 2H), 7.51 (d, *J*=1.9 Hz, 1H), 7.44 - 7.33 (m, 2H), 7.29 - 7.15 (m, 2H), 5.22 (s, 2H), 4.67 (s, 2H)
I-3		N-(1-phenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.1	A:5.12 B:5.59	(400MHz, CD_3OD) 8.78 (d, *J*=6.2 Hz, 1H), 8.75 (s, 1H), 8.39 (d, *J*=6.2 Hz, 1H), 8.17 (d, *J*=8.4 Hz, 1H), 7.67 (dd, *J*=8.3, 1.7 Hz, 1H), 7.56 (d, *J*=1.8 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.38 - 7.31 (m, 2H), 7.28 - 7.21 (m, 1H), 5.41 (s, 2H), 5.24 (q, *J*=7.0 Hz, 1H), 1.58 (d, *J*=7.0 Hz, 3H)

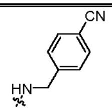
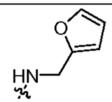
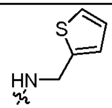
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-4		N-phenethyl-5H-chromeno [3,4-c]pyridine-8-carboxamide	331.1	A:4.92 B:5.49	(400MHz, CD_3OD) 8.86 - 8.68 (m, 2H), 8.37 (d, *J*=5.5 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.60 (d, *J*=7.9 Hz, 1H), 7.48 (s, 1H), 7.36 - 7.11 (m, 5H), 5.40 (s, 2H), 3.61 (t, *J*=7.3 Hz, 2H), 2.93 (t, *J*=7.4 Hz, 2H)
I-5		N-(3-phenylpropyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	345.0	A:6.04 B:6.04	(400MHz, CD_3OD) 8.83 - 8.66 (m, 2H), 8.38 (d, *J*=5.7 Hz, 1H), 8.17 (d, *J*=8.4 Hz, 1H), 7.63 (dd, *J*=8.4, 1.5 Hz, 1H), 7.52 (d, *J*=1.5 Hz, 1H), 7.31 - 7.08 (m, 5H), 5.41 (s, 2H), 3.45 - 3.38 (t, *J*=7.5 Hz, 2H), 2.74 - 2.67 (t, *J*=7.5 Hz, 2H), 1.95 (quin, *J*=7.5 Hz, 2H)

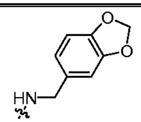
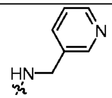
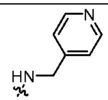
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-6		N-(1-(2-chlorophenyl) cyclopropyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	377.0	A:5.45 B:6.20	(400MHz, CD_3OD) 9.31 (s, 1H), 8.78 (d, *J*=6.2 Hz, 1H), 8.75 (s, 1H), 8.39 (d, *J*=6.2 Hz, 1H), 8.14 (d, *J*=8.4 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.58 (dd, *J*=8.3, 1.7 Hz, 1H), 7.48 (d, *J*=1.5 Hz, 1H), 7.41 - 7.37 (m, 1H), 7.30 - 7.25 (m, 2H), 5.40 (s, 2H), 1.37 - 1.29 (m, 2H), 1.29 - 1.21 (m, 2H)
I-7		N-(cyclohexylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	323.3	C:2.49 D:3.71	(500MHz, DMSO-d_6) 8.64 (d, *J*=4.9 Hz, 2H), 8.55 (br. s., 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.91 (d, *J*=4.6 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.49 (s, 1H), 5.28 (s, 2H), 4.05 - 3.93 (m, 1H), 3.77 (d, *J*=6.7 Hz, 1H), 3.68 - 3.59 (m, 1H), 3.55 - 3.31 (m, 7H),1.96 - 1.73 (m, 2H), 1.64 - 1.51 (m, 1H)

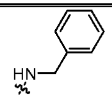
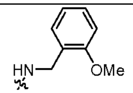
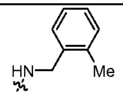
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-8		N-((tetrahydrofuran-2-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	311.2	C:1.67 D:2.83	(500MHz, DMSO-d_6) 8.64 (d, J=4.9 Hz, 2H), 8.55 (br. s., 1H), 8.08 (d, J=8.2 Hz, 1H), 7.91 (d, J=4.6 Hz, 1H), 7.61 (d, J=8.2 Hz, 1H), 7.49 (s, 1H), 5.28 (s, 2H), 4.04 - 3.93 (m, 1H), 3.77 (d, J=6.7 Hz, 1H), 3.69 - 3.59 (m, 1H), 3.31 (d, J=6.4 Hz, 3H), 1.97 - 1.70 (m, 2H), 1.65 - 1.49 (m, 1H)
I-9		N-(2,2-diphenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	407.4	C:2.80 D:3.92	(500MHz, DMSO-d_6) 8.61 (br. s., 2H), 8.51 (br. s., 1H), 8.01 (d, J=7.6 Hz, 1H), 7.84 (br. s., 1H), 7.45 (d, J=7.9 Hz, 1H), 7.38 - 7.24 (m, 8H), 7.19 (br. s., 2H), 5.24 (br. s., 2H), 4.43 (br. s., 1H), 3.90 (br. s., 2H)
I-10		N-(2-chlorophenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	365.3	C:2.53 D:3.70	(500MHz, DMSO-d_6) 8.69 (br. s., 1H), 8.64 (br. s., 1H), 8.56 (br. s., 1H), 8.08 (d, J=7.9 Hz, 1H), 7.92 (br. s., 1H), 7.56 (d, J=8.2 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.38 - 7.18 (m, 3H), 5.28 (br. s., 2H), 3.51 (br. s., 2H), 3.03 - 2.93 (m, 2H)

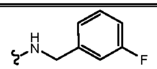
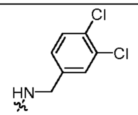
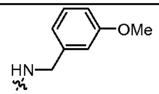
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-11		N-(4-chlorophenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	365.3	C:2.59 D:3.76	(500MHz, DMSO-d_6) 8.63 (br. s., 2H), 8.54 (s, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.88 (d, *J*=4.6 Hz, 1H), 7.55 (d, *J*=7.9 Hz, 1H), 7.43 (s, 1H), 7.34 (d, *J*=7.9 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 2H), 5.27 (s, 2H), 3.52 - 3.45 (m, 2H), 2.84 (t, *J*=6.9 Hz, 2H)
I-12		N-(4-methoxyphenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	361.3	C:2.31 D:3.47	(500MHz, DMSO-d_6) 8.62 (d, *J*=4.0 Hz, 2H), 8.53 (s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.56 (d, *J*=7.9 Hz, 1H), 7.45 (s, 1H), 7.15 (d, *J*=8.2 Hz, 2H), 6.86 (d, *J*=8.2 Hz, 2H), 5.27 (s, 2H), 3.71 (s, 3H), 3.51 - 3.41 (m, 2H), 2.78 (t, *J*=7.2 Hz, 2H)
I-13		N-(4-hydroxyphenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.3	C:1.90 D:3.01	(500MHz, DMSO-d_6) 8.68 (d, *J*=5.2 Hz, 1H), 8.66 - 8.53 (m, 2H), 8.11 (d, *J*=8.2 Hz, 1H), 8.01 (d, *J*=5.2 Hz, 1H), 7.58 (d, *J*=8.2 Hz, 1H), 7.46 (s, 1H), 7.02 (d, *J*=7.9 Hz, 2H), 6.68 (d, *J*=8.2 Hz, 2H), 5.30 (s, 2H), 3.41 (m, 2H), 2.72 (t, *J*=7.2 Hz, 2H)

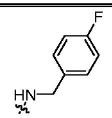
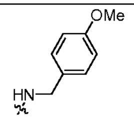
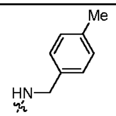
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-14		N-(2-phenoxyethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.5	C:2.32 D:3.45	(500MHz, DMSO-d_6) 8.82 (br. s., 1H), 8.67 (br. s., 1H), 8.59 (br. s., 1H), 8.11 (d, *J*=7.9 Hz, 1H), 7.98 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=7.3 Hz, 1H), 7.52 (s, 1H), 7.29 (t, *J*=7.6 Hz, 2H), 6.99 - 6.86 (m, 3H), 5.30 (s, 2H), 4.12 (t, *J*=5.6 Hz, 2H), 3.64 (d, *J*=5.8 Hz, 2H)
I-15		N-(1-benzylpyrrolidin-3-yl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	386.4	C:1.96 D:3.50	(500MHz, DMSO-d_6) 8.70 (br. s., 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 7.54 - 7.36 (m, 4H), 7.13 (br. s., 1H), 5.27 (s, 2H), 4.50 (br. s., 1H), 3.15 - 2.69 (m, 4H), 2.04 (br. s., 2H), 1.91 (s, 2H)

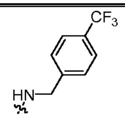
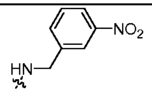
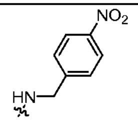
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-16		N-(4-cyanobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	342.3	C:2.10 D:3.12	(500MHz, DMSO-d_6) 9.25 (br. s., 1H), 8.63 (d, *J*=4.9 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=7.6 Hz, 1H), 7.89 (d, *J*=5.5 Hz, 1H), 7.81 (d, *J*=7.9 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 1H), 7.56 - 7.45 (m, 3H), 5.28 (s, 2H), 4.56 (d, *J*=5.5 Hz, 2H)
I-17		N-(furan-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	307.3	C:1.96 D:3.06	(500MHz, DMSO-d_6) 9.10 (br. s., 1H), 8.70 (d, *J*=4.9 Hz, 1H), 8.62 (s, 1H), 8.13 (d, *J*=8.2 Hz, 1H), 8.04 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 6.40 (br. s., 1H), 6.29 (br. s., 1H), 5.31 (s, 2H), 4.47 (d, *J*=5.2 Hz, 2H)
I-18		N-(thiophen-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	323.2	C:2.14 D:3.24	(500MHz, DMSO-d_6) 9.25 (br. s., 1H), 8.63 (d, *J*=4.9 Hz, 1H), 8.55 (s, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=4.9 Hz, 1H), 7.62 (d, *J*=8.2 Hz, 1H), 7.51 (s, 1H), 7.39 (d, *J*=4.9 Hz, 1H), 7.02 (br. s., 1H), 6.99 - 6.93 (m, 1H), 5.28 (s, 2H), 4.63 (d, *J*=5.5 Hz, 2H)

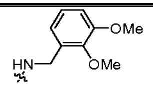
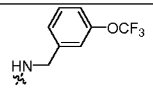
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-19		N-(benzo[d][1,3]dioxol-5-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	361.3	C:2.19 D:3.30	(500MHz, DMSO-d_6) 9.09 (br. s., 1H), 8.67 (d, *J*=4.6 Hz, 1H), 8.59 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 7.99 (d, *J*=5.5 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.53 (s, 1H), 6.95 - 6.83 (m, 2H), 6.80 (d, *J*=7.9 Hz, 1H), 5.98 (s, 2H), 5.30 (s, 2H), 4.38 (d, *J*=5.5 Hz, 2H)
I-20		N-(pyridin-3-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	318.3	C:1.68 D:2.81	(500MHz, DMSO-d_6) 9.23 (br. s., 1H), 8.64 (d, *J*=4.6 Hz, 1H), 8.60 (br. s., 1H), 8.55 (br. s., 1H), 8.51 (br. s., 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.91 (d, *J*=4.9 Hz, 1H), 7.84 (d, *J*=7.3 Hz, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 7.53 (br. s., 1H), 7.46 (br. s., 1H), 5.28 (s, 2H), 4.52 (d, *J*=5.2 Hz, 2H)
I-21		N-(pyridin-4-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	318.5	C:1.64 D:2.63	(500MHz, DMSO-d_6) 9.30 (br. s., 1H), 8.66 (br. s., 1H), 8.58 (br. s., 3H), 8.14 (d, *J*=7.9 Hz, 1H), 7.93 (br. s., 1H), 7.69 (d, *J*=7.6 Hz, 1H), 7.59 (br. s., 1H), 7.45 (br. s., 2H), 5.32 (br. s., 2H), 4.57 (br. s., 2H)

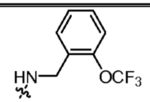
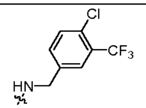
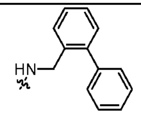
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-22		N-benzyl-5H-chromeno[3,4-c] pyridine-8-carboxamide	317.5	C:2.21 D:3.28	(500MHz, DMSO-d_6) 9.14 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=4.3 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.54 (s, 1H), 7.38 - 7.21 (m, 4H), 5.27 (s, 2H), 4.49 (d, *J*=5.8 Hz, 2H)
I-23		N-(2-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.2	C:2.86 C-1:2.86	(500MHz, DMSO-d_6) 8.96 (br. s., 1H), 8.64 (d, *J*=4.6 Hz, 1H), 8.55 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.66 (d, *J*=8.2 Hz, 1H), 7.55 (s, 1H), 7.32 - 7.20 (m, 1H), 7.18 (d, *J*=7.3 Hz, 1H), 7.00 (d, *J*=7.9 Hz, 1H), 6.91 (t, *J*=7.3 Hz, 1H), 5.28 (s, 2H), 4.45 (d, *J*=5.5 Hz, 2H), 3.83 (s, 3H)
I-24		N-(2-methylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.5	C:2.37 D:3.48	(500MHz, DMSO-d_6) 9.02 (br. s., 1H), 8.63 (d, *J*=4.6 Hz, 1H), 8.55 (s, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=5.2 Hz, 1H), 7.66 (d, *J*=7.3 Hz, 1H), 7.55 (s, 1H), 7.24 (d, *J*=4.3 Hz, 1H), 7.16 (br. s., 3H), 5.28 (s, 2H), 4.46 (d, *J*=5.8 Hz, 2H), 2.32 (s, 3H)

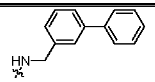
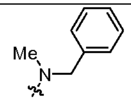
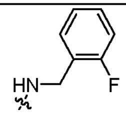
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-25		N-(3-fluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	335.3	C:2.34 D:3.42	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.64 (d, *J*=5.2 Hz, 1H), 8.56 (s, 1H), 8.10 (d, *J*=7.9 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.54 (s, 1H), 7.44 - 7.32 (m, 1H), 7.20 - 7.02 (m, 3H), 5.28 (s, 2H), 4.49 (d, *J*=5.5 Hz, 2H)
I-26		N-(3,4-dichlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.3	C:2.69 D:3.88	(500MHz, DMSO-d_6) 9.21 (br. s., 1H), 8.66 (br. s., 1H), 8.58 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 7.96 (br. s., 1H), 7.69 - 7.50 (m, 4H), 7.32 (d, *J*=8.2 Hz, 1H), 5.30 (s, 2H), 4.47 (d, *J*=5.8 Hz, 2H)
I-27		N-(3-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.3	C:2.27 D:3.37	(500MHz, DMSO-d_6) 9.14 (br. s., 1H), 8.67 (br. s., 1H), 8.59 (br. s., 1H), 8.12 (d, *J*=7.9 Hz, 1H), 7.99 (d, *J*=4.3 Hz, 1H), 7.66 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 7.25 (t, *J*=7.5 Hz, 1H), 6.88 (br. s., 2H), 6.82 (d, *J*=6.7 Hz, 1H), 5.30 (s, 2H), 4.46 (d, *J*=5.2 Hz, 2H), 3.73 (s, 3H)

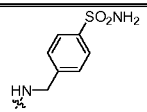
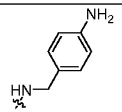
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-28		N-(4-fluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	335.3	C:2.20 D:3.32	(500MHz, DMSO-d_6) 9.16 (br. s., 1H), 8.66 (d, *J*=5.2 Hz, 1H), 8.58 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.96 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 7.41 - 7.32 (m, 2H), 7.16 (t, *J*=8.7 Hz, 2H), 5.29 (s, 2H), 4.46 (d, *J*=5.8 Hz, 2H)
I-29		N-(4-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.3	C:2.25 D:3.34	(500MHz, DMSO-d_6) 9.10 (br. s., 1H), 8.69 (d, *J*=4.6 Hz, 1H), 8.61 (br. s., 1H), 8.12 (d, *J*=8.2 Hz, 1H), 8.01 (d, *J*=4.6 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.53 (s, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 6.89 (d, *J*=8.5 Hz, 2H), 5.30 (s, 2H), 4.41 (d, *J*=5.5 Hz, 2H), 3.72 (s, 3H)
I-30		N-(4-methylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.1	C:2.44 D:3.58	(500MHz, DMSO-d_6) 9.11 (br. s., 1H), 8.65 (br. s., 1H), 8.58 (br. s., 1H), 8.11 (d, *J*=7.9 Hz, 1H), 7.96 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.53 (s, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 7.13 (d, *J*=7.6 Hz, 2H), 5.29 (s, 2H), 4.43 (d, *J*=5.8 Hz, 2H), 2.27 (s, 3H)

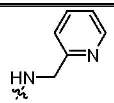
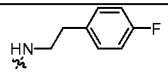
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-31		N-(4-(trifluoromethyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.3	C:2.61 D:3.74	(500MHz, DMSO-d_6) 9.28 (br. s., 1H), 8.71 (br. s., 1H), 8.63 (br. s., 1H), 8.16 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=4.9 Hz, 1H), 7.81 - 7.63 (m, 3H), 7.60 - 7.45 (m, 3H), 5.32 (s, 2H), 4.57 (d, *J*=4.6 Hz, 2H)
I-32		N-(3-nitrobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	362.3	C:2.24 D:3.31	(500MHz, DMSO-d_6) 9.30 (br. s., 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.19 (br. s., 1H), 8.11 (dd, *J*=12.4, 8.1 Hz, 2H), 7.88 (d, *J*=4.9 Hz, 1H), 7.80 (d, *J*=7.6 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.54 (s, 1H), 5.28 (s, 2H), 4.60 (d, *J*=5.8 Hz, 2H)
I-33		N-(4-nitrobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	362.7	C:2.20 D:3.22	(500MHz, DMSO-d_6) 9.30 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.21 (d, *J*=8.2 Hz, 2H), 8.10 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.59 (d, *J*=8.2 Hz, 2H), 7.54 (s, 1H), 5.28 (s, 2H), 4.60 (d, *J*=5.5 Hz, 2H)

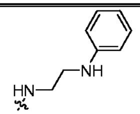
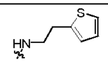
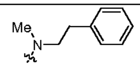
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-34		N-(2,3-dimethoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	377.6	C:2.22 D:3.27	(500MHz, DMSO-d_6) 9.01 (br. s., 1H), 8.61 (br. s., 1H), 8.53 (br. s., 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.53 (s, 1H), 7.07 - 6.99 (m, 1H), 6.95 (d, *J*=7.9 Hz, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 5.27 (s, 2H), 4.49 (d, *J*=5.5 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H)
I-35		N-(3-(trifluoromethoxy) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	401.3	C:2.67 D:3.80	(500MHz, DMSO-d_6) 9.22 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 1H), 7.53 (s, 1H), 7.48 (t, *J*=7.8 Hz, 1H), 7.36 (d, *J*=7.6 Hz, 1H), 7.30 (br. s., 1H), 7.25 (d, *J*=7.9 Hz, 1H), 5.28 (s, 2H), 4.53 (d, *J*=5.5 Hz, 2H)

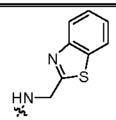
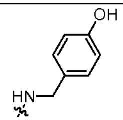
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-36		N-(2-(trifluoromethoxy) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	401.1	C:3.21 C-1:3.19	(500MHz, DMSO-d_6) 9.17 (br. s., 1H), 8.70 (d, *J*=4.9 Hz, 1H), 8.62 (s, 1H), 8.15 (d, *J*=7.9 Hz, 1H), 8.03 (d, *J*=5.2 Hz, 1H), 7.67 (d, *J*=7.9 Hz, 1H), 7.56 (s, 1H), 7.49 - 7.24 (m, 4H), 5.32 (s, 2H), 4.55 (d, *J*=5.5 Hz, 2H)
I-37		N-(4-chloro-3-(trifluoromethyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	419.5	C:2.77 D:3.90	(500MHz, DMSO-d_6) 9.24 (br. s., 1H), 8.63 (br. s., 1H), 8.55 (br. s., 1H), 8.10 (d, *J*=7.9 Hz, 1H), 7.90 (d, *J*=4.9 Hz, 1H), 7.81 (s, 1H), 7.74 - 7.67 (m, 1H), 7.63 (d, *J*=7.9 Hz, 2H), 7.52 (s, 1H), 5.28 (s, 2H), 4.54 (d, *J*=5.5 Hz, 2H)
I-38		N-(biphenyl-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	393.6	C:2.74 D:3.89	(500MHz, DMSO-d_6) 9.04 (br. s., 1H), 8.65 (br. s., 1H), 8.57 (br. s., 1H), 8.10 (d, *J*=7.9 Hz, 1H), 7.94 (br. s., 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.55 - 7.30 (m, 8H), 7.24 (d, *J*=7.0 Hz, 1H), 5.29 (br. s., 2H), 4.43 (d, *J*=5.2 Hz, 2H)

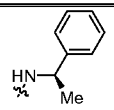
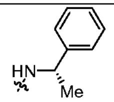
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-39		N-(biphenyl-3-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	393.4	C:2.78 D:3.96	(500MHz, DMSO-d_6) 9.18 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=4.9 Hz, 1H), 7.74 - 7.59 (m, 4H), 7.55 (br. s., 2H), 7.50 - 7.40 (m, 3H), 7.39 - 7.31 (m, 2H), 5.27 (s, 2H), 4.56 (d, *J*=5.5 Hz, 2H)
I-40		N-benzyl-N-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.5	C:2.35 D:3.48	(500MHz, DMSO-d_6) 8.66 (br. s., 1H), 8.59 (br. s., 1H), 8.08 (d, *J*=13.1 Hz, 1H), 7.97 (d, *J*=17.4 Hz, 1H), 7.45 - 7.05 (m, 7H), 5.29 (s, 2H), 4.44 (s, 2H), 2.79 (s, 3H)
I-41		N-(2-fluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	335.5	C:2.28 D:3.30	(500MHz, DMSO-d_6) 9.13 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=4.9 Hz, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 7.53 (s, 1H), 7.41 - 7.27 (m, 2H), 7.23 - 7.11 (m, 2H), 5.27 (s, 2H), 4.52 (d, *J*=5.2 Hz, 2H)

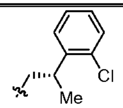
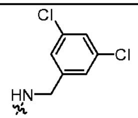
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-42		N-(4-sulfamoylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	396.3	C:1.70 D:2.64	(500MHz, DMSO-d_6) 9.23 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.78 (d, *J*=7.9 Hz, 2H), 7.65 (d, *J*=7.9 Hz, 1H), 7.57 - 7.43 (m, 3H), 7.31 (s, 2H), 5.27 (s, 2H), 4.54 (d, *J*=5.2 Hz, 2H)
I-43		N-(4-aminobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	332.5	C:1.75 D:2.63	(500MHz, DMSO-d_6) 8.95 (br. s., 1H), 8.61 (d, *J*=4.6 Hz, 1H), 8.52 (br. s., 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.86 (d, *J*=4.3 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.51 (br. s., 1H), 6.99 (d, *J*=7.9 Hz, 2H), 6.53 (d, *J*=8.2 Hz, 2H), 5.26 (br. s., 2H), 4.29 (br. s., 2H)

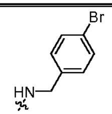
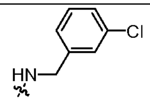
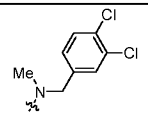
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-44		N-(pyridin-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	318.3	C:1.75 D:2.91	(500MHz, DMSO-d_6) 9.23 (d, *J*=4.6 Hz, 1H), 8.63 (t, *J*=4.6 Hz, 1H), 8.59 - 8.48 (m, 2H), 8.16 - 8.08 (m, 1H), 7.91 (br. s., 1H), 7.79 (br. s., 1H), 7.67 (br. s., 1H), 7.57 (br. s., 1H), 7.36 (d, *J*=6.7 Hz, 1H), 7.30 (br. s., 1H), 7.23 (br. s., 1H), 7.13 (d, *J*=4.0 Hz, 1H), 7.03 (br. s., 1H), 5.28 (br, s, 2H), 4.58 (br. s., 2H)
I-45		N-(4-fluorophenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	349.2	C:2.35 D:3.43	(500MHz, DMSO-d_6) 8.67 - 8.57 (m, 2H), 8.52 (s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=5.2 Hz, 1H), 7.55 (d, *J*=7.9 Hz, 1H), 7.43 (s, 1H), 7.32 - 7.24 (m, 2H), 7.11 (t, *J*=8.9 Hz, 2H), 5.26 (s, 2H), 3.52 - 3.44 (m, 2H), 2.84 (t, *J*=7.0 Hz, 2H)

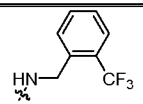
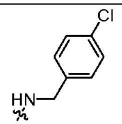
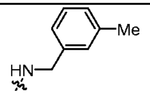
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-46		N-(2-(phenylamino)ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	346.2	C:2.21 D:3.21	(500MHz, DMSO-d_6) 8.70 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.50 (s, 1H), 7.08 (t, *J*=7.5 Hz, 2H), 6.62 (d, *J*=7.9 Hz, 2H), 6.53 (t, *J*=6.9 Hz, 1H), 5.73 (br. s., 1H), 5.27 (s, 2H), 3.44 (br. s., 2H), 3.21 (d, *J*=5.8 Hz, 2H)
I-47		N-(2-(thiophen-2-yl)ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	337.2	C:2.23 D:3.27	(500MHz, DMSO-d_6) 8.72 (br. s., 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=7.9 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.47 (s, 1H), 7.34 (d, *J*=4.9 Hz, 1H), 6.96 (d, *J*=3.4 Hz, 1H), 6.92 (br. s., 1H), 5.27 (s, 2H), 3.57 - 3.46 (m, 2H), 3.07 (t, *J*=6.7 Hz, 2H)
I-48		N-methyl-N-phenethyl-5H-chromeno[3,4-c]pyridine-8-carboxamide	345.2	C:2.38 D:3.38	(500MHz, DMSO-d_6) 8.59 (d, *J*=4.9 Hz, 1H), 8.51 (s, 1H), 8.08 - 7.90 (m, 1H), 7.83 (br. s., 1H), 7.42 - 7.15 (m, 4H), 7.02-6.82 (m,3H), 5.24 (s, 2H), 3.30 (br. s., 3H), 2.86 (m, 2H), 2.73 (m, 2H)

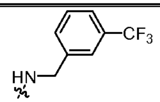
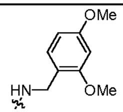
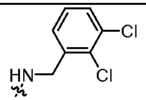
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-49		N-(benzo[d]thiazol-2-ylmethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	374.1	C:2.24 D:3.37	(500MHz, DMSO-d_6) 9.62 (t, *J*=5.8 Hz, 1H), 8.63 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.13 (d, *J*=7.9 Hz, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.96 (d, *J*=8.2 Hz, 1H), 7.89 (d, *J*=4.9 Hz, 1H), 7.68 (dd, *J*=8.1, 1.7 Hz, 1H), 7.57 (d, *J*=1.8 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.48 - 7.38 (m, 1H), 5.29 (s, 2H), 4.88 (d, *J*=6.1 Hz, 2H)
I-50		N-(4-hydroxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	333.2	C:1.80 D:2.70	(500MHz, DMSO-d_6) 9.28 (s, 1H), 9.08 - 8.96 (m, 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.51 (s, 1H), 7.12 (d, *J*=8.2 Hz, 2H), 6.71 (d, *J*=8.2 Hz, 2H), 5.26 (s, 2H), 4.36 (d, *J*=5.5 Hz, 2H)

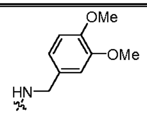
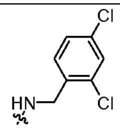
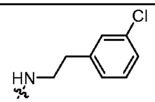
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-51		(R)-N-(1-phenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.1	A:5.04 B:6.08	(400MHz, DMSO-d_6) 8.93 (d, *J*=7.9 Hz, 1H), 8.74 (d, *J*=5.7 Hz, 1H), 8.67 (s, 1H), 8.19 - 8.09 (m, 2H), 7.67 (dd, *J*=8.1, 1.8 Hz, 1H), 7.58 (d, *J*=1.5 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.36 - 7.29 (m, 2H), 7.27 - 7.19 (m, 1H), 5.33 (s, 2H), 5.16 (quin, *J*=7.3 Hz, 1H), 1.48 (d, *J*=7.0 Hz, 3H)
I-52		(S)-N-(1-phenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.1	A:5.12 B:5.59	(400MHz, methanol-d_4) 8.74 (d, *J*=6.2 Hz, 1H), 8.70 (s, 1H), 8.30 (d, *J*=5.9 Hz, 1H), 8.15 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=8.1, 1.8 Hz, 1H), 7.56 (d, *J*=1.5 Hz, 1H), 7.45 - 7.38 (m, 2H), 7.34 (t, *J*=7.6 Hz, 2H), 7.29 - 7.18 (m, 1H), 5.39 (s, 2H), 5.30 - 5.18 (m, 1H), 1.58 (d, *J*=7.0 Hz, 3H)

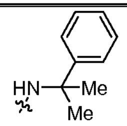
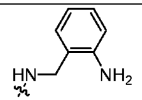
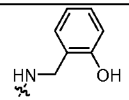
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-53		(S)-N-(1-(2-chlorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	365.0	A:5.56 B:6.22	(400MHz, methanol-d_4) 9.08 (d, *J*=7.5 Hz, 1H), 8.74 (d, *J*=5.9 Hz, 1H), 8.69 (s, 1H), 8.28 (d, *J*=5.9 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=8.3, 1.4 Hz, 1H), 7.58 (d, *J*=1.3 Hz, 1H), 7.48 (d, *J*=7.5 Hz, 1H), 7.41 (d, *J*=7.9 Hz, 1H), 7.36 - 7.28 (m, 1H), 7.28 - 7.21 (m, 1H), 5.57 (t, *J*=7.2 Hz, 1H), 5.39 (s, 2H), 1.56 (d, *J*=7.0 Hz, 3H)
I-54		N-(3,5-dichlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.1	C:2.74 C-1:2.30	(500MHz, DMSO-d_6) 9.26 - 9.14 (m, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 7.36 (s, 2H), 5.27 (s, 2H), 4.47 (d, *J*=5.5 Hz, 2H)

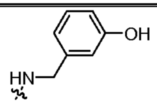
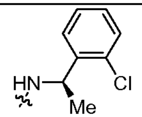
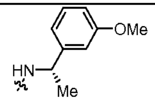
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-55		N-(4-bromobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	395.1	C:2.50 D:3.67	(500MHz, DMSO-d_6) 9.25 - 9.14 (m, 1H), 8.61 - 8.43 (m, 2H), 8.02 (d, *J*=8.2 Hz, 1H), 7.82 (d, *J*=5.2 Hz, 1H), 7.59 (d, *J*=8.2 Hz, 1H), 7.53 - 7.42 (m, 3H), 7.26 (d, *J*=7.9 Hz, 2H), 5.23 (s, 2H), 4.41 (d, *J*=5.8 Hz, 2H)
I-56		N-(3-chlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	351.1	C:2.45 D:3.59	(500MHz, DMSO-d_6) 9.18 (br. s., 1H), 8.61 (d, *J*=4.0 Hz, 1H), 8.53 (d, *J*=2.1 Hz, 1H), 8.09 (dd, *J*=7.8, 3.2 Hz, 1H), 7.87 (br. s., 1H), 7.64 (d, *J*=6.1 Hz, 1H), 7.53 (br. s., 1H), 7.42 - 7.22 (m, 4H), 5.27 (d, *J*=2.7 Hz, 2H), 4.48 (br. s., 2H)
I-57		N-(3,4-dichlorobenzyl)-N-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamide	399.1	C:2.79 D:3.88	(500MHz, DMSO-d_6) 8.60 (br. s., 1H), 8.52 (br. s., 1H), 8.04 (br. s., 1H), 7.84 (br. s., 1H), 7.64 (d, *J*=7.9 Hz, 2H), 7.48 - 7.00 (m, 3H), 5.27 (br. s., 2H), 4.66 (m, 2H), 2.89 (br. s., 3H)

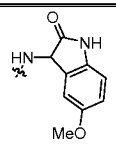
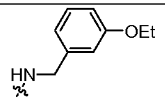
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-58		N-(2-(trifluoromethyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.2	C:2.56 D:3.57	(500MHz, DMSO-d_6) 9.23 (br. s., 1H), 8.58 (d, *J*=4.9 Hz, 1H), 8.49 (s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=4.9 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.63 (d, *J*=7.3 Hz, 2H), 7.54 - 7.43 (m, 3H), 5.24 (s, 2H), 4.64 (d, *J*=5.2 Hz, 2H)
I-59		N-(4-chlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	351.1	C:2.45 D:3.58	(500MHz, DMSO-d_6) 9.25 - 9.07 (m, 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=7.3 Hz, 1H), 7.52 (s, 1H), 7.43 - 7.37 (m, 2H), 7.37 - 7.25 (m, 2H), 5.27 (s, 2H), 4.46 (d, *J*=5.8 Hz, 2H)
I-60		N-(3-methylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	331.2	C:2.38 D:3.53	(500MHz, DMSO-d_6) 9.11 (br. s., 1H), 8.61 (d, *J*=4.6 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.6 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=7.9 Hz, 1H), 7.53 (s, 1H), 7.28 - 7.17 (m, 1H), 7.16 - 7.00 (m, 3H), 5.27 (s, 2H), 4.45 (d, *J*=5.2 Hz, 2H), 2.29 (s, 3H)

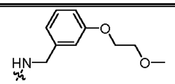
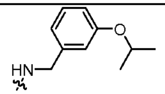
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-61		N-(3-(trifluoromethyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.1	C:3.25 C-1:3.27	(500MHz, DMSO-d_6) 9.24 (br. s., 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.71 - 7.56 (m, 5H), 7.53 (s, 1H), 5.27 (s, 2H), 4.57 (d, *J*=5.2 Hz, 2H)
I-62		N-(2,4-dimethoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	377.2	C:2.32 D:3.38	(500MHz, DMSO-d_6) 8.86 (br. s., 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.85 (d, *J*=5.2 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.51 (s, 1H), 7.09 (d, *J*=8.2 Hz, 1H), 6.55 (s, 1H), 6.47 (d, *J*=8.5 Hz, 1H), 5.26 (s, 2H), 4.36 (d, *J*=5.2 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H)
I-63		N-(2,3-dichlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.1	C:2.62 D:3.76	(500MHz, DMSO-d_6) 9.21 (br. s., 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.51 (s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.85 (d, *J*=4.6 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.58 - 7.47 (m, 2H), 7.39 - 7.29 (m, 2H), 5.26 (s, 2H), 4.55 (d, *J*=5.5 Hz, 2H)

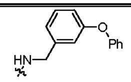
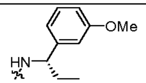
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-64		N-(3,4-dimethoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	377.2	C:2.04 D:3.09	(500MHz, DMSO-d_6) 9.17 - 9.03 (m, 1H), 8.57 (d, *J*=4.0 Hz, 1H), 8.48 (s, 1H), 8.02 (d, *J*=6.4 Hz, 1H), 7.82 (d, *J*=4.3 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.46 (s, 1H), 6.92 (br. s., 1H), 6.89 - 6.80 (m, 2H), 5.23 (s, 2H), 4.38 (d, *J*=4.3 Hz, 2H), 3.71 (s, 3H), 3.69 (s, 3H)
I-65		N-(2,4-dichlorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.1	C:2.68 D:3.87	(500MHz, DMSO-d_6) 9.16 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.55 (s, 1H), 7.47 - 7.29 (m, 2H), 5.28 (s, 2H), 4.51 (d, *J*=5.2 Hz, 2H)
I-66		N-(3-chlorophenethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	365.1	C:2.52 D:3.71	(500MHz, DMSO-d_6) 8.69 - 8.59 (m, 2H), 8.52 (s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.55 (d, *J*=7.3 Hz, 1H), 7.43 (s, 1H), 7.37 - 7.17 (m, 4H), 5.26 (s, 2H), 3.50 (m, 2H), 2.87 (t, *J*=7.2 Hz, 2H)

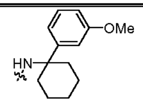
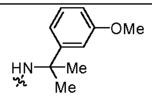
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-67		N-(2-phenylpropan-2-yl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	345.2	C:2.48 D:3.54	(500MHz, DMSO-d_6) 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (d, *J*=4.0 Hz, 2H), 8.05 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.58 (d, *J*=8.2 Hz, 1H), 7.51 (s, 1H), 7.38 (d, *J*=7.3 Hz, 2H), 7.28 (t, *J*=7.6 Hz, 2H), 7.22 - 7.10 (m, 1H), 5.27 (s, 2H), 1.67 (s, 6H)
I-68		N-(2-aminobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	332.4	C:2.00 D:3.11	(500MHz, DMSO-d_6) 9.02 (br. s., 1H), 8.61 (d, *J*=4.6 Hz, 1H), 8.52 (s, 1H), 8.07 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.51 (s, 1H), 7.03 (d, *J*=7.3 Hz, 1H), 6.96 (t, *J*=7.6 Hz, 1H), 6.62 (d, *J*=7.9 Hz, 1H), 6.51 (t, *J*=7.2 Hz, 1H), 5.26 (s, 2H), 5.12 (br. s., 2H), 4.32 (d, *J*=5.8 Hz, 2H)
I-69		N-(2-hydroxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	333.1	C:2.07 D:3.17	(500MHz, DMSO-d_6) 9.78 (s, 1H), 9.17 - 8.93 (m, 1H), 8.57 (d, *J*=4.3 Hz, 1H), 8.48 (s, 1H), 8.13 - 7.98 (m, 1H), 7.82 (d, *J*=5.5 Hz, 1H), 7.60 (d, *J*=7.9 Hz, 1H), 7.48 (s, 1H), 7.16 - 6.99 (m, 2H), 6.88 - 6.70 (m, 2H), 5.23 (s, 2H), 4.40 (d, *J*=5.5 Hz, 2H)

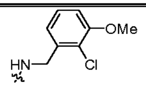
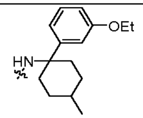
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-70		N-(3-hydroxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	333.2	C:2.54 D:2.89	
I-71		(R)-N-(1-(2-chlorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	365.0	A:5.60 B:6.20	(400MHz, methanol-d_4) 9.06 (d, *J*=6.6 Hz, 1H), 8.73 (d, *J*=5.9 Hz, 1H), 8.68 (s, 1H), 8.27 (d, *J*=5.9 Hz, 1H), 8.15 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=8.1, 1.8 Hz, 1H), 7.57 (d, *J*=1.5 Hz, 1H), 7.48 (dd, *J*=7.8, 1.7 Hz, 1H), 7.40 (dd, *J*=7.9, 1.3 Hz, 1H), 7.35 - 7.19 (m, 2H), 5.57 (quin, *J*=7.0 Hz, 1H), 5.38 (s, 2H), 1.56 (d, *J*=7.0 Hz, 3H)
I-72		(S)-N-(1-(3-methoxyphenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	361.1	E:1.30 F:1.63	(500MHz, DMSO-d_6) 8.86 (d, *J*=7.7 Hz, 1H), 8.66 - 8.59 (m, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.86 (d, *J*=4.7 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.54 (s, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 6.96 (br. s., 2H), 6.80 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 5.13 (quin, *J*=6.9 Hz, 1H), 3.74 (s, 3H), 1.47 (d, *J*=6.9 Hz, 3H)

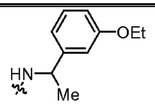
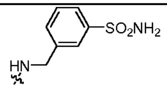
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-73		N-(5-methoxy-2-oxoindolin-3-yl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	388.1	E:1.09 F:1.32	(500MHz, DMSO-d_6) 10.31 (br. s., 1H), 9.41 (d, *J*=7.4 Hz, 1H), 8.69 (br. s., 1H), 8.61 (br. s., 1H), 8.15 (d, *J*=8.0 Hz, 1H), 8.03 (br. s., 1H), 7.66 (d, *J*=8.3 Hz, 1H), 7.55 (br. s., 1H), 6.82 - 6.72 (m, 3H), 5.31 (s., 2H), 5.21 (d, *J*=7.2 Hz, 1H), 3.68 (s., 3H)
I-74		N-(3-ethoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	361.1	E:1.37 F:1.67	(500MHz, DMSO-d_6) 9.10 (br. s., 1H), 8.61 (br. s., 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (br. s., 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.23 (t, *J*=7.7 Hz, 1H), 6.91 - 6.84 (m, 2H), 6.80 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 4.45 (d, *J*=5.2 Hz, 2H), 4.00 (q, *J*=6.6 Hz, 2H), 1.31 (t, *J*=6.9 Hz, 3H)

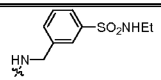
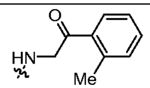
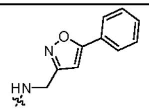
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-75		N-(3-(2-methoxyethoxy) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	391.1	E:1.27 F:1.53	(500MHz, DMSO-d_6) 9.10 (br. s., 1H), 8.61 (d, *J*=2.8 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (br. s., 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 6.88 (br. s., 2H), 6.82 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 4.45 (d, *J*=4.7 Hz, 2H), 4.06 (br. s., 2H), 3.64 (d, *J*=2.8 Hz, 2H), 3.27 (s, 3H)
I-76		N-(3-isopropoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	375.1	E:1.46 F:1.77	(500MHz, DMSO-d_6) 9.09 (br. s., 1H), 8.61 (br. s., 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (br. s., 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.22 (t, *J*=7.8 Hz, 1H), 6.89 - 6.83 (m, 2H), 6.79 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 4.64 - 4.52 (m, 1H), 4.44 (d, *J*=5.0 Hz, 2H), 1.29 - 1.16 (m, 6H)

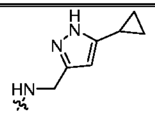
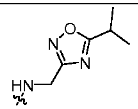
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-77		N-(3-phenoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	409.1	E:1.62 F:1.92	(500MHz, DMSO-d_6) 9.12 (br. s., 1H), 8.61 (d, *J*=2.5 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.87 (br. s., 1H), 7.61 (d, *J*=8.0 Hz, 1H), 7.50 (s, 1H), 7.43 - 7.29 (m, 3H), 7.18 - 7.07 (m, 2H), 7.03 - 6.95 (m, 3H), 6.87 (d, *J*=8.0 Hz, 1H), 5.27 (s, 2H), 4.47 (d, *J*=5.0 Hz, 2H)
I-78		(S)-N-(1-(3-methoxyphenyl) propyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	375.1	E:1.33 F:1.67	(500MHz, DMSO-d_6) 8.82 (d, *J*=8.3 Hz, 1H), 8.71 (d, *J*=4.7 Hz, 1H), 8.63 (s, 1H), 8.13 (d, *J*=8.0 Hz, 1H), 8.05 (br. s., 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.56 (s, 1H), 7.28 - 7.18 (m, 1H), 7.02 - 6.93 (m, 2H), 6.80 (d, *J*=8.0 Hz, 1H), 5.32 (s, 2H), 4.88 (m, 1H), 3.74 (s, 3H), 1.92 - 1.73 (m, 2H), 0.90 (t, *J*=7.0 Hz, 3H)

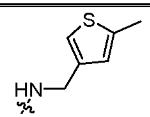
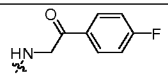
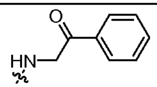
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-79		N-(1-(3-methoxyphenyl) cyclohexyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	415.2	E:1.58 F:1.96	(500MHz, DMSO-d_6) 8.21 (br. s., 1H), 8.06 (d, *J*=7.7 Hz, 1H), 7.87 (br. s., 1H), 7.56 (d, *J*=7.4 Hz, 1H), 7.49 (br. s., 1H), 7.21 (t, *J*=7.4 Hz, 1H), 6.99 (d, *J*=7.7 Hz, 1H), 6.94 (br. s., 1H), 6.76 (d, *J*=8.0 Hz, 1H), 5.28 (br. s., 2H), 3.71 (br. s., 3H), 2.56 (d, *J*=11.6 Hz, 2H), 1.73 - 1.52 (m, 7H), 1.32 (s, 1H)
I-80		N-(2-(3-methoxyphenyl) propan-2-yl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	375.1	E:1.31 F:1.65	(500MHz, DMSO-d_6) 8.62 (d, *J*=5.2 Hz, 1H), 8.52 (d, *J*=8.5 Hz, 2H), 8.06 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.57 (dd, *J*=8.3, 1.7 Hz, 1H), 7.50 (d, *J*=1.4 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 6.95 (d, *J*=8.0 Hz, 1H), 6.89 (t, *J*=2.1 Hz, 1H), 6.76 (dd, *J*=8.1, 2.3 Hz, 1H), 5.27 (s, 2H), 3.71 (s, 3H), 1.65 (s, 6H)

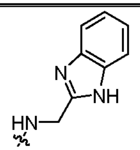
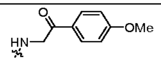
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-81		N-(2-chloro-3-methoxybenzyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	381.0	E:1.22 F:1.55	(500MHz, DMSO-d_6) 9.15 (t, *J*=5.9 Hz, 1H), 8.63 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=8.0 Hz, 1H), 7.89 (d, *J*=5.2 Hz, 1H), 7.67 (dd, *J*=8.0, 1.7 Hz, 1H), 7.56 (d, *J*=1.7 Hz, 1H), 7.29 (t, *J*=8.1 Hz, 1H), 7.07 (d, *J*=7.4 Hz, 1H), 6.94 (d, *J*=7.7 Hz, 1H), 5.29 (s, 2H), 4.54 (d, *J*=5.8 Hz, 2H), 3.87 (s, 3H)
I-82		N-(1-(3-ethoxyphenyl)-4-methylcyclohexyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	443.1	E:1.81 F:2.19	(500MHz, DMSO-d_6) 8.61 (d, *J*=5.0 Hz, 1H), 8.52 (s, 1H), 8.23 (s, 1H), 8.03 (d, *J*=8.3 Hz, 1H), 7.85 (d, *J*=5.2 Hz, 1H), 7.51 (d, *J*=8.3 Hz, 1H), 7.44 (s, 1H), 7.25 - 7.17 (m, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.99 (s, 1H), 6.75 (dd, *J*=8.0, 1.9 Hz, 1H), 5.26 (s, 2H), 3.98 (q, *J*=6.9 Hz, 2H), 2.36 (br. s., 2H), 2.11 (d, *J*=9.1 Hz, 2H), 1.74 (br. s., 3H), 1.31 (t, *J*=6.9 Hz, 3H), 1.14 (br. s., 2H), 0.92 (d, *J*=6.1 Hz, 3H)

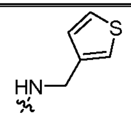
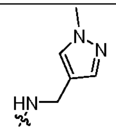
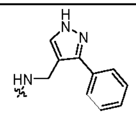
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-83		N-(1-(3-ethoxyphenyl)ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	375.1	E:1.37	(500MHz, DMSO-d_6) 8.87 (d, *J*=8.0 Hz, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.54 (s, 1H), 7.22 (t, *J*=7.8 Hz, 1H), 6.98 - 6.90 (m, 2H), 6.78 (d, *J*=8.3 Hz, 1H), 5.27 (s, 2H), 5.12 (quin, *J*=7.2 Hz, 1H), 4.00 (q, *J*=6.9 Hz, 2H), 1.46 (d, *J*=7.2 Hz, 3H), 1.31 (t, *J*=6.9 Hz, 3H)
I-84		N-(3-sulfamoylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	396.0	E:0.91 F:1.14	(500MHz, DMSO-d_6) 9.29 (br. s., 1H), 8.63 (br. s., 1H), 8.55 (s, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 7.89 (br. s., 1H), 7.80 (br. s., 1H), 7.76 - 7.63 (m, 2H), 7.56 (br. s., 3H), 7.39 (br. s., 2H), 5.29 (s, 2H), 4.57 (d, *J*=4.7 Hz, 2H)

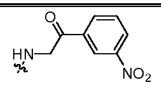
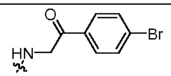
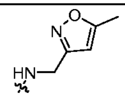
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-85		N-(3-(N-ethylsulfamoyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	424.0	E:1.09 F:1.33	(500MHz, DMSO-d_6) 9.28 (br. s., 1H), 8.63 (br. s., 1H), 8.55 (br. s., 1H), 8.12 (d, *J*=8.0 Hz, 1H), 7.99 - 7.86 (m, 1H), 7.76 (br. s., 1H), 7.72 - 7.52 (m, 6H), 5.29 (br. s., 2H), 4.58 (br. s., 2H), 2.76 (d, *J*=17.6 Hz, 2H), 0.97 (t, *J*=7.0 Hz, 3H)
I-86		N-(2-oxo-2-o-tolylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	359.2	C:2.50 D:3.59	(500MHz, DMSO-d_6) 9.03 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=7.9 Hz, 1H), 7.95 - 7.74 (m, 2H), 7.62 (dd, *J*=8.2, 1.5 Hz, 1H), 7.51 (d, *J*=1.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.38 - 7.26 (m, 2H), 5.28 (s, 2H), 4.59 (d, *J*=5.5 Hz, 2H), 2.42 (s, 3H)
I-87		N-((5-phenylisoxazol-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	384.2	C:2.58 D:3.71	(500MHz, DMSO-d_6) 9.24 (t, *J*=5.3 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.8 Hz, 3H), 7.66 (d, *J*=8.2 Hz, 1H), 7.58 - 7.43 (m, 4H), 6.97 (s, 1H), 5.28 (s, 2H), 4.58 (d, *J*=5.8 Hz, 2H)

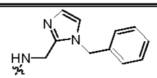
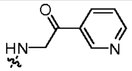
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-88		N-((5-cyclopropyl-1H-pyrazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	347.2	C:2.08 D:3.27	(500MHz, DMSO-d_6) 8.95 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.51 (s, 1H), 5.82 (s, 1H), 5.26 (s, 2H), 4.38 (d, *J*=5.8 Hz, 2H), 1.87 - 1.77 (m, 1H), 0.85 (d, *J*=6.1 Hz, 2H), 0.61 (d, *J*=3.7 Hz, 2H)
I-89		N-((5-isopropyl-1,2,4-oxadiazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	351.2	C:2.22 D:3.30	(500MHz, DMSO-d_6) 9.24 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=4.9 Hz, 1H), 7.63 (dd, *J*=8.2, 1.5 Hz, 1H), 7.52 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.57 (d, *J*=5.8 Hz, 2H), 3.29 - 3.20 (m, 1H), 1.31 (d, *J*=7.0 Hz, 6H)

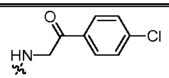
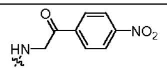
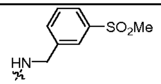
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-90		N-((5-methylthiophen-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	337.2	C:2.49 D:3.63	(500MHz, DMSO-d_6) 9.02 (br. s., 1H), 8.61 (d, *J*=4.6 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=7.6 Hz, 1H), 7.86 (d, *J*=4.6 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.52 (s, 1H), 7.04 (s, 1H), 6.77 (br. s., 1H), 5.20 (s, 2H), 4.37 (d, *J*=5.5 Hz, 2H), 2.40 (s, 3H)
I-91		N-(2-(4-fluorophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	363.2	C:2.22 D:3.28	(500MHz, DMSO-d_6) 8.98 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.18 - 8.05 (m, 3H), 7.88 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.2, 1.5 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 7.40 (t, *J*=8.9 Hz, 2H), 5.29 (s, 2H), 4.78 (d, *J*=5.5 Hz, 2H)
I-92		N-(2-oxo-2-phenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	345.2	C:2.13 D:3.22	(500MHz, DMSO-d_6) 8.98 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 8.05 (d, *J*=7.6 Hz, 2H), 7.88 (d, *J*=5.2 Hz, 1H), 7.73 - 7.62 (m, 2H), 7.60 - 7.50 (m, 3H), 5.29 (s, 2H), 4.80 (d, *J*=5.8 Hz, 2H)

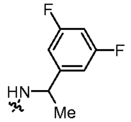
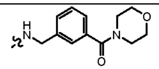
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-93		N-((1H-benzo[d]imidazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	357.2	C:1.85 D:3.10	(500MHz, DMSO-d_6) 12.26 (br. s., 1H), 9.28 (t, *J*=5.6 Hz, 1H), 8.80 - 8.47 (m, 2H), 8.11 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.69 (d, *J*=7.9 Hz, 1H), 7.60 (s, 1H), 7.55 (d, *J*=7.6 Hz, 1H), 7.44 (d, *J*=6.7 Hz, 1H), 7.14 (br. s., 2H), 5.28 (s, 2H), 4.70 (d, *J*=5.5 Hz, 2H)
I-94		N-(2-(4-methoxyphenyl)-2-oxoethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	375.2	C:2.18 D:3.28	(500MHz, DMSO-d_6) 8.92 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 8.03 (d, *J*=8.5 Hz, 2H), 7.88 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=7.9, 1.5 Hz, 1H), 7.54 (d, *J*=1.5 Hz, 1H), 7.08 (d, *J*=8.9 Hz, 2H), 5.29 (s, 2H), 4.74 (d, *J*=5.5 Hz, 2H), 3.86 (s, 3H)

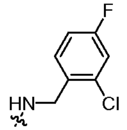
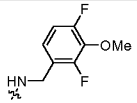
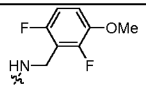
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-95		N-(thiophen-3-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	323.1	C:2.13 D:3.23	(500MHz, DMSO-d_6) 9.15 - 8.99 (m, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.52 (s, 1H), 7.48 (dd, *J*=4.6, 3.1 Hz, 1H), 7.33 (br. s., 1H), 7.09 (d, *J*=4.6 Hz, 1H), 5.27 (s, 2H), 4.47 (d, *J*=6.1 Hz, 2H)
I-96		N-((1-methyl-1H-pyrazol-4-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	321.2	C:1.62 D:2.59	(500MHz, DMSO-d_6) 8.91 (t, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.06 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.66 - 7.56 (m, 2H), 7.49 (s, 1H), 7.35 (s, 1H), 5.26 (s, 2H), 4.29 (d, *J*=5.8 Hz, 2H), 3.78 (s, 3H)
I-97		N-((3-phenyl-1H-pyrazol-4-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	383.2	C:2.03 D:3.18	(500MHz, DMSO-d_6) 8.94 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=4.9 Hz, 1H), 7.66 (d, *J*=7.3 Hz, 3H), 7.61 (d, *J*=8.2 Hz, 1H), 7.53 - 7.42 (m, 3H), 7.40 - 7.31 (m, 1H), 5.26 (s, 2H), 4.49 (d, *J*=4.9 Hz, 2H)

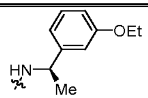
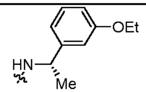
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-98		N-(2-(3-nitrophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	390.2	C:2.14 D:3.17	(500MHz, DMSO-d_6) 9.10 (br. s., 1H), 8.71 (s, 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.56 - 8.45 (m, 3H), 8.10 (d, *J*=7.9 Hz, 1H), 7.91 - 7.84 (m, 2H), 7.65 (d, *J*=7.9 Hz, 1H), 7.53 (s, 1H), 5.28 (s, 2H), 4.87 (d, *J*=5.2 Hz, 2H)
I-99		N-(2-(4-bromophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	423.1	C:2.44 D:3.58	(500MHz, DMSO-d_6) 8.99 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.98 (d, *J*=8.5 Hz, 2H), 7.88 (d, *J*=5.2 Hz, 1H), 7.79 (d, *J*=8.5 Hz, 2H), 7.64 (dd, *J*=8.1, 1.7 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.77 (d, *J*=5.5 Hz, 2H)
I-100		N-((5-methylisoxazol-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	322.2	D:2.91	(500MHz, DMSO-d_6) 9.16 (t, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.62 (dd, *J*=8.1, 1.7 Hz, 1H), 7.51 (d, *J*=1.5 Hz, 1H), 6.17 (s, 1H), 5.27 (s, 2H), 4.46 (d, *J*=6.1 Hz, 2H), 2.37 (s, 3H)

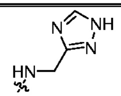
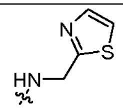
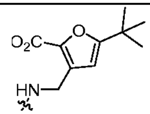
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-101		N-((5-phenyl-1H-imidazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	397.2	C:2.05	(500MHz, DMSO-d_6) 9.12 - 8.97 (m, 1H), 8.60 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.02 (d, *J*=7.9 Hz, 1H), 7.85 (d, *J*=5.2 Hz, 1H), 7.54 (d, *J*=8.2 Hz, 1H), 7.41 (s, 1H), 7.35 - 7.27 (m, 2H), 7.27 - 7.20 (m, 1H), 7.19 - 7.10 (m, 3H), 6.88 (s, 1H), 5.29 (s, 2H), 5.25 (s, 2H), 4.52 (d, *J*=5.2 Hz, 2H)
I-102		N-(2-oxo-2-(pyridin-3-yl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	346.2	C:1.47 D:2.68	(500MHz, DMSO-d_6) 9.21 (s, 1H), 9.05 (t, *J*=5.3 Hz, 1H), 8.83 (d, *J*=4.9 Hz, 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.54 (s, 1H), 8.37 (d, *J*=7.9 Hz, 1H), 8.11 (d, *J*=7.9 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.69 - 7.58 (m, 2H), 7.53 (s, 1H), 5.29 (s, 2H), 4.81 (d, *J*=5.5 Hz, 2H)

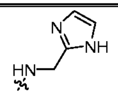
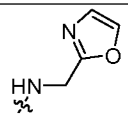
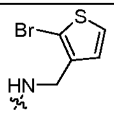
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-103		N-(2-(4-chlorophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	379.2	D:3.54	(500MHz, DMSO-d_6) 9.00 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 2H), 7.88 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 3H), 7.53 (d, *J*=1.5 Hz, 1H), 5.29 (s, 2H), 4.78 (d, *J*=5.5 Hz, 2H)
I-104		N-(2-(4-nitrophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	390.2	D:3.23	(500MHz, DMSO-d_6) 9.09 (t, *J*=5.3 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.37 (d, *J*=8.9 Hz, 2H), 8.26 (d, *J*=8.9 Hz, 2H), 8.09 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.5 Hz, 1H), 7.64 (dd, *J*=8.1, 1.7 Hz, 1H), 7.52 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.84 (d, *J*=5.5 Hz, 2H)
I-105		N-(3-(methylsulfonyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	395.0	E:1.02 F:1.23	(500MHz, DMSO-d_6) 9.33 (br. s., 1H), 8.75 (br. s., 1H), 8.67 (br. s., 1H), 8.19 (d, *J*=7.4 Hz, 1H), 8.11 (br. s., 1H), 7.94 - 7.80 (m, 2H), 7.76 - 7.54 (m, 4H), 5.35 (br. s., 2H), 4.61 (br. s., 2H), 3.23 (br. s., 3H)

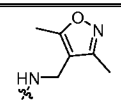
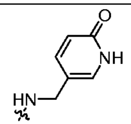
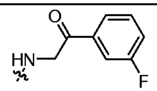
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-106		N-(1-(3,5-difluorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	367.0	E:1.35 F:1.66	(500MHz, DMSO-d_6) 8.96 (d, *J*=7.7 Hz, 1H), 8.73 (d, *J*=5.5 Hz, 1H), 8.65 (s, 1H), 8.16 (d, *J*=8.0 Hz, 1H), 8.08 (d, *J*=5.5 Hz, 1H), 7.67 (dd, *J*=8.0, 1.7 Hz, 1H), 7.59 (d, *J*=1.7 Hz, 1H), 7.20 - 7.05 (m, 3H), 5.34 (s, 2H), 5.18 (t, *J*=7.3 Hz, 1H), 1.49 (d, *J*=7.2 Hz, 3H)
I-107		N-(3-(morpholine-4-carbonyl) benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	430.1	E:1.04 F:1.22	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.7 Hz, 1H), 7.41 (d, *J*=5.2 Hz, 2H), 7.35 (s, 1H), 7.28 (td, *J*=4.4, 1.7 Hz, 1H), 5.27 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H), 3.58 (br. s., 8H)

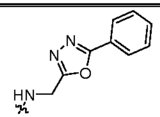
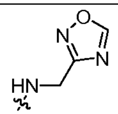
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-108		N-(2-chloro-4-fluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	369.0	E:1.34 F:1.65	(500MHz, DMSO-d_6) 9.12 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.3, 1.7 Hz, 1H), 7.55 (d, *J*=1.7 Hz, 1H), 7.49 - 7.38 (m, 2H), 7.22 (td, *J*=8.5, 2.8 Hz, 1H), 5.28 (s, 2H), 4.51 (d, *J*=5.5 Hz, 2H)
I-109		N-(2,4-difluoro-3-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	383.0	E:1.27 F:1.56	(500MHz, DMSO-d_6) 9.10 (t, *J*=5.8 Hz, 1H), 8.60 (br. s., 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.89 (br. s., 1H), 7.63 (dd, *J*=8.1, 1.8 Hz, 1H), 7.52 (d, *J*=1.7 Hz, 1H), 7.15 - 7.04 (m, 2H), 5.27 (s, 2H), 4.48 (d, *J*=5.8 Hz, 2H), 3.92 (s, 3H)
I-110		N-(2,6-difluoro-3-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	383.0	E:1.22 F:1.49	(500MHz, DMSO-d_6) 8.98 (br. s., 1H), 8.61 (br. s., 1H), 8.52 (br. s., 1H), 8.05 (d, *J*=7.7 Hz, 1H), 7.86 (br. s., 1H), 7.59 (d, *J*=8.0 Hz, 1H), 7.48 (br. s., 1H), 7.19 - 7.09 (m, 1H), 7.08 - 6.96 (m, 1H), 5.25 (br. s., 2H), 4.51 (br. s., 2H), 3.82 (br. s., 3H)

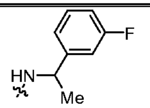
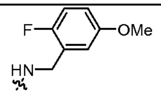
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-111		(R)-N-(1-(3-ethoxyphenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	375.1	A:5.71 B:6.36	(400MHz, methanol-d_4) 8.67 - 8.30 (m, 2H), 7.93 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=3.7 Hz, 1H), 7.55 (dd, *J*=8.1, 1.5 Hz, 1H), 7.46 (d, *J*=1.5 Hz, 1H), 7.22 (t, *J*=8.0 Hz, 1H), 7.02 - 6.91 (m, 2H), 6.83 - 6.72 (m, 1H), 5.2 (s, 2H), 5.20 - 5.13 (m, 1H), 4.01 (q, *J*=6.9 Hz, 2H), 1.55 (d, *J*=7.0 Hz, 3H), 1.36 (t, *J*=6.9 Hz, 3H)
I-112		(S)-N-(1-(3-ethoxyphenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	375.0	A:5.65 B:6.34	(400MHz, methanol-d_4) 8.51 (d, *J*=5.3 Hz, 1H), 8.40 (s, 1H), 7.92 (d, *J*=8.1 Hz, 1H), 7.75 (d, *J*=5.3 Hz, 1H), 7.54 (dd, *J*=8.0, 1.7 Hz, 1H), 7.45 (d, *J*=1.5 Hz, 1H), 7.27 - 7.15 (m, 1H), 7.01 - 6.91 (m, 2H), 6.82 - 6.72 (m, 1H), 5.24 - 5.13 (m, 3H), 4.00 (q, *J*=6.9 Hz, 2H), 1.54 (d, *J*=7.0 Hz, 3H), 1.35 (t, *J*=6.9 Hz, 3H)

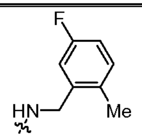
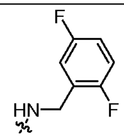
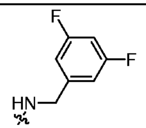
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-113		N-((1H-1,2,4-triazol-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	308.2	C:1.24	(500MHz, DMSO-d_6) 9.14 (br. s., 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.18 (br. s., 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 7.53 (s, 1H), 5.27 (s, 2H), 4.55 (d, *J*=5.5 Hz, 2H)
I-114		N-(thiazol-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	324.5	D:2.70	(500MHz, DMSO-d_6) 9.49 (t, *J*=6.0 Hz, 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.74 (d, *J*=3.4 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.54 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.76 (d, *J*=5.8 Hz, 2H)
I-115		3-((5H-chromeno[3,4-c] pyridine-8-carboxamido) methyl)-5-*tert*-butylfuran-2-carboxylic acid	324.5	D:2.70	(500MHz, DMSO-d_6) 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 6.19 (s, 1H), 5.27 (s, 2H), 4.60 (d, *J*=5.2 Hz, 2H), 1.23 (s, 9H)

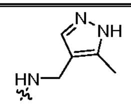
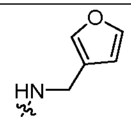
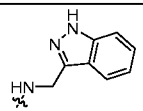
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-116		N-((1H-imidazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	307.2	C:1.40	(500MHz, DMSO-d_6) 9.09 (t, *J*=5.5 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=7.9, 1.5 Hz, 1H), 7.55 (d, *J*=1.8 Hz, 1H), 6.94 (s, 2H), 5.27 (s, 2H), 4.50 (d, *J*=5.8 Hz, 2H)
I-117		N-(oxazol-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	308.5	C:1.66	(500MHz, DMSO-d_6) 9.25 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 8.05 (s, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.63 (d, *J*=8.2 Hz, 1H), 7.52 (d, *J*=1.2 Hz, 1H), 7.16 (s, 1H), 5.28 (s, 2H), 4.59 (d, *J*=5.8 Hz, 2H)
I-118		N-((2-bromothiophen-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	401.0	D:3.57	(500MHz, DMSO-d_6) 9.11 (br. s., 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=4.9 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.58 - 7.45 (m, 2H), 7.00 (d, *J*=5.5 Hz, 1H), 5.27 (s, 2H), 4.38 (d, *J*=5.5 Hz, 2H)

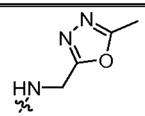
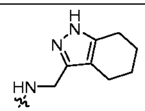
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-119		N-((3,5-dimethylisoxazol-4-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	336.2	C:1.84	(500MHz, DMSO-d_6) 8.89 (t, *J*=5.3 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.06 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.59 (dd, *J*=8.1, 1.7 Hz, 1H), 7.48 (d, *J*=1.5 Hz, 1H), 5.26 (s, 2H), 4.21 (d, *J*=5.5 Hz, 2H), 2.40 (s, 3H), 2.22 (s, 3H)
I-120		N-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	334.2	C:1.69	(500MHz, DMSO-d_6) 8.96 (t, *J*=5.6 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.60 (dd, *J*=7.9, 1.5 Hz, 1H), 7.49 (d, *J*=1.5 Hz, 1H), 7.43 (dd, *J*=9.5, 2.7 Hz, 1H), 7.29 (d, *J*=1.8 Hz, 1H), 6.31 (d, *J*=9.5 Hz, 1H), 5.26 (s, 2H), 4.19 (d, *J*=5.8 Hz, 2H)
I-121		N-(2-(3-fluorophenyl)-2-oxoethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	363.2	C:2.16	(500MHz, DMSO-d_6) 9.01 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=7.9 Hz, 1H), 7.95 - 7.86 (m, 2H), 7.83 (d, *J*=9.5 Hz, 1H), 7.69 - 7.60 (m, 2H), 7.58 - 7.48 (m, 2H), 5.29 (s, 2H), 4.79 (d, *J*=5.8 Hz, 2H)

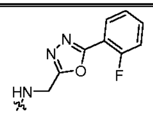
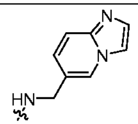
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-122		N-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	385.2	C:2.02	(500MHz, DMSO-d_6) 9.40 (t, J=5.3 Hz, 1H), 8.62 (d, J=5.2 Hz, 1H), 8.53 (s, 1H), 8.11 (d, J=7.9 Hz, 1H), 8.02 - 7.96 (m, 2H), 7.87 (d, J=5.2 Hz, 1H), 7.70 - 7.51 (m, 5H), 5.28 (s, 2H), 4.80 (d, J=5.5 Hz, 2H)
I-123		N-((1,2,4-oxadiazol-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	309.2	C:1.45	(500MHz, DMSO-d_6) 9.56 (s, 1H), 9.28 (t, J=5.6 Hz, 1H), 8.62 (d, J=5.2 Hz, 1H), 8.53 (s, 1H), 8.10 (d, J=8.2 Hz, 1H), 7.87 (d, J=5.2 Hz, 1H), 7.63 (d, J=7.9 Hz, 1H), 7.51 (s, 1H), 5.28 (s, 2H), 4.64 (d, J=5.5 Hz, 2H)

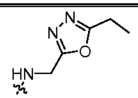
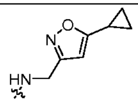
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-124		N-(1-(3-fluorophenyl)ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	349.0	E:1.30 F:1.59	(500MHz, DMSO-d_6) 8.96 (d, *J*=7.7 Hz, 1H), 8.74 (d, *J*=5.5 Hz, 1H), 8.66 (s, 1H), 8.16 (d, *J*=8.0 Hz, 1H), 8.10 (d, *J*=5.5 Hz, 1H), 7.68 (dd, *J*=8.3, 1.7 Hz, 1H), 7.59 (d, *J*=1.7 Hz, 1H), 7.39 (td, *J*=8.0, 6.1 Hz, 1H), 7.30 - 7.19 (m, 2H), 7.07 (td, *J*=8.5, 2.3 Hz, 1H), 5.34 (s, 2H), 5.19 (t, *J*=7.3 Hz, 1H), 1.50 (d, *J*=6.9 Hz, 3H)
I-125		N-(2-fluoro-5-methoxybenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	365.2	E:1.14 F:1.50	(500MHz, DMSO-d_6) 9.08 (t, *J*=5.8 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.7 Hz, 1H), 7.12 (t, *J*=9.2 Hz, 1H), 6.90 (dd, *J*=6.1, 3.0 Hz, 1H), 6.85 (dt, *J*=8.9, 3.7 Hz, 1H), 5.27 (s, 2H), 4.48 (d, *J*=5.8 Hz, 2H), 3.71 (s, 3H)

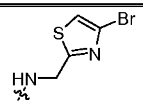
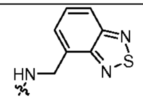
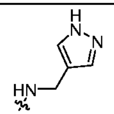
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-126		N-(5-fluoro-2-methylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	349.0	E:1.22 F:1.60	(500MHz, DMSO-d_6) 9.06 (br. s., 1H), 8.72 - 8.49 (m, 2H), 8.10 (d, *J*=8.0 Hz, 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.56 (s, 1H), 7.27 - 7.19 (m, 1H), 7.01 (t, *J*=8.8 Hz, 2H), 5.29 (s, 2H), 4.45 (d, *J*=5.2 Hz, 2H), 2.31 (s, 3H)
I-127		N-(2,5-difluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	353.0	E:1.14 F:1.52	(500MHz, DMSO-d_6) 9.15 (t, *J*=5.8 Hz, 1H), 8.63 (d, *J*=5.0 Hz, 1H), 8.55 (s, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=5.2 Hz, 1H), 7.66 (dd, *J*=8.0, 1.7 Hz, 1H), 7.55 (d, *J*=1.7 Hz, 1H), 7.34 - 7.23 (m, 1H), 7.22 - 7.12 (m, 2H), 5.29 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H)
I-128		N-(3,5-difluorobenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	353.1	E:1.18 F:1.55	(500MHz, DMSO-d_6) 9.19 (t, *J*=5.8 Hz, 1H), 8.66 (d, *J*=5.0 Hz, 1H), 8.58 (s, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 7.95 (s, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.55 (s, 1H), 7.15 - 7.00 (m, 3H), 5.30 (s, 2H), 4.50 (d, *J*=6.1 Hz, 2H)

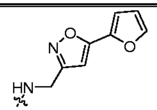
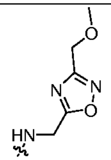
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-129		N-((5-methyl-1H-pyrazol-4-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	321.2	C:1.42 D:2.64	(500MHz, DMSO-d_6) 8.79 (t, *J*=5.2 Hz, 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=5.2 Hz, 1H), 7.60 (d, *J*=8.2 Hz, 1H), 7.48 (s, 1H), 7.42 (br. s., 1H), 5.25 (s, 2H), 4.26 (d, *J*=5.2 Hz, 2H), 2.20 (s, 3H)
I-130		N-(furan-3-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	307.2	C:1.76 D:3.03	(500MHz, DMSO-d_6) 8.95 (t, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.64 - 7.57 (m, 3H), 7.50 (d, *J*=1.5 Hz, 1H), 6.47 (s, 1H), 5.26 (s, 2H), 4.31 (d, *J*=5.8 Hz, 2H)
I-131		N-((1H-indazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	357.2	C:2.12 D:3.14	(500MHz, DMSO-d_6) 12.85 (br. s., 1H), 9.19 (br. s., 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.51 (s, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.90 - 7.75 (m, 2H), 7.64 (d, *J*=7.9 Hz, 1H), 7.56 - 7.44 (m, 2H), 7.32 (t, *J*=7.2 Hz, 1H), 7.07 (t, *J*=7.2 Hz, 1H), 5.25 (s, 2H), 4.83 (d, *J*=5.8 Hz, 2H)

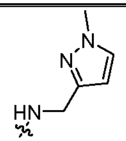
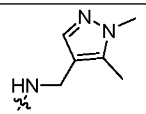
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-132		N-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	323.2	C:1.66 D:2.44	(500MHz, DMSO-d_6) 9.44 - 9.24 (m, 1H), 8.64 (d, *J*=5.2 Hz, 1H), 8.56 (s, 1H), 8.12 (d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=5.2 Hz, 1H), 7.66 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 5.30 (s, 2H), 4.69 (d, *J*=5.5 Hz, 2H), 2.52 (br. s., 3H)
I-133		N-((4,5,6,7-tetrahydro-1H-indazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	361.3	C:2.13 D:3.26	(500MHz, DMSO-d_6) 8.84 (t, *J*=5.2 Hz, 1H), 8.59 (d, *J*=5.2 Hz, 1H), 8.50 (s, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=5.2 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.49 (s, 1H), 5.24 (s, 2H), 4.38 (d, *J*=5.5 Hz, 2H), 2.52-2.49 (m, 2H), 2.36 (t, *J*=5.8 Hz, 2H), 1.72 - 1.54 (m, 4H)

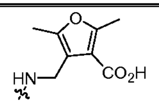
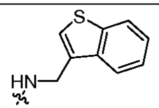
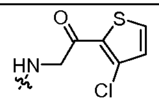
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-134		N-((5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	403.2	C:2.17 D:3.13	(500MHz, DMSO-d_6) 9.40 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 8.00 (td, *J*=7.6, 1.7 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.75 - 7.67 (m, 1H), 7.65 (dd, *J*=8.1, 1.7 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 7.52 - 7.36 (m, 2H), 5.28 (s, 2H), 4.81 (d, *J*=5.5 Hz, 2H)
I-135		N-(imidazo[1,2-a]pyridin-6-ylmethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	357.2	C:1.79 D:2.73	(500MHz, DMSO-d_6) 9.16 (t, *J*=5.6 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.96 (s, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.2, 1.5 Hz, 1H), 7.57 - 7.49 (m, 3H), 7.23 (dd, *J*=9.5, 1.5 Hz, 1H), 5.27 (s, 2H), 4.48 (d, *J*=5.8 Hz, 2H)

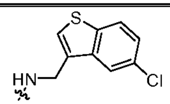
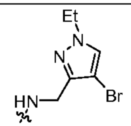
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-136		N-((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	337.2	C:1.79 D:2.67	(500MHz, DMSO-d_6) 9.30 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.10 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.63 (dd, *J*=8.2, 1.5 Hz, 1H), 7.51 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.67 (d, *J*=5.5 Hz, 2H), 2.84 (q, *J*=7.6 Hz, 2H), 1.24 (t, *J*=7.5 Hz, 3H)
I-137		N-((5-cyclopropylisoxazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	348.2	C:2.19 D:3.14	(500MHz, DMSO-d_6) 9.13 (br. s., 1H), 8.62 (d, *J*=4.9 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.62 (d, *J*=7.6 Hz, 1H), 7.51 (br. s., 1H), 6.12 (s, 1H), 5.27 (s, 2H), 4.44 (d, *J*=5.8 Hz, 2H), 2.11 (br. s., 1H), 1.08 - 0.98 (m, 2H), 0.90 - 0.77 (m, 2H)

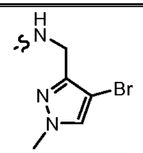
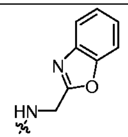
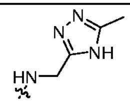
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-138		N-((4-bromothiazol-2-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	402.1 404.1	C:2.19 D:3.15	(500MHz, DMSO-d_6) 9.53 (t, *J*=5.8 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.75 (s, 1H), 7.64 (dd, *J*=7.9, 1.5 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 5.28 (s, 2H), 4.74 (d, *J*=5.8 Hz, 2H)
I-139		N-(benzo[c][1,2,5]thiadiazol-4-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	375.2	C:2.33 D:3.34	(500MHz, DMSO-d_6) 9.28 (t, *J*=5.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 8.00 (d, *J*=8.5 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.76 - 7.65 (m, 2H), 7.62 - 7.47 (m, 2H), 5.28 (s, 2H), 4.99 (d, *J*=5.5 Hz, 2H)
I-140		N-((1H-pyrazol-4-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	307.2	C:1.62 D:2.44	(500MHz, DMSO-d_6) 8.90 (t, *J*=5.5 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.61 (dd, *J*=8.2, 1.5 Hz, 2H), 7.49 (d, *J*=1.5 Hz, 2H), 5.26 (s, 1H), 4.34 (d, *J*=5.5 Hz, 1H)

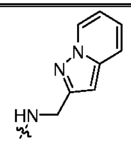
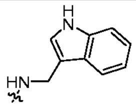
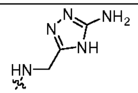
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-141		N-((5-(furan-2-yl)isoxazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	374.1	C:2.32 D:3.26	(500MHz, DMSO-d_6) 9.24 (t, J=5.8 Hz, 1H), 8.62 (d, J=5.2 Hz, 1H), 8.53 (s, 1H), 8.10 (d, J=8.2 Hz, 1H), 7.92 (s, 1H), 7.87 (d, J=5.2 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.54 (d, J=1.5 Hz, 1H), 7.14 (d, J=3.4 Hz, 1H), 6.77 - 6.69 (m, 2H), 5.28 (s, 2H), 4.56 (d, J=5.8 Hz, 2H)
I-142		N-((3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	353.2	C:1.82 D:2.65	(500MHz, DMSO-d_6) 9.44 (t, J=5.6 Hz, 1H), 8.62 (d, J=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, J=8.2 Hz, 1H), 7.88 (d, J=5.2 Hz, 1H), 7.64 (dd, J=7.9, 1.5 Hz, 1H), 7.53 (d, J=1.2 Hz, 1H), 5.28 (s, 2H), 4.76 (d, J=5.8 Hz, 2H), 4.53 (s, 2H), 3.33 (br. s., 3H)

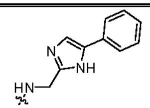
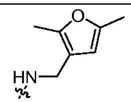
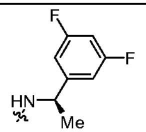
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-143		N-((1-methyl-1H-pyrazol-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	321.1	C:1.74 D:2.98	(500MHz, DMSO-d_6) 8.99 (t, *J*=5.8 Hz, 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.06 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=5.5 Hz, 1H), 7.62 (dd, *J*=7.9, 1.5 Hz, 1H), 7.57 (d, *J*=1.8 Hz, 1H), 7.50 (d, *J*=1.5 Hz, 1H), 6.12 (d, *J*=2.1 Hz, 1H), 5.26 (s, 2H), 4.40 (d, *J*=5.8 Hz, 2H), 3.78 (s, 3H)
I-144		N-((1,5-dimethyl-1H-pyrazol-3-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	335.1	C:1.86 D:3.17	(500MHz, DMSO-d_6) 8.94 (t, *J*=5.6 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.62 (dd, *J*=7.9, 1.5 Hz, 1H), 7.50 (d, *J*=1.2 Hz, 1H), 5.93 (s, 1H), 5.26 (s, 2H), 4.33 (d, *J*=5.5 Hz, 2H), 3.65 (s, 3H), 2.19 (s, 3H)

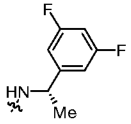
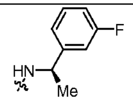
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-145		4-((5H-chromeno[3,4-c]pyridine-8-carboxamido)methyl)-2,5-dimethylfuran-3-carboxylic acid	379.2	C:1.77 D:2.93	(500MHz, DMSO-d_6) 8.75 (br. s., 1H), 8.60 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=5.5 Hz, 1H), 7.59 - 7.51 (m, 1H), 7.44 (s, 1H), 5.25 (s, 2H), 4.38 (d, *J*=4.6 Hz, 2H), 2.45 (s, 3H), 2.23 (s, 3H)
I-146		N-(benzo[b]thiophen-3-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	373.1	C:2.65 D:3.68	(500MHz, DMSO-d_6) 9.14 (t, *J*=5.5 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.07 (d, *J*=7.9 Hz, 1H), 7.97 (dd, *J*=16.9, 7.8 Hz, 2H), 7.86 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.48 - 7.34 (m, 2H), 5.26 (s, 2H), 4.73 (d, *J*=5.5 Hz, 2H)
I-147		N-(2-(3-chlorothiophen-2-yl)-2-oxoethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	385.1	C:2.25 D:3.50	(500MHz, DMSO-d_6) 9.04 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.16 - 8.08 (m, 2H), 7.88 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.1, 1.4 Hz, 1H), 7.53 (d, *J*=1.2 Hz, 1H), 7.32 (d, *J*=5.2 Hz, 1H), 5.29 (s, 2H), 4.70 (d, *J*=5.5 Hz, 2H)

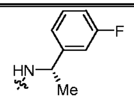
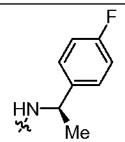
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-148		N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	407.0	C:2.79 D:4.09	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.6 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.12 - 8.06 (m, 2H), 8.03 (d, *J*=8.5 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, *J*=7.9, 1.5 Hz, 1H), 7.52 (d, *J*=1.5 Hz, 1H), 7.41 (dd, *J*=8.5, 2.1 Hz, 1H), 5.26 (s, 2H), 4.69 (d, *J*=5.5 Hz, 2H)
I-149		N-((4-bromo-1-ethyl-1H-pyrazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	413.0 415.0	C:2.15 D:3.44	(500MHz, DMSO-d_6) 8.91 (t, *J*=5.3 Hz, 1H), 8.60 (d, *J*=5.2 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.95 (s, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 7.51 (s, 1H), 5.26 (s, 2H), 4.43 (d, *J*=5.2 Hz, 2H), 4.08 (q, *J*=7.3 Hz, 2H), 1.34 (t, *J*=7.2 Hz, 3H)

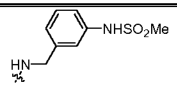
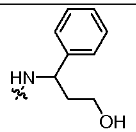
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-150		N-((4-bromo-1-methyl-1H-pyrazol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	399.1 401.1	C:1.98 D:3.28	(500MHz, DMSO-d_6) 8.97 - 8.86 (m, 1H), 8.61 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 7.89 (s, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.62 (dd, *J*=7.9, 1.5 Hz, 1H), 7.51 (d, *J*=1.5 Hz, 1H), 5.26 (s, 2H), 4.41 (d, *J*=5.5 Hz, 2H), 3.79 (s, 3H)
I-151		N-(benzo[d]oxazol-2-ylmethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	358.1	C:2.14 D:3.48	(500MHz, DMSO-d_6) 9.41 (t, *J*=5.5 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.76 - 7.63 (m, 3H), 7.56 (d, *J*=1.5 Hz, 1H), 7.43 - 7.30 (m, 2H), 5.28 (s, 2H), 4.78 (d, *J*=5.5 Hz, 2H)
I-152		N-((5-methyl-4H-1,2,4-triazol-3-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	322.1	C:1.53 D:2.69	(500MHz, DMSO-d_6) 8.61 (d, *J*=4.9 Hz, 1H), 8.52 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=4.9 Hz, 1H), 7.64 (d, *J*=8.2 Hz, 1H), 7.53 (s, 1H), 5.27 (s, 2H), 4.46 (br. s., 2H), 2.29 (br. s., 3H)

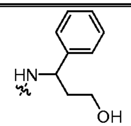
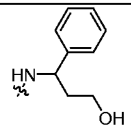
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-153		N-(pyrazolo[1,5-a]pyridin-2-ylmethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	357.1	C:2.03 D:3.39	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.8 Hz, 1H), 8.68 - 8.57 (m, 2H), 8.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.66 (dd, *J*=7.9, 1.5 Hz, 1H), 7.61 (d, *J*=8.9 Hz, 1H), 7.55 (d, *J*=1.5 Hz, 1H), 7.25 - 7.11 (m, 1H), 6.82 (td, *J*=6.9, 1.2 Hz, 1H), 6.50 (s, 1H), 5.27 (s, 2H), 4.65 (d, *J*=5.8 Hz, 2H)
I-154		N-((1H-indol-3-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	356.1	C:2.25 D:3.20	(500MHz, DMSO-d_6) 10.91 (br. s., 1H), 8.91 (br. s., 1H), 8.59 (d, *J*=4.9 Hz, 1H), 8.51 (s, 1H), 8.03 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=4.9 Hz, 1H), 7.62 (t, *J*=9.2 Hz, 2H), 7.50 (s, 1H), 7.35 (d, *J*=7.9 Hz, 1H), 7.29 (br. s., 1H), 7.07 (t, *J*=7.5 Hz, 1H), 7.00 - 6.92 (m, 1H), 5.24 (s, 2H), 4.62 (d, *J*=5.5 Hz, 2H)
I-155		N-((5-amino-1H-1,2,4-triazol-3-yl)methyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	323.1	C:1.47 D:2.52	(500MHz, DMSO-d_6) 8.60 (d, *J*=5.2 Hz, 1H), 8.51 (s, 1H), 8.04 (d, *J*=8.2 Hz, 1H), 7.93 (s, 1H), 7.85 (d, *J*=4.9 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.50 (s, 1H), 5.25 (s, 2H), 4.29 (br. s., 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-156		N-((5-phenyl-1H-imidazol-2-yl)methyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	383.2	C:2.19 D:3.33	(400MHz, CD_3OD) 8.55 (d, *J*=5.5 Hz, 1H), 8.44 (s, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.81 (d, *J*=5.3 Hz, 1H), 7.71 - 7.61 (m, 3H), 7.55 (d, *J*=1.8 Hz, 1H), 7.41 - 7.31 (m, 3H), 7.26 - 7.17 (m, 1H), 5.24 (s, 2H), 4.67 (s, 2H)
I-157		N-((2,5-dimethylfuran-3-yl) methyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	335.2	C:2.35 D:3.69	(400MHz, CD_3OD) 8.54 (d, *J*=5.3 Hz, 1H), 8.43 (s, 1H), 7.96 (d, *J*=8.3 Hz, 1H), 7.79 (d, *J*=5.3 Hz, 1H), 7.54 (dd, *J*=8.0, 1.8 Hz, 1H), 7.43 (d, *J*=1.8 Hz, 1H), 5.92 (s, 1H), 5.23 (s, 2H), 4.26 (s, 2H), 2.25 (s, 3H), 2.17 (d, *J*=0.5 Hz, 3H)
I-158		(R)-N-(1-(3,5-difluorophenyl) ethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	367.0	A:5.95 B:5.95	(400MHz, CD_3OD) 8.6 - 8.46 (m, 2H), 7.92 (d, *J*=8.1 Hz, 1H), 7.74 (d, *J*=4.8 Hz, 1H), 7.55 (d, *J*=8.1 Hz, 1H), 7.45 (s, 1H), 6.99 (d, *J*=6.6 Hz, 2H), 6.87 - 6.56 (m, 1H), 5.20 (s, 2H), 1.55 (d, *J*=7.0 Hz, 3H)

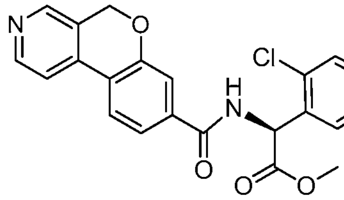
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-159		(S)-N-(1-(3,5-difluorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	367.1	A:5.43 B:6.00	(400MHz, CD_3OD) 8.54 (d, *J*=3.3 Hz, 1H), 8.44 (br. s., 1H), 7.98 (d, *J*=7.9 Hz, 1H), 7.80 (d, *J*=5.3 Hz, 1H), 7.58 (dd, *J*=8.0, 1.7 Hz, 1H), 7.49 (d, *J*=1.5 Hz, 1H), 7.00 (dd, *J*=8.4, 2.0 Hz, 2H), 6.88 - 6.73 (m, 1H), 5.23 (s, 2H), 1.56 (d, *J*=7.3 Hz, 3H)
I-160		(R)-N-(1-(3-fluorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	349.0	A:5.17 B:5.78	(400MHz, CD_3OD) 8.51 (br. s., 1H), 8.41 (br. s., 1H), 7.95 (d, *J*=8.1 Hz, 1H), 7.78 (d, *J*=5.1 Hz, 1H), 7.55 (dd, *J*=8.1, 1.8 Hz, 1H), 7.45 (d, *J*=1.5 Hz, 1H), 7.31 (td, *J*=8.0, 6.1 Hz, 1H), 7.18 (d, *J*=7.9 Hz, 1H), 7.10 (dt, *J*=10.2, 2.0 Hz, 1H), 6.99 - 6.87 (m, 1H), 5.25 - 5.13 (m, 3H), 1.53 (d, *J*=7.3 Hz, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, NM)
I-161		(S)-N-(1-(3-fluorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	349.0	A:5.17 B:5.79	(400MHz, CD_3OD) 8.74 - 8.30 (m, 2H), 7.98 (d, *J*=8.1 Hz, 1H), 7.82 (d, *J*=3.3 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.49 (s, 1H), 7.40 - 7.28 (m, 1H), 7.21 (d, *J*=7.7 Hz, 1H), 7.14 (d, *J*=10.3 Hz, 1H), 7.02 - 6.92 (m, 1H), 5.28 - 5.18 (m, 3H), 1.57 (d, *J*=7.0 Hz, 3H)
I-162		(R)-N-(1-(4-fluorophenyl) ethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	349.0	E:1.28 F:1.62	(500MHz, DMSO-d_6) 8.91 (d, *J*=7.7 Hz, 1H), 8.69 (d, *J*=5.0 Hz, 1H), 8.61 (s, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=5.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.56 (s, 1H), 7.43 (t, *J*=6.3 Hz, 2H), 7.15 (t, *J*=8.4 Hz, 2H), 5.31 (s, 2H), 5.16 (t, *J*=7.0 Hz, 1H), 1.48 (d, *J*=6.9 Hz, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-163		N-(3-(methylsulfonamido) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	410.0	E:0.90 F:1.17	(500MHz, DMSO-d_6) 9.14 (t, *J*=5.2 Hz, 1H), 8.62 (d, *J*=4.7 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.36 - 7.23 (m, 1H), 7.17 (s, 1H), 7.09 (d, *J*=8.0 Hz, 1H), 7.05 (d, *J*=7.4 Hz, 1H), 5.27 (s, 2H), 4.46 (d, *J*=5.5 Hz, 2H), 2.97 (s, 3H)
I-164		N-(3-hydroxy-1-phenylpropyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	361.1	E:0.96 F:1.24	(500MHz, DMSO-d_6) 8.85 (d, *J*=8.0 Hz, 1H), 8.61 (d, *J*=4.7 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=7.7 Hz, 1H), 7.86 (d, *J*=4.4 Hz, 1H), 7.61 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.42 - 7.36 (m, 2H), 7.32 (t, *J*=7.2 Hz, 2H), 7.25 - 7.18 (m, 1H), 5.27 (s, 2H), 5.15 (q, *J*=7.1 Hz, 1H), 4.56 (br. s., 1H), 3.44 (dd, *J*=13.9, 6.2 Hz, 2H), 2.13 - 1.98 (m, 1H), 1.97 - 1.83 (m, 1H)

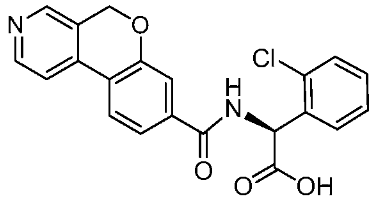
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, NM)
I-165 (Enantiomer 1)		N-(3-hydroxy-1-phenylpropyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	361.1	A:4.05 B:4.40	(400MHz, DMSO-d_6) 8.85 (d, *J*=8.1 Hz, 1H), 8.62 (d, *J*=5.1 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.1 Hz, 1H), 7.86 (d, *J*=5.3 Hz, 1H), 7.61 (dd, *J*=8.1, 1.8 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.35 - 7.29 (m, 2H), 7.26 - 7.17 (m, 1H), 5.27 (s, 2H), 5.21 - 5.08 (m, 1H), 4.56 (t, *J*=4.8 Hz, 1H), 3.53 - 3.36 (m, 2H), 2.13 - 1.99 (m, 1H), 1.91 (dt, *J*=13.3, 6.8 Hz, 1H)
I-166 (Enantiomer 2)		N-(3-hydroxy-1-phenylpropyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	361.1	A:4.05 B:4.38	(400MHz, DMSO-d_6) 8.85 (d, *J*=8.1 Hz, 1H), 8.62 (d, *J*=5.1 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J*=8.1 Hz, 1H), 7.87 (d, *J*=5.3 Hz, 1H), 7.61 (dd, *J*=8.0, 1.7 Hz, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.35 - 7.29 (m, 2H), 7.27 - 7.18 (m, 1H), 5.27 (s, 2H), 5.20 - 5.07 (m, 1H), 4.56 (t, *J*=5.0 Hz, 1H), 3.53 - 3.37 (m, 2H), 2.14 - 1.99 (m, 1H), 1.90 (dq, *J*=13.3, 6.6 Hz, 1H)

Example II-1: (S)-Methyl 2-(2-chlorophenyl)-2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)acetate



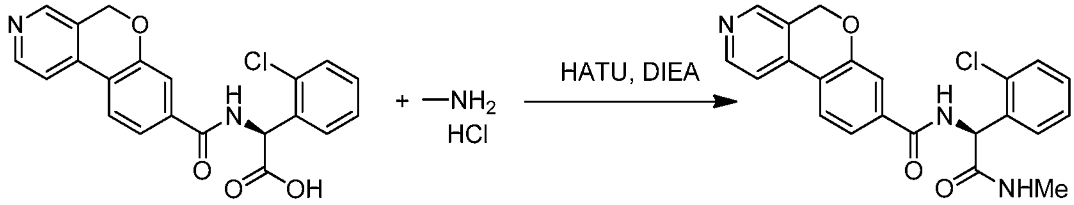
To a suspension of Intermediate 1 (40 mg, 0.176 mmol) in DCM (2 mL) were added (S)-methyl 2-amino-2-(2-chlorophenyl)acetate, HCl salt (49.9 mg, 0.211 mmol), DIEA (0.154 mL, 0.880 mmol), and T_3P (50% in EtOAc, 0.293 mL, 0.493 mmol) at rt. The reaction was stirred under argon at rt for 3 h. Purification by reverse phase chromatography afforded Example II-1 (12 mg, 13%). LC-MS (ESI) *m/z*: 409.1 $[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.78 (d, *J*=6.2 Hz, 1H), 8.74 (s, 1H), 8.38 (d, *J*=6.2 Hz, 1H), 8.17 (d, *J*=8.4 Hz, 1H), 7.68 (dd, *J*=8.3, 1.7 Hz, 1H), 7.57 (d, *J*=1.8 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.40 - 7.36 (m, 2H), 6.18 (s, 1H), 5.41 (s, 2H), 3.80 (s, 3H); Analytical HPLC RT A: 5.34 min, B: 6.41 min.

Example II-2: (S)-2-(2-Chlorophenyl)-2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)acetic acid



To a solution of Example II-1 (130 mg, 0.249 mmol) in EtOH (5mL) was added NaOH (1N, 1.740 mL, 1.740 mmol) at rt. The reaction was stirred under argon at RT for 1.5 h. To the reaction mixture was added HCl (4 N, 0.373 mL, 1.492 mmol) dropwise to adjust pH to ~4. Purification by reverse phase chromatography afforded Example II-2 as TFA salt (95 mg, 75% yield). LC-MS (ESI) *m/z*: 395.0 $[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.84 - 8.67 (m, 2H), 8.39 (d, *J*=6.4 Hz, 1H), 8.15 (d, *J*=8.4 Hz, 1H), 7.66 (dd, *J*=8.1, 1.8 Hz, 1H), 7.58 - 7.45 (m, 3H), 7.41 - 7.30 (m, 2H), 6.14 (s, 1H), 5.40 (s, 2H), 2.03 (s, 1H); Analytical HPLC RT A: 4.40 min, B: 4.99 min.

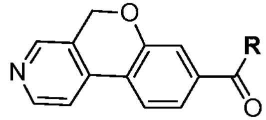
Example II-3: (S)-N-(1-(2-Chlorophenyl)-2-(methylamino)-2-oxoethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide

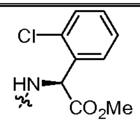
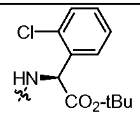
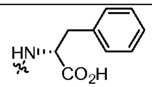


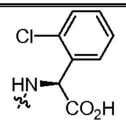
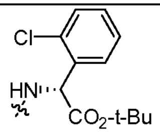
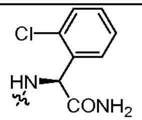
To a solution of Example II-2 (20 mg, 0.039 mmol) in DMF (1 mL) were added methanamine hydrochloride (31.8 mg, 0.472 mmol), DIEA (0.124 mL, 0.708 mmol), and HATU (26.9 mg, 0.071 mmol) at rt. The reaction was stirred under argon at rt overnight. Purification by reverse phase chromatography afforded Example II-3 (10.6 mg, 66%). LC-MS (ESI) *m/z*: 408.1[M+H]$^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.10 (d, *J*=7.7 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.13 (d, *J*=4.7 Hz, 1H), 8.06 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.66 (dd, *J*=8.1, 1.5 Hz, 1H), 7.59 (d, *J*=1.4 Hz, 1H), 7.47 (dt, *J*=6.0, 2.9 Hz, 2H), 7.38 - 7.30 (m, 2H), 5.92 (d, *J*=7.7 Hz, 1H), 5.26 (s, 2H), 2.65 (d, *J*=4.7 Hz, 3H); Analytical HPLC RT E: 0.96 min, F: 1.32 min.

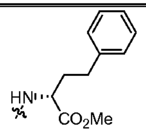
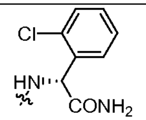
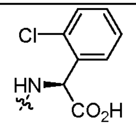
The compounds listed in Table II were prepared following the similar procedures as described in Examples II-1 to II-3.

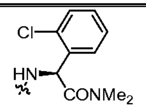
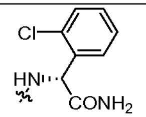
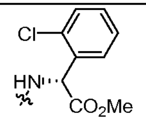
Table II

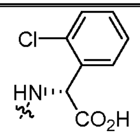


Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
II-4		(S)-methyl 2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)-2-phenylacetate	375.1	A:4.90 B:5.47	(400MHz, $CDCl_3$) 8.63 (d, *J*=5.1 Hz, 1H), 8.46 (s, 1H), 7.80 (d, *J*=7.9 Hz, 1H), 7.65 - 7.32 (m, 8H), 7.21 (d, *J*=6.6 Hz, 1H), 5.78 (d, *J*=6.8 Hz, 1H), 5.20 (s, 2H), 3.79 (s, 3H)
II-5		(S)-*tert*-butyl 2-(5H-chromeno [3,4-c]pyridine-8-carboxamido)-3-phenylpropanoate	431.2	A:6.50 B:6.90	(400MHz, CD_3OD) 8.55 (d, *J*=5.3 Hz, 1H), 8.45 (d, *J*=0.4 Hz, 1H), 7.97 (d, *J*=8.1 Hz, 1H), 7.81 (d, *J*=5.3 Hz, 1H), 7.48 (dd, *J*=7.9, 1.8 Hz, 1H), 7.38 (d, *J*=1.5 Hz, 1H), 7.33 - 7.26 (m, 4H), 7.25 - 7.16 (m, 1H), 5.24 (s, 2H), 1.44 (s, 9H)
II-6		(R)-2-(5H-chromeno[3,4-c] pyridine-8-carboxamido)-3-phenylpropanoic acid	375.1	A:4.47 B:4.63	(400MHz, DMF-d_7) 8.87 - 8.75 (m, 3H), 8.21 - 8.11 (m, 2H), 7.70 (dd, *J*=8.0, 1.7 Hz, 1H), 7.59 (d, *J*=1.5 Hz, 1H), 7.46 - 7.39 (m, 2H), 7.36 - 7.28 (m, 2H), 7.26 - 7.17 (m, 1H), 5.42 (s, 2H), 4.89 (ddd, *J*=10.5, 8.3, 4.4 Hz, 1H), 3.42 - 3.31 (m, 1H), 3.21 (dd, *J*=13.9, 10.6 Hz, 1H)

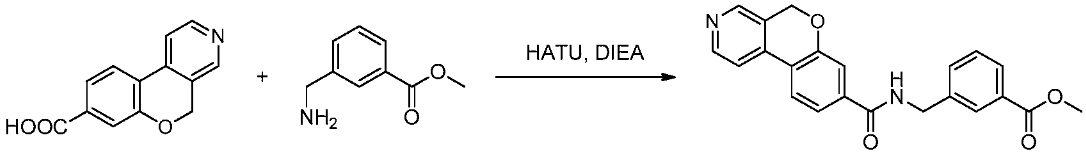
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
II-7		(S)-2-(5H-chromeno[3,4-c] pyridine-8-carboxamido)-2-phenylacetic acid	361.0	E:0.98 F:0.98	(500MHz, CD_3OD) 8.60 (d, *J*=5.5 Hz, 1H), 8.50 (s, 1H), 7.98 - 7.88 (m, 2H), 7.61 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.4 Hz, 1H), 7.48 (d, *J*=7.2 Hz, 2H), 7.41 - 7.29 (m, 3H), 5.27 (s, 2H)
II-8		(R)-*tert*-butyl 2-(5H-chromeno [3,4-c]pyridine-8-carboxamido)-3-phenylpropanoate	431.2	E:1.56 F:1.92	(500MHz, CD_3OD) 8.64 - 8.47 (m, 2H), 7.95 - 7.87 (m, 2H), 7.49 (dd, *J*=8.3, 1.7 Hz, 1H), 7.41 (d, *J*=1.7 Hz, 1H), 7.31 - 7.17 (m, 6H), 5.26 (s, 2H), 4.79 (dd, *J*=7.7, 6.3 Hz, 1H), 3.26 - 3.09 (m, 2H), 1.46 - 1.38 (s, 9H)
II-9		(S)-N-(2-amino-2-oxo-1-phenylethyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	360.1	E:0.90 F:1.19	(500MHz, DMSO-d_6) 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.06 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.56 (d, *J*=1.7 Hz, 1H), 7.52 (d, *J*=7.2 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.31 (d, *J*=7.2 Hz, 1H), 7.22 (s, 1H), 5.61 (d, *J*=8.0 Hz, 1H), 5.27 (s, 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
II-10		(R)-methyl 2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)-4-phenylbutanoate	403.1	A:5.87 B:6.10	(400MHz, CD_3OD) 8.78 (d, *J*=6.2 Hz, 1H), 8.74 (s, 1H), 8.38 (d, *J*=6.2 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.68 (dd, *J*=8.3, 1.7 Hz, 1H), 7.57 (d, *J*=1.5 Hz, 1H), 7.33 - 7.15 (m, 5H), 5.42 (s, 2H), 4.63 - 4.55 (m, 1H), 3.75 (s, 3H), 2.87 - 2.69 (m, 2H), 2.33 - 2.11 (m, 2H)
II-11		(R)-N-(1-amino-1-oxo-3-phenylpropan-2-yl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	374.1	A:4.11 B:4.08	(400MHz, CD_3OD) 8.73 (d, *J*=5.9 Hz, 1H), 8.69 (s, 1H), 8.29 (d, *J*=6.2 Hz, 1H), 8.12 (d, *J*=8.1 Hz, 1H), 7.54 (dd, *J*=8.1, 1.8 Hz, 1H), 7.44 (d, *J*=1.5 Hz, 1H), 7.35 - 7.25 (m, 4H), 7.24 - 7.19 (m, 1H), 5.38 (s, 2H), 4.90 - 4.85 (m, 1H), 3.42 - 3.31 (m, 1H), 3.06 (dd, *J*=14.0, 9.6 Hz, 1H)
II-12		(S)-2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)-3-phenylpropanoic acid	375.1	E:1.04 F:1.04	(500MHz, DMSO-d_6) 8.82 (d, *J*=8.3 Hz, 1H), 8.66 (d, *J*=5.2 Hz, 1H), 8.58 (s, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.95 (d, *J*=5.5 Hz, 1H), 7.55 (dd, *J*=8.3, 1.7 Hz, 1H), 7.44 (d, *J*=1.4 Hz, 1H), 7.34 - 7.25 (m, 4H), 7.22 - 7.15 (m, 1H), 5.29 (s, 2H), 4.62 (ddd, *J*=10.8, 8.2, 4.4 Hz, 1H), 3.20 (dd, *J*=13.9, 4.3 Hz, 1H), 3.07 (dd, *J*=13.8, 10.7 Hz, 1H) (

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
II-13		(S)-N-(1-(2-chlorophenyl)-2-(dimethylamino)-2-oxoethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	422.1	E:1.08 F:1.44	(500MHz, DMSO-d_6) 9.25 (d, *J*=8.0 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.06 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.68 (dd, *J*=8.1, 1.5 Hz, 1H), 7.59 (d, *J*=1.7 Hz, 1H), 7.51 (dd, *J*=5.6, 3.7 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.38 (dd, *J*=5.8, 3.6 Hz, 2H), 6.28 (d, *J*=7.7 Hz, 1H), 5.26 (s, 2H), 2.91 (d, *J*=3.9 Hz, 6H)
II-14		(S)-N-(2-amino-1-(2-chlorophenyl)-2-oxoethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	394.0	A:3.79 B:4.24	(400MHz, CD_3OD) 8.77 (d, *J*=6.2 Hz, 1H), 8.73 (s, 1H), 8.37 (d, *J*=6.2 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.70 (dd, *J*=8.1, 1.8 Hz, 1H), 7.63 - 7.56 (m, 2H), 7.53 - 7.48 (m, 1H), 7.40 - 7.35 (m, 2H), 6.09 (s, 1H), 5.41 (s, 2H)
II-15		(R)-methyl 2-(2-chlorophenyl)-2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)acetate	409.0	A:5.27 B:6.07	(400MHz, CD_3OD) 8.78 (d, *J*=6.2 Hz, 1H), 8.75 (s, 1H), 8.39 (d, *J*=6.2 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 7.68 (dd, *J*=8.1, 1.8 Hz, 1H), 7.58 (d, *J*=1.5 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.43 - 7.34 (m, 2H), 6.18 (s, 1H), 5.42 (s, 2H), 3.80 (s, 3H)

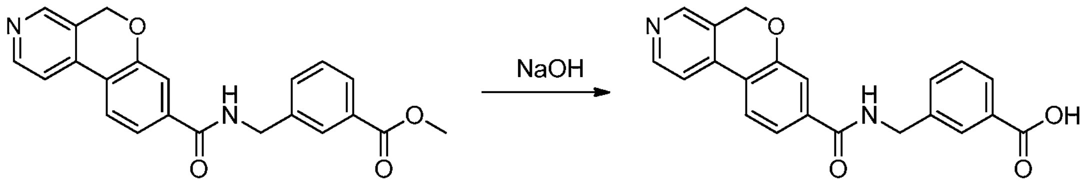
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
II-16		(R)-2-(2-chlorophenyl)-2-(5H-chromeno[3,4-c]pyridine-8-carboxamido)acetic acid	395.0	A:4.40 B:4.90	(400MHz, CD_3OD) 8.79 - 8.69 (m, 2H), 8.36 (d, *J*=6.2 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=8.1, 1.8 Hz, 1H), 7.57 - 7.46 (m, 3H), 7.41 - 7.30 (m, 2H), 6.13 (s, 1H), 5.39 (s, 2H)

Example III-1: Methyl 3-((5H-chromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoate



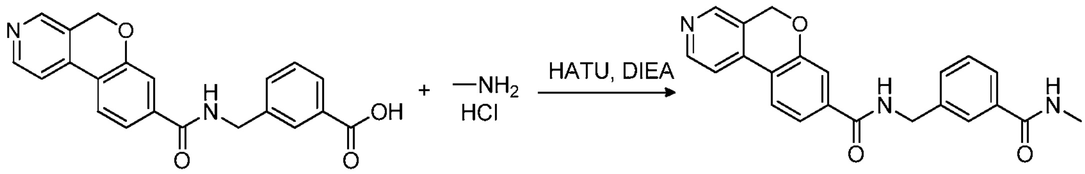
Example III-1 was prepared by following a similar procedure as described in Example I-1 by replacing (R)-1-(3-methoxyphenyl)ethanamine with methyl 3-(aminomethyl)benzoate, HCl salt. LC-MS (ESI) *m/z*: 375.1$[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.79 (d, *J*=6.2 Hz, 1H), 8.76 (s, 1H), 8.41 (d, *J*=6.2 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.94 (dt, *J*=7.8, 1.4 Hz, 1H), 7.71 (dd, *J*=8.3, 1.7 Hz, 1H), 7.63 (dd, *J*=7.7, 0.7 Hz, 1H), 7.60 (d, *J*=1.5 Hz, 1H), 7.51 - 7.44 (m, 1H), 5.43 (s, 2H), 4.68 - 4.63 (m, 2H), 3.91 (s, 3H); Analytical HPLC RT A: 4.70 min, B: 5.10 min.

Example III-2: 3-((5H-Chromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoic acid



To a suspension of Example III-1 (40 mg, 0.107 mmol) (estimated weight) in EtOH (3 mL) was added NaOH (1N, 0.855 mL, 0.855 mmol) at rt. After stirred under argon for 2.5 h, the reaction was neutralized with 6N HCl to pH ~8. Purification by reverse phase chromatography afforded Example III-2 as white solid (40 mg, 77%). LC-MS (ESI) *m/z*: 361.0$[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.74 (d, *J*=6.2 Hz, 1H), 8.70 (s, 1H), 8.30 (d, *J*=5.9 Hz, 1H), 8.16 (d, *J*=8.4 Hz, 1H), 8.05 (s, 1H), 7.98 - 7.89 (m, 1H), 7.69 (dd, *J*=8.3, 1.7 Hz, 1H), 7.62 (d, *J*=8.1 Hz, 1H), 7.59 (d, *J*=1.5 Hz, 1H), 7.51 - 7.42 (m, 1H), 5.39 (s, 2H), 4.65 (d, *J*=4.4 Hz, 2H); Analytical HPLC RT A: 3.98 min, B: 4.14 min.

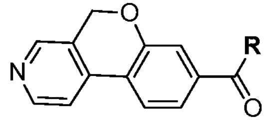
Example III-3: N-(3-(Methylcarbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide

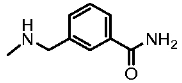
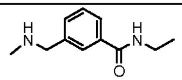


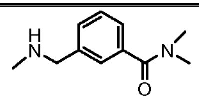
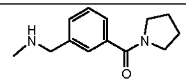
To a solution of Example III-2 (12 mg, 0.025 mmol) in DMF (1 mL) were added methanamine hydrochloride (17.08 mg, 0.253 mmol), DIEA (0.053 mL, 0.304 mmol), and HATU (17.31 mg, 0.046 mmol) at rt. The reaction was stirred under argon at rt for 3 h. Purification by reverse phase chromatography afforded Example III-3 as white solid (6.7 mg, 70%). LC-MS (ESI) *m/z*: 374.0$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.20 (t, *J*=5.9 Hz, 1H), 8.71 - 8.39 (m, 3H), 8.09 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.54 (d, *J*=1.1 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.43 - 7.35 (m, 1H), 5.27 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H), 2.77 (d, *J*=4.7 Hz, 3H); Analytical HPLC RT E: 0.93 min, F: 1.15 min.

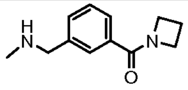
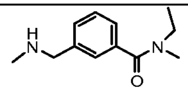
The compounds listed in Table III were prepared by following the similar procedure as described in Examples III-1 to III-3.

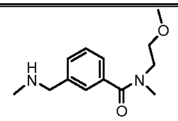
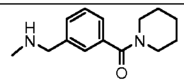
Table III

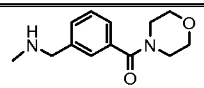
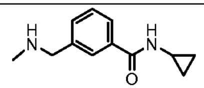


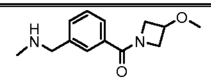
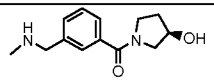
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
III-4		N-(3-carbamoylbenzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	360.0	E:0.90 F:1.10	(500MHz, DMSO-d_6) 9.19 (t, *J*=5.9 Hz, 1H), 8.69 - 8.49 (m, 2H), 8.09 (d, *J*=8.3 Hz, 1H), 7.98 (br. S., 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.84 (s, 1H), 7.75 (d, *J*=7.7 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.55 (s, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.38 (m, 1H), 7.36 (br. S., 1H), 5.27 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H)
III-5		N-(3-(ethylcarbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	388.1	A:3.72 B:4.50	(400MHz, DMSO-d_6) 9.22 (t, *J*=5.9 Hz, 1H), 8.76 (d, *J*=5.7 Hz, 1H), 8.69 (s, 1H), 8.44 (t, *J*=5.3 Hz, 1H), 8.24 - 8.13 (m, 2H), 7.80 (s, 1H), 7.74 - 7.64 (m, 2H), 7.57 (d, *J*=1.5 Hz, 1H), 7.52 - 7.34 (m, 2H), 5.35 (s, 2H), 4.53 (d, *J*=5.9 Hz, 2H), 3.35 - 3.17 (m, 2H), 1.11 (t, *J*=7.3 Hz, 3H)

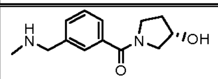
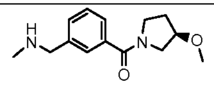
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
III-6		N-(3-(dimethylcarbamoyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	388.1	E:1.04 F:1.24	(500MHz, DMSO-d_6) 9.17 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.3, 1.7 Hz, 1H), 7.54 (d, *J*=1.7 Hz, 1H), 7.41 - 7.37 (m, 2H), 7.34 (s, 1H), 7.29 - 7.23 (m, 1H), 5.28 (s, 2H), 4.52 (d, *J*=6.1 Hz, 2H), 2.97 (br. s., 3H), 2.89 (s, 3H)
III-7		N-(3-(pyrrolidine-1-carbonyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	414.1	E:1.11 F:1.33	^{1}H NMR (500MHz, DMSO-d_6) δ 9.17 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.0, 1.7 Hz, 1H), 7.53 (d, *J*=1.4 Hz, 1H), 7.45 (s, 1H), 7.41 - 7.34 (m, 3H), 5.27 (s, 2H), 4.52 (d, *J*=6.1 Hz, 2H), 3.45 (t, *J*=6.9 Hz, 2H), 3.36 (t, *J*=6.5 Hz, 2H), 1.93 - 1.71 (m, 4H)

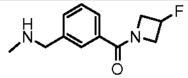
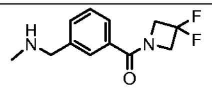
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
III-8		N-(3-(azetidine-1-carbonyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	400.1	E:1.06 F:1.26	(500MHz, DMSO-d_6) 9.19 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.3, 1.7 Hz, 1H), 7.57 (s, 1H), 7.54 (d, *J*=1.7 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.43 - 7.36 (m, 1H), 5.28 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H), 4.26 (t, *J*=7.4 Hz, 2H), 4.02 (t, *J*=7.6 Hz, 2H), 2.24 (quin, *J*=7.8 Hz, 2H)
III-9		N-(3-(ethyl(methyl)carbamoyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	402.2	E:1.11 F:1.32	(500MHz, DMSO-d_6) 9.20 (br. s., 1H), 8.62 (br. s., 1H), 8.53 (br. s., 1H), 8.09 (d, *J*=7.7 Hz, 1H), 7.87 (br. s., 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (br. s., 1H), 7.38 (br. s., 2H), 7.35 - 7.20 (m, 2H), 5.27 (br. s., 2H), 4.52 (br. s., 2H), 2.96 - 2.74 (m, 5H), 1.18 - 0.98 (m, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
III-10		N-(3-((2-methoxyethyl)(methyl) carbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	432.2	E:1.07 F:1.28	(500MHz, DMSO-d_6) 9.20 (br. s., 1H), 8.62 (br. s., 1H), 8.53 (br. s., 1H), 8.09 (d, *J*=7.4 Hz, 1H), 7.87 (br. s., 1H), 7.65 (d, *J*=7.7 Hz, 1H), 7.54 (br. s., 1H), 7.38 (br. s., 2H), 7.30 (br. s., 1H), 7.25 (br. s., 1H), 5.27 (br. s., 2H), 4.51 (br. s., 2H), 3.66 - 3.49 (m, 2H), 3.33 - 3.22 (m, 3H), 3.10 (br. s., 2H), 2.93 (d, *J*=17.1 Hz, 3H)
III-11		N-(3-(piperidine-1-carbonyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	428.1	E:1.21 F:1.45	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.7 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.30 (s, 1H), 7.25 - 7.19 (m, 1H), 5.27 (s, 2H), 4.52 (d, *J*=6.1 Hz, 2H), 3.56 (br. s., 2H), 3.35 - 3.18 (m, 2H), 1.59 (d, *J*=4.1 Hz, 2H), 1.56 - 1.34 (m, 4H)

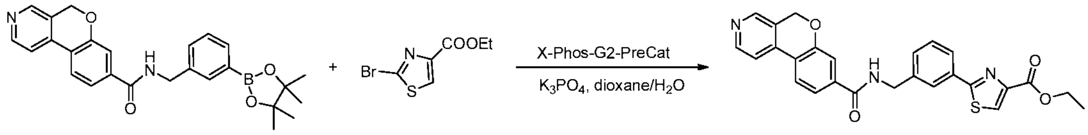
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
III-12		N-(3-(morpholine-4-carbonyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	430.1	E:1.04 F:1.23	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.64 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.7 Hz, 1H), 7.41 (d, *J*=5.2 Hz, 2H), 7.35 (s, 1H), 7.28 (td, *J*=4.4, 1.7 Hz, 1H), 5.27 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H), 3.58 (br. s., 8H)
III-13		N-(3-(cyclopropylcarbamoyl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	400.1	E:1.05 F:1.27	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.62 (br. s., 1H), 8.53 (br. s., 1H), 8.45 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.88 (br. s., 1H), 7.78 (br. s., 1H), 7.66 (dd, *J*=16.1, 7.6 Hz, 2H), 7.54 (br. s., 1H), 7.45 (br. s., 1H), 7.42 - 7.36 (m, 1H), 5.27 (br. s., 2H), 4.52 (br. s., 2H), 2.83 (br. s., 1H), 0.68 (d, *J*=2.2 Hz, 2H), 0.56 (br. s., 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
III-14		N-(3-(3-methoxyazetidine-1-carbonyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	430.1	E:0.95 F:1.24	(500MHz, DMSO-d_6) 9.19 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.0, 1.7 Hz, 1H), 7.59 (s, 1H), 7.54 (d, *J*=1.7 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.44 - 7.39 (m, 1H), 5.28 (s, 2H), 4.53 (d, *J*=5.8 Hz, 2H), 4.39 (br. s., 1H), 4.26 - 4.18 (m, 2H), 4.09 (d, *J*=8.3 Hz, 1H), 3.82 (d, *J*=5.5 Hz, 1H), 3.20 (s, 3H)
III-15		(R)-N-(3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	430.1	E:0.86 F:1.09	(500MHz, DMSO-d_6) δ 9.18 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.54 (s, 1H), 7.45 (br. s., 1H), 7.42 - 7.36 (m, 3H), 5.28 (s, 2H), 5.02 - 4.88 (m, 1H), 4.52 (d, *J*=6.1 Hz, 2H), 4.37 - 4.17 (m, 1H), 3.61 - 3.45 (m, 3H), 1.99 - 1.71 (m, 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
III-16		(S)-N-(3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	430.1	E:0.86 F:1.09	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.0 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.54 (s, 1H), 7.45 (br. s., 1H), 7.42 - 7.35 (m, 3H), 5.28 (s, 2H), 5.03 - 4.89 (m, 1H), 4.52 (d, *J*=6.1 Hz, 2H), 4.36 - 4.18 (m, 1H), 3.61 - 3.46 (m, 3H), 2.00 - 1.70 (m, 2H)
III-17		(R)-N-(3-(3-methoxypyrrolidine-1-carbonyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	444.1	E:0.96 F:1.25	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.45 (d, *J*=6.3 Hz, 1H), 7.42 - 7.33 (m, 3H), 5.27 (s, 2H), 4.52 (d, *J*=5.8 Hz, 2H), 4.05 - 3.86 (m, 1H), 3.62 - 3.42 (m, 4H), 3.26 - 3.10 (m, 3H), 2.03 - 1.81 (m, 2H)

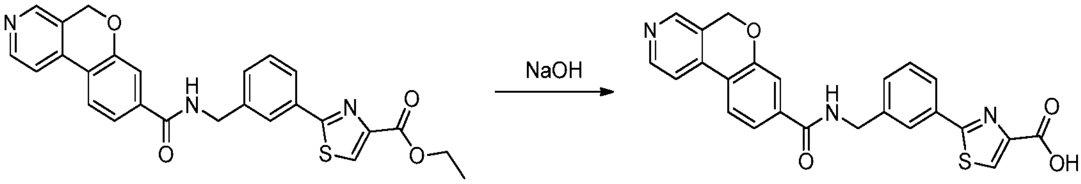
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
III-18		N-(3-(3-fluoroazetidine-1-carbonyl)benzyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	418.0	E:0.95 F:1.25	(500MHz, DMSO-d_6) 9.19 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.65 (dd, *J*=8.1, 1.8 Hz, 1H), 7.61 (s, 1H), 7.56 - 7.46 (m, 3H), 7.45 - 7.37 (m, 1H), 5.54 - 5.32 (m, 1H), 5.27 (s, 2H), 4.53 (d, *J*=5.8 Hz, 3H), 4.46 - 3.99 (m, 3H)
III-19		N-(3-(3,3-difluoroazetidine-1-carbonyl)benzyl)-5H-chromeno [3,4-c]pyridine-8-carboxamide	436.1	E:1.04 F:1.36	(500MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.71 - 7.61 (m, 2H), 7.59 - 7.49 (m, 3H), 7.48 - 7.40 (m, 1H), 5.28 (s, 2H), 4.85 - 4.64 (m, 2H), 4.54 (d, *J*=5.8 Hz, 3H), 4.49 (br. s., 2H)

Example IV-1: Ethyl 2-(3-((5H-chromeno[3,4-c]pyridine-8-carboxamido)methyl)phenyl)thiazole-4-carboxylate



To a solution of Intermediate 5 (47 mg, 0.106 mmol) in dioxane (1.2 mL) and H_2O (0.324 mL) were added ethyl 2-bromothiazole-4-carboxylate (25.09 mg, 0.106 mmol), K_3PO_4 (56.4 mg, 0.266 mmol) and XPhos-G2-PreCat (4.19 mg, 5.31 μmol). The reaction was heated with microwave at 140 °C for 15 min. The solvent was removed. Purification by reverse phase chromatography afforded Example IV-1 as white solid (21 mg, 41%). LC-MS (ESI) *m/z*: 472.2$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.25 (br. s., 1H), 8.67 - 8.46 (m, 3H), 8.13 - 7.80 (m, 4H), 7.71 - 7.43 (m, 5H), 5.27 (br. s., 2H), 4.57 (br. s., 2H), 4.33 (br. s., 2H), 1.31 (br. s., 3H); Analytical HPLC RT E: 1.28 min, F: 1.59 min.

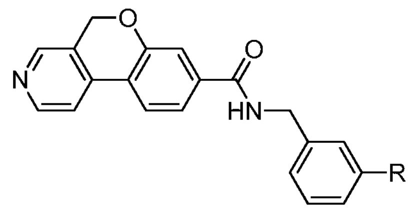
Example IV-2: 2-(3-((5H-Chromeno[3,4-c]pyridine-8-carboxamido) methyl)phenyl)thiazole-4-carboxylic acid

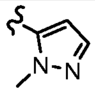


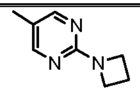
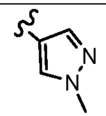
Example IV-2 was prepared by following a similar procedure as described in Example III-2. LC-MS (ESI) *m/z*: 444.0$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.25 (t, *J*=6.1 Hz, 1H), 8.63 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.97 (s, 1H), 7.89 (d, *J*=5.2 Hz, 1H), 7.86 (dt, *J*=6.7, 1.9 Hz, 1H), 7.66 (dd, *J*=8.0, 1.7 Hz, 1H), 7.55 (d, *J*=1.7 Hz, 1H), 7.49-53 (m, 2H), 5.28 (s, 2H), 4.58 (d, *J*=6.1 Hz, 2H); Analytical HPLC RT E: 1.13 min, F: 1.07 min.

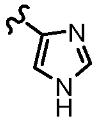
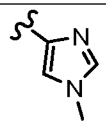
The compounds listed in Table IV were prepared by following the similar procedures as described in Examples IV-1 and IV-2.

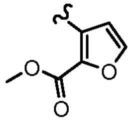
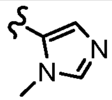
Table IV

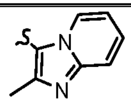
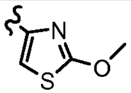


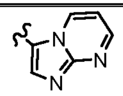
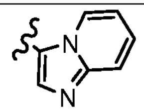
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IV-3		N-(3-(1-methyl-1H-pyrazol-5-yl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	397.2	E:1.14 F:1.43	(500MHz, DMSO-d_6) 9.19 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.0 Hz, 1H), 7.65 (dd, *J*=8.3, 1.7 Hz, 1H), 7.54 (d, *J*=1.4 Hz, 1H), 7.50 - 7.44 (m, 3H), 7.43 - 7.36 (m, 2H), 6.38 (d, *J*=1.9 Hz, 1H), 5.27 (s, 2H), 4.56 (d, *J*=6.1 Hz, 2H), 3.84 (s, 3H)

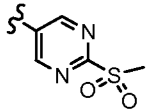
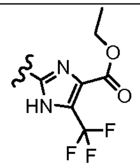
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
IV-4		N-(3-(2-(azetidin-1-yl)pyrimidin-5-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	450.2	E:1.10 F:1.53	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.9 Hz, 1H), 8.71 (d, *J*=5.5 Hz, 1H), 8.66 - 8.62 (m, 3H), 8.15 (d, *J*=8.3 Hz, 1H), 8.06 (d, *J*=5.5 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.57 (d, *J*=2.5 Hz, 2H), 7.51 (d, *J*=7.7 Hz, 1H), 7.41 (t, *J*=7.7 Hz, 1H), 7.29 (d, *J*=7.7 Hz, 1H), 5.32 (s, 2H), 4.54 (d, *J*=5.8 Hz, 2H), 4.08 (t, *J*=7.6 Hz, 4H), 2.33 (quin, *J*=7.5 Hz, 2H)
IV-5		N-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	397.2	E:1.17 F:1.43	(500MHz, DMSO-d_6) 9.13 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.11 - 8.04 (m, 2H), 7.86 (d, *J*=5.2 Hz, 1H), 7.81 (s, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 7.43 (d, *J*=7.7 Hz, 1H), 7.31 (t, *J*=7.6 Hz, 1H), 7.14 (d, *J*=7.7 Hz, 1H), 5.27 (s, 2H), 4.50 (d, *J*=5.8 Hz, 2H), 3.85 (s, 3H)

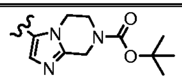
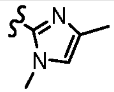
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
IV-6		N-(3-(1H-imidazol-4-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	383.1	E:0.97 F:1.25	(500MHz, DMSO-d_6) 9.21 (t, *J*=5.9 Hz, 1H), 9.15 (s, 1H), 8.67 (d, *J*=5.2 Hz, 1H), 8.59 (s, 1H), 8.15 - 8.09 (m, 2H), 7.97 (d, *J*=5.2 Hz, 1H), 7.77 (s, 1H), 7.68 (t, *J*=8.9 Hz, 2H), 7.57 (s, 1H), 7.50 (t, *J*=7.7 Hz, 1H), 7.40 (d, *J*=7.7 Hz, 1H), 5.30 (s, 2H), 4.55 (d, *J*=5.8 Hz, 2H)
IV-7		N-(3-(1-methyl-1H-imidazol-4-yl)benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	397.2	E:0.98 F:1.33	(500MHz, DMSO-d_6) 9.21 (t, *J*=5.8 Hz, 1H), 9.01 (s, 1H), 8.67 (d, *J*=5.2 Hz, 1H), 8.59 (s, 1H), 8.12 (d, *J*=8.3 Hz, 1H), 8.08 (s, 1H), 7.97 (d, *J*=5.2 Hz, 1H), 7.71 (s, 1H), 7.66 (dd, *J*=16.1, 7.8 Hz, 2H), 7.57 (s, 1H), 7.49 (t, *J*=7.7 Hz, 1H), 7.39 (d, *J*=7.7 Hz, 1H), 5.30 (s, 2H), 4.55 (d, *J*=5.8 Hz, 2H), 3.87 (s, 3H)

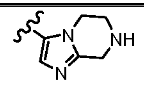
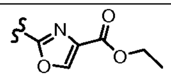
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IV-8		methyl 3-(3-((5H-chromeno[3,4-c]pyridine-8-carboxamido) methyl)phenyl)furan-2-carboxylate	441.1	E:1.34 F:1.62	(500MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.70 (d, *J*=5.5 Hz, 1H), 8.63 (s, 1H), 8.14 (d, *J*=8.0 Hz, 1H), 8.05 (d, *J*=5.5 Hz, 1H), 7.99 (d, *J*=1.1 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.57 (d, *J*=3.9 Hz, 2H), 7.49 (d, *J*=7.7 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.36 - 7.29 (m, 1H), 6.87 (d, *J*=1.1 Hz, 1H), 5.32 (s, 2H), 4.53 (d, *J*=6.1 Hz, 2H), 3.72 (s, 3H)
IV-9		N-(3-(1-methyl-1H-imidazol-5-yl)benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	397.2	E:0.98 F:1.31	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.69 (s, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.54 (s, 1H), 7.46 - 7.40 (m, 2H), 7.39 - 7.35 (m, 1H), 7.32 (d, *J*=7.4 Hz, 1H), 7.02 (s, 1H), 5.27 (s, 2H), 4.54 (d, *J*=5.8 Hz, 2H), 3.67 (s, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
IV-10		N-(3-(2-methylimidazo[1,2-a]pyridin-3-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	447.2	E:1.04 F:1.49	(500MHz, DMSO-d_6) 9.19 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.28 (d, *J*=6.9 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.58 - 7.48 (m, 4H), 7.42 (dd, *J*=12.1, 7.7 Hz, 2H), 7.28 - 7.17 (m, 1H), 6.86 (t, *J*=6.7 Hz, 1H), 5.27 (s, 2H), 4.59 (d, *J*=5.8 Hz, 2H), 2.37 (s, 3H)
IV-11		N-(3-(2-methoxythiazol-4-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	430.2	E:1.45 F:1.76	(500MHz, DMSO-d_6) 9.17 (t, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.87 (d, *J*=5.2 Hz, 1H), 7.83 (s, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.65 (d, *J*=8.3 Hz, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 7.38 (t, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.7 Hz, 1H), 5.27 (s, 2H), 4.53 (d, *J*=5.8 Hz, 2H), 4.09 (s, 3H)

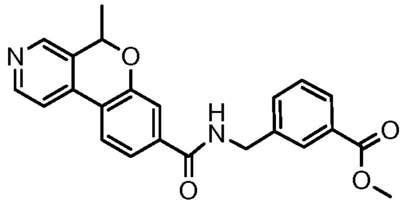
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
IV-12		N-(3-(imidazo[1,2-a]pyrimidin-3-yl)benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	434.1	E:0.97 F:1.30	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.9 Hz, 1H), 9.05 - 9.00 (m, 1H), 8.64 - 8.57 (m, 2H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.95 (s, 1H), 7.86 (d, *J*=5.0 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.61 - 7.57 (m, 1H), 7.56 - 7.50 (m, 2H), 7.41 (d, *J*=7.7 Hz, 1H), 7.12 (dd, *J*=6.9, 3.9 Hz, 1H), 5.27 (s, 2H), 4.59 (d, *J*=5.8 Hz, 2H)
IV-13		N-(3-(imidazo[1,2-a]pyridin-3-yl) benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	433.2	E:1.02 F:1.47	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.9 Hz, 1H), 8.61 (d, *J*=5.2 Hz, 1H), 8.57 (d, *J*=7.2 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.86 (d, *J*=5.2 Hz, 1H), 7.75 (s, 1H), 7.69 - 7.60 (m, 3H), 7.57 - 7.49 (m, 3H), 7.40 (d, *J*=7.2 Hz, 1H), 7.33 - 7.28 (m, 1H), 6.97 (t, *J*=6.7 Hz, 1H), 5.27 (s, 2H), 4.59 (d, *J*=5.8 Hz, 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IV-14		N-(3-(2-(methylsulfonyl) pyrimidin-5-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	473.2	E:1.12 F:1.36	(500MHz, DMSO-d_6) 9.39 (s, 2H), 9.21 (t, *J*=5.8 Hz, 1H), 8.66 (d, *J*=5.0 Hz, 1H), 8.57 (s, 1H), 8.11 (d, *J*=8.0 Hz, 1H), 7.95 - 7.92 (m, 1H), 7.87 (s, 1H), 7.80 (d, *J*=7.7 Hz, 1H), 7.67 (d, *J*=8.3 Hz, 1H), 7.60 - 7.54 (m, 2H), 7.52 - 7.48 (m, 1H), 5.29 (s, 2H), 4.60 (d, *J*=6.1 Hz, 2H), 3.45 (s, 3H)
IV-15		ethyl 2-(3-((5H-chromeno[3,4-c] pyridine-8-carboxamido)methyl) phenyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate	523.1	E:1.50 F:1.78	(500MHz, DMSO-d_6) 9.20 (br. s., 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.13 - 8.07 (m, 2H), 8.02 (d, *J*=7.4 Hz, 1H), 7.87 (d, *J*=4.7 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.55 (s, 1H), 7.49 - 7.38 (m, 2H), 5.27 (s, 2H), 4.55 (d, *J*=5.2 Hz, 2H), 4.35 (q, *J*=6.9 Hz, 2H), 1.32 (t, *J*=7.0 Hz, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
IV-16		*tert*-butyl 3-(3-((5H-chromeno [3,4-c]pyridine-8-carboxamido) methyl)phenyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate	538.2	E:1.15 F:1.56	(500MHz, DMSO-d_6) 9.16 (br. s., 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.86 (d, *J*=4.4 Hz, 1H), 7.65 (d, *J*=7.7 Hz, 1H), 7.54 (s, 1H), 7.46 - 7.35 (m, 3H), 7.31 (d, *J*=7.2 Hz, 1H), 7.05 (s, 1H), 5.27 (s, 2H), 4.60 (br. s., 2H), 4.53 (d, *J*=5.5 Hz, 2H), 4.02 (br. s., 2H), 3.73 (br. s., 2H), 1.44 (s, 9H)
IV-17		N-(3-(1,4-dimethyl-1H-imidazol-2-yl)benzyl)-5H-chromeno[3,4-c] pyridine-8-carboxamide	411.1	E:0.88 F:1.32	(500MHz, DMSO-d_6) 9.25 - 9.09 (m, 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.87 (d, *J*=5.0 Hz, 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.62 (s, 1H), 7.56 - 7.49 (m, 2H), 7.42 (t, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.4 Hz, 1H), 6.92 (s, 1H), 5.27 (s, 2H), 4.54 (d, *J*=5.8 Hz, 2H), 3.66 (s, 3H), 2.10 (s, 3H)

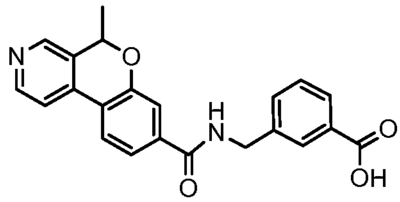
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IV-18		N-(3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	438.2	E:0.78 F:1.11	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.62 (br. s., 1H), 8.53 (br. s., 1H), 8.08 (d, *J*=7.7 Hz, 1H), 7.86 (br. s., 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (br. s., 1H), 7.48 - 7.42 (m, 2H), 7.39 - 7.34 (m, 2H), 7.15 (br. s., 1H), 5.27 (br. s., 2H), 4.53 (br. s., 2H), 4.28 (br. s., 2H), 4.11 (br. s., 2H), 3.5(m., 2H)
IV-19		ethyl 2-(3-((5H-chromeno[3,4-c]pyridine-8-carboxamido)methyl)phenyl)oxazole-4-carboxylate	456.0	E:1.34 F:1.66	(500MHz, DMSO-d_6) 9.26 (t, *J*=6.1 Hz, 1H), 8.93 (s, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 8.01 (s, 1H), 7.93 - 7.82 (m, 2H), 7.66 (dd, *J*=8.1, 1.5 Hz, 1H), 7.59 - 7.48 (m, 3H), 5.28 (s, 2H), 4.57 (d, *J*=6.1 Hz, 2H), 4.31 (q, *J*=7.1 Hz, 2H), 1.30 (t, *J*=7.2 Hz, 3H)

Example V-1: Methyl 3-((5-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoate



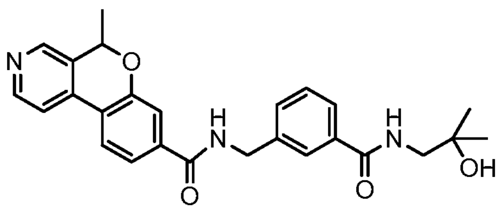
Example V-1 was prepared by following the similar procedure as described in Example I-1 by replacing Intermediate 1 with Intermediate 4. LC-MS (ESI) *m/z*: 389.0[M+H]$^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.57 (d, *J*=5.3 Hz, 1H), 8.46 (s, 1H), 8.08 - 8.00 (m, 2H), 7.98 - 7.91 (m, 1H), 7.85 (d, *J*=5.3 Hz, 1H), 7.68 - 7.55 (m, 2H), 7.54 - 7.42 (m, 2H), 5.49 (q, *J*=6.6 Hz, 1H), 4.64 (s, 2H), 3.91 (s, 3H), 1.65 (d, *J*=6.6 Hz, 3H); Analytical HPLC RT A: 4.94 min, B: 5.40 min.

Example V-2: 3-((5-Methyl-5H-chromeno[3,4-c]pyridine-8-carboxamido) methyl)benzoic acid



Example V-2 was prepared by following the similar procedure as described in Example III-2 using Example V-1. LC-MS (ESI) *m/z*: 375.0[M+H]$^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.73 (d, *J*=5.9 Hz, 1H), 8.68 (s, 1H), 8.28 (d, *J*=6.2 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 8.05 (s, 1H), 7.95 (dd, *J*=7.7, 1.3 Hz, 1H), 7.68 (dd, *J*=8.3, 1.7 Hz, 1H), 7.62 (d, *J*=7.7 Hz, 1H), 7.57 (d, *J*=1.8 Hz, 1H), 7.51 - 7.43 (m, 1H), 5.60 (q, *J*=6.6 Hz, 1H), 4.70 - 4.63 (m, 2H), 1.73 (d, *J*=6.6 Hz, 3H); Analytical HPLC RT A: 4.10 min, B: 4.35 min.

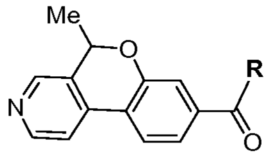
Example V-3: N-(3-(2-Hydroxy-2-methylpropylcarbamoyl)benzyl)-5-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamide

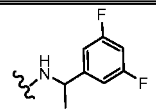
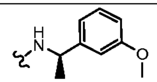


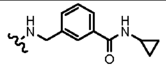
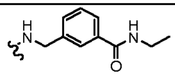
To a solution of V-2 (10 mg, 0.020 mmol) in DMF (1 mL) were added 1-amino-2-methylpropan-2-ol (9.13 mg, 0.102 mmol), DIEA (0.036 mL, 0.205 mmol) and HATU (14.01 mg, 0.037 mmol) at rt. The reaction was stirred under argon at rt for 1.5 h. Purification by reverse phase chromatography afforded Example V-3 as white solid (9.0 mg, 98%). LC-MS (ESI) *m/z*: 446.1$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.18 (br. s., 1H), 8.61 (d, *J*=4.7 Hz, 1H), 8.54 (s, 1H), 8.21 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.83 (s, 1H), 7.75 (d, *J*=7.4 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.45 (m, 1H), 7.45 - 7.38 (m, 1H), 5.52 (q, *J*=6.2 Hz, 1H), 4.62 - 4.47 (m, 3H), 3.25 (d, *J*=5.8 Hz, 2H), 1.58 (d, *J*=6.3 Hz, 3H), 1.10 (s, 6H); Analytical HPLC RT E: 0.99 min, F: 1.27 min.

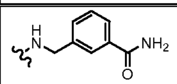
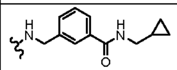
The compounds listed in Table V were prepared by following the similar procedures as described in Examples V-1 to V-3.

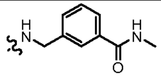
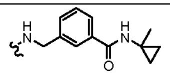
Table V

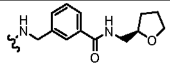


Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
V-4		N-(1-(3,5-difluorophenyl) ethyl)-5-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamide	381.0	E:1.36 F:1.61	(500MHz, DMSO-d_6) 8.93 (d, *J*=7.4 Hz, 1H), 8.69 (d, *J*=5.5 Hz, 1H), 8.62 (s, 1H), 8.14 (d, *J*=8.3 Hz, 1H), 8.02 (d, *J*=5.2 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.57 (d, *J*=5.0 Hz, 1H), 7.16 - 7.05 (m, 3H), 5.56 (q, *J*=6.6 Hz, 1H), 5.16 (quin, *J*=7.0 Hz, 1H), 1.61 (d, *J*=6.6 Hz, 3H), 1.47 (d, *J*=6.9 Hz, 3H)
V-5		N-((R)-1-(3-methoxyphenyl) ethyl)-5-methyl-5H-chromeno[3,4-c]pyridine-8-carboxamide	375.1	E:1.27 F:1.62	(500MHz, DMSO-d_6) 8.87 (d, *J*=8.0 Hz, 1H), 8.68 (d, *J*=5.0 Hz, 1H), 8.60 (s, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 8.00 (d, *J*=5.2 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.55 (d, *J*=4.4 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 6.97 (br. s., 2H), 6.80 (d, *J*=8.0 Hz, 1H), 5.55 (q, *J*=6.4 Hz, 1H), 5.13 (q, *J*=7.2 Hz, 1H), 3.74 (s, 3H), 1.61 (d, *J*=6.3 Hz, 3H), 1.47 (d, *J*=6.9 Hz, 3H)

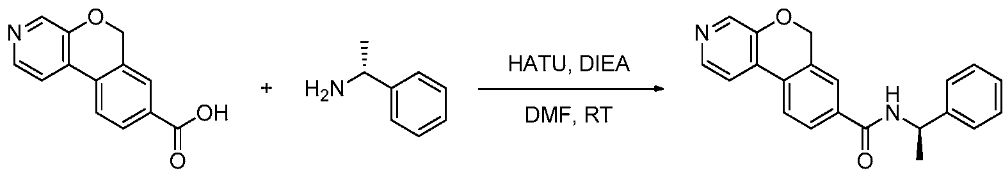
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
V-6		N-(3-(cyclopropylcarbamoyl) benzyl)-5-methyl-5H-chromeno [3,4-c]pyridine-8-carboxamide	414.1	E:1.05 F:1.35	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.69 (d, *J*=4.7 Hz, 1H), 8.62 (s, 1H), 8.42 (br. s., 1H), 8.15 (d, *J*=8.3 Hz, 1H), 8.04 (d, *J*=5.0 Hz, 1H), 7.78 (s, 1H), 7.67 (dd, *J*=15.1, 7.7 Hz, 2H), 7.55 (s, 1H), 7.49 - 7.44 (m, 1H), 7.43 - 7.35 (m, 1H), 5.56 (q, *J*=6.4 Hz, 1H), 4.52 (d, *J*=5.2 Hz, 2H), 2.83 (d, *J*=3.0 Hz, 1H), 1.60 (d, *J*=6.6 Hz, 3H), 0.68 (d, *J*=6.9 Hz, 2H), 0.56 (br. s., 2H)
V-7		N-(3-(ethylcarbamoyl)benzyl)-5-methyl-5H-chromeno[3,4-c] pyridine-8-carboxamide	402.1	E:1.04 F:1.33	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.70 (d, *J*=5.0 Hz, 1H), 8.63 (s, 1H), 8.45 (br. s., 1H), 8.15 (d, *J*=8.0 Hz, 1H), 8.05 (d, *J*=5.0 Hz, 1H), 7.80 (s, 1H), 7.71 (d, *J*=7.4 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.55 (s, 1H), 7.50 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 5.57 (q, *J*=6.1 Hz, 1H), 4.53 (d, *J*=5.2 Hz, 2H), 3.27 (quin, *J*=6.4 Hz, 2H), 1.61 (d, *J*=6.3 Hz, 3H), 1.11 (t, *J*=7.0 Hz, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
V-8		N-(3-carbamoylbenzyl)-5-methyl-5H-chromeno[3,4-c] pyridine-8-carboxamide	374.1	E:0.92 F:1.18	(500MHz, DMSO-d_6) 9.15 (br. S., 1H), 8.61 (d, *J*=5.0 Hz, 1H), 8.54 (s, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.88 (d, *J*=4.7 Hz, 1H), 7.84 (s, 1H), 7.75 (d, *J*=7.4 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.37 (m, 1H), 7.33 (br. S., 1H), 5.52 (q, *J*=6.2 Hz, 1H), 4.52 (d, *J*=5.5 Hz, 2H), 1.59 (d, *J*=6.3 Hz, 3H)
V-9		N-(3-(cyclopropylmethylcarbamoyl) benzyl)-5-methyl-5H-chromeno [3,4-c]pyridine-8-carboxamide	428.1	E:1.17 F:1.48	(500MHz, DMSO-d_6) 9.22 - 9.11 (m, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.54 (s, 2H), 8.09 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=4.7 Hz, 1H), 7.82 (s, 1H), 7.73 (d, *J*=7.4 Hz, 1H), 7.64 (d, *J*=8.3 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.44 (m, 1H), 7.44 - 7.38 (m, 1H), 5.52 (q, *J*=6.5 Hz, 1H), 4.53 (d, *J*=5.5 Hz, 2H), 3.13 (t, *J*=6.1 Hz, 2H), 1.59 (d, *J*=6.3 Hz, 3H), 1.03 (d, *J*=6.1 Hz, 1H), 0.42 (d, *J*=7.2 Hz, 2H), 0.22 (d, *J*=4.1 Hz, 2H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
V-10		5-methyl-N-(3-(methylcarbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	388.1	E:0.96 F:1.24	(500MHz, DMSO-d_6) 9.16 (br. s., 1H), 8.62 (d, *J*=5.0 Hz, 1H), 8.54 (s, 1H), 8.41 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.80 (s, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.53 (s, 1H), 7.49 - 7.44 (m, 1H), 7.43 - 7.37 (m, 1H), 5.52 (q, *J*=6.3 Hz, 1H), 4.52 (d, *J*=5.5 Hz, 2H), 2.77 (d, *J*=1.9 Hz, 3H), 1.59 (d, *J*=6.3 Hz, 3H)
V-11		5-methyl-N-(3-(1-methylcyclopropylcarbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	428.1	E:1.14 F:1.43	(500MHz, DMSO-d_6) 9.14 (t, *J*=5.9 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 2H), 8.54 (s, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=5.0 Hz, 1H), 7.78 (s, 1H), 7.68 (d, *J*=7.7 Hz, 1H), 7.63 (dd, *J*=8.3, 1.7 Hz, 1H), 7.53 (d, *J*=1.9 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.41 - 7.32 (m, 1H), 5.52 (q, *J*=6.6 Hz, 1H), 4.51 (d, *J*=6.1 Hz, 2H), 1.59 (d, *J*=6.6 Hz, 3H), 1.35 (s, 3H), 0.76 - 0.70 (m, 2H), 0.62 - 0.56 (m, 2H)

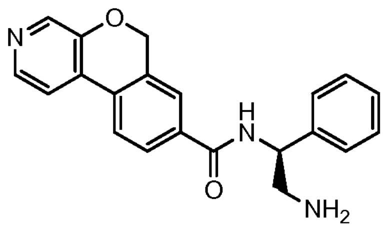
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
V-12		5-methyl-N-(3-(((R)-tetrahydrofuran-2-yl) methylcarbamoyl)benzyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide	458.1	E:1.05 F:1.36	(500MHz, DMSO-d_6) 9.16 (t, *J*=6.1 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.54 (s, 1H), 8.49 (t, *J*=5.8 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=5.0 Hz, 1H), 7.81 (s, 1H), 7.72 (d, *J*=7.7 Hz, 1H), 7.63 (dd, *J*=8.1, 1.8 Hz, 1H), 7.53 (d, *J*=1.7 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.36 (m, 1H), 5.52 (q, *J*=6.6 Hz, 1H), 4.52 (d, *J*=5.8 Hz, 2H), 3.96 (quin, *J*=6.3 Hz, 1H), 3.76 (ddd, *J*=8.2, 7.1, 6.2 Hz, 1H), 3.65 - 3.57 (m, 1H), 3.31-3.26 (m, 2H), 1.94 - 1.74 (m, 3H), 1.62 - 1.53 (m, 4H)

Example VI-1: (R)-N-(1-Phenylethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide

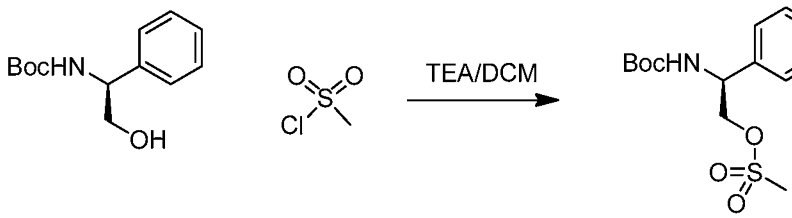


To a solution of Intermediate 3 (15 mg, 0.066 mmol) in DMF (1 mL) were added (R)-1-phenylethanamine (8.0 mg, 0.066 mmol), DIEA (0.058 mL, 0.330 mmol) and HATU (30.1 mg, 0.079 mmol) at rt. The reaction was stirred under argon at rt for 1hr. Purification by reverse phase chromatography afforded Example VI-1 as white solid (9.4 mg 42%). LC-MS (ESI) *m/z*: 331.15 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 8.93 (d, *J*=8.0 Hz, 1H), 8.33 (s, 1H), 8.30 (d, *J*=5.0 Hz, 1H), 8.06 (d, *J*=8.0 Hz, 1H), 7.96 (dd, *J*=8.3, 1.7 Hz, 1H), 7.92 (d, *J*=5.0 Hz, 1H), 7.84 (s, 1H), 7.40 (d, *J*=7.2 Hz, 2H), 7.33 (t, *J*=7.6 Hz, 2H), 7.25 - 7.20 (m, 1H), 5.31 (s, 2H), 5.18 (quin, *J*=7.3 Hz, 1H), 1.49 (d, *J*=6.9 Hz, 3H). Analytical HPLC RT E: 1.17 min; F: 1.53 min.

Example VI-2: (S)-N-(2-Amino-1-phenylethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide



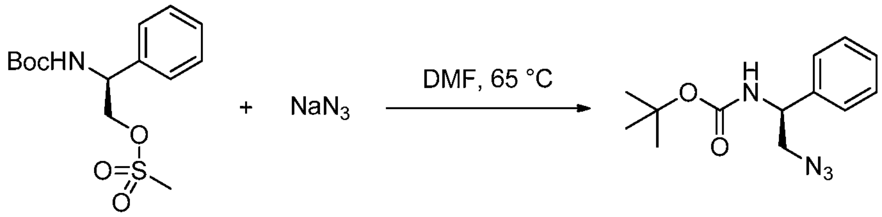
Example VI-2a: (S)-2-((*tert*-Butoxycarbonyl)amino)-2-phenylethyl methanesulfonate



To a solution of (S)-*tert*-butyl (2-hydroxy-1-phenylethyl)carbamate (3.45 g, 14.54 mmol) in DCM (40 mL) were added TEA (3.04 mL, 21.81 mmol) and methanesulfonyl chloride (1.246 mL, 15.99 mmol) at -5 °C. The reaction was stirred under argon at -5 °C for 2 h. The reaction mixture was diluted with DCM, washed with 1M HCl, sat $NaHCO_3$ and brine. The organic phase was dried over sodium sulfate, filtered and concentrated.

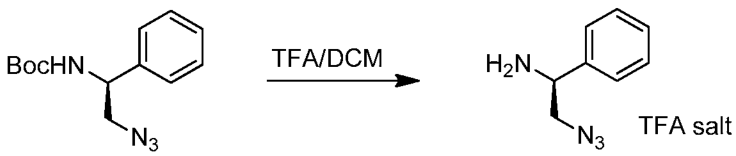
After dried *in vacuo*, VI-2a was obtained as white solid (4.59g, 100%). LC-MS (ESI) *m/z*: 316.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.43 - 7.36 (m, 2H), 7.36 - 7.29 (m, 3H), 5.14 (br. s., 1H), 5.02 (br. s., 1H), 4.55 - 4.34 (m, 2H), 2.89 (s, 3H), 1.45 (s, 9H).

Example VI-2b: (S)-*tert*-Butyl (2-azido-1-phenylethyl)carbamate



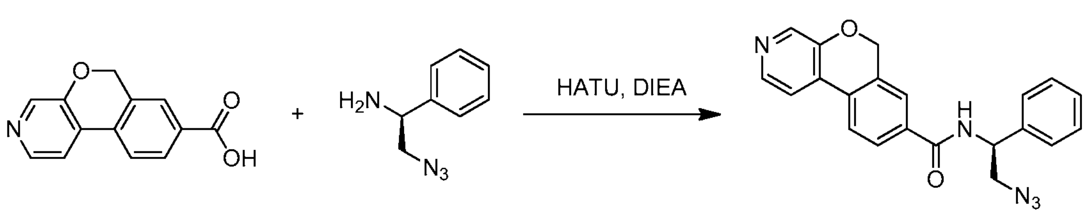
To a solution of VI-2a (4.59 g, 14.55 mmol) in DMF (20 mL) was added NaN_3 (1.892 g, 29.1 mmol) at rt. The reaction was stirred under argon at 65 °C for 3 h. The reaction was cooled to rt and diluted with water. The white precipitate formed was collected by filtration and was further washed with water, then was dried *in vacuo* to afford VI-2b as white solid (3.01 g, 79%). LC-MS (ESI) *m/z*: 263.1 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.43 - 7.35 (m, 2H), 7.35 - 7.29 (m, 3H), 5.05 (br. s., 1H), 4.88 (br. s., 1H), 3.76 - 3.52 (m, 2H), 1.45 (s, 9H).

Example VI-2c: (S)-2-Azido-1-phenylethanamine, TFA salt



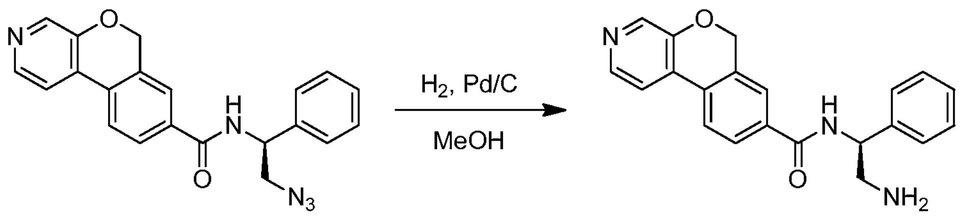
To a solution of VI-2b (295 mg, 1.125 mmol) in DCM (3 mL) was added TFA (1 mL) at rt. The reaction was stirred under argon at rt for 2 h. The solvent was removed and the resulted residue was dried *in vacuo* to give VI2-c as white solid (311 mg, 100%). LC-MS (ESI) *m/z*: 163.1 $[M+H]^+$.

Example VI-2d: (S)-N-(2-Azido-1-phenylethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide, TFA salt



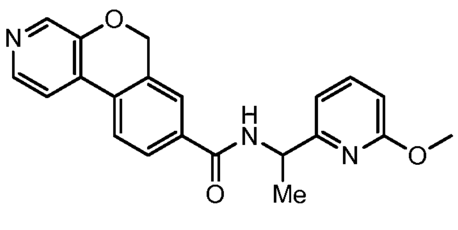
To a solution of Intermediate 2 (30 mg, 0.132 mmol) in DMF (1 mL) were added VI-2c (36.5 mg, 0.132 mmol), DIEA (0.115 mL, 0.660 mmol) and HATU (60.2 mg, 0.158 mmol) at rt. The reaction was stirred under argon at rt for 1.5 h. The crude product was purified by reverse phase chromatography to give VI-2d as white solid (22mg, 34.3%). LC-MS (ESI) *m/z*: 372.1$[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.54 (s, 1H), 8.47 - 8.43 (m, 1H), 8.42 - 8.37 (m, 1H), 8.19 (d, *J*=8.4 Hz, 1H), 8.02 (dd, *J*=8.1, 1.8 Hz, 1H), 7.83 (d, *J*=0.9 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.41 - 7.35 (m, 2H), 7.34 - 7.28 (m, 1H), 5.51 (s, 2H), 5.41 - 5.29 (m, 1H), 3.83 - 3.65 (m, 2H).

Example VI-2:

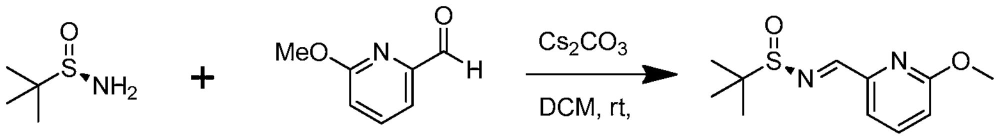


To a solution of VI-2d (22 mg, 0.045 mmol) in MeOH (3 mL) was added catalytic amount of 5% Pd/C. The reaction was stirred under a hydrogen balloon at rt for 2 h. The catalyst was filtered and the solvent was removed from the filtrate to afford Example VI-2 as white solid (13.3 mg, 82%). LC-MS (ESI) *m/z*: 346.1 $[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.28 (s, 1H), 8.26 (d, *J*=5.1 Hz, 1H), 8.02 (s, 2H), 7.91 - 7.83 (m, 2H), 7.54 - 7.49 (m, 2H), 7.45 (t, *J*=7.5 Hz, 2H), 7.41 - 7.35 (m, 1H), 5.50 (dd, *J*=9.7, 4.6 Hz, 1H), 5.31 (s, 2H), 3.56 - 3.41 (m, 2H); Analytical HPLC RT A: 5.14 min, B: 5.67 min.

Example VI-3: (±)-N-(1-(6-Methoxypyridin-2-yl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide

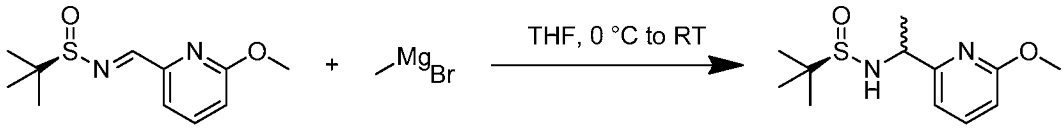


Example VI-3a: (R,E)-N-((6-Methoxypyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide



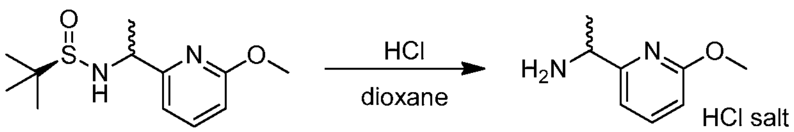
To a stirred suspension of (R)-2-methylpropane-2-sulfinamide (1.0g, 8.25 mmol) and Cs_2CO_3 (4.03 g, 12.38 mmol) in DCM (15 mL) was added a solution of 6-methoxypicolinaldehyde (1.092 mL, 9.08 mmol) in DCM (2 mL) dropwise. The solution was then stirred at rt for 5 h. The solid was filtered and solvent was removed. The crude product was purified by normal phase chromatography to provide VI-3a as clear colorless oil (1.91 g, 96%). LC-MS (ESI) *m/z*: 241.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.72 - 7.58 (m, 2H), 6.85 (dd, *J*=7.9, 1.1 Hz, 1H), 3.99 (s, 3H), 1.29 (s, 9H).

Example VI-3b: (R)-N-(1-(6-Methoxypyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide



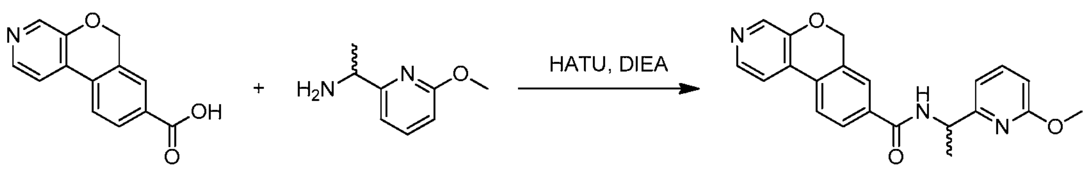
To a solution of VI-3a (650 mg, 2.70 mmol) in THF (6 mL) was added methylmagnesium bromide (1.4 M in toluene, 2.90 mL, 4.06 mmol) at 0 ºC. The reaction was stirred under argon at 0 ºC for 2 h and then was warmed up to rt. After stirred for another 30 min, it was cooled to 0 ºC and NH_4Cl solution was carefully added. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by normal phase chromatography. Two close peaks of two diastereomers were collected and combined. After removal of solvent, VI-3b was obtained as clear colorless oil (578 mg, 83%). LC-MS (ESI) *m/z*: 257.0 $[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 7.53 (dt, *J*=8.3, 7.1 Hz, 2H), 6.86 (d, *J*=7.3 Hz, 1H), 6.82 (d, *J*=7.0 Hz, 1H), 6.62 (d, *J*=8.1 Hz, 2H), 4.83 (br. d, *J*=4.6 Hz, NH) 4.59 - 4.44 (m, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 1.60 (d, *J*=6.8 Hz, 3H), 1.50 (d, *J*=6.6 Hz, 3H), 1.26 (s, 6H), 1.21 (s, 6H).

Example VI-3c: 1-(6-Methoxypyridin-2-yl)ethanamine, 2 HCl



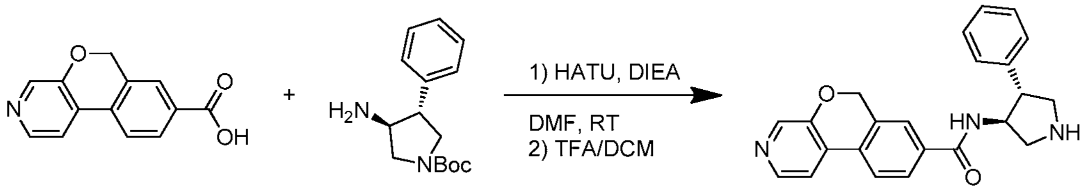
To a solution of VI-3b (578 mg, 2.255 mmol) in MeOH (5 mL) was added HCl (4 M in dioxane, 2.818 mL, 11.27 mmol) at RT. The reaction was stirred under argon at rt for 2 h. The solvent was removed to give VI-3c as white solid (520 mg, 100%). LC-MS (ESI) *m/z*: 153.0$[M+H]^+$.

Example VI-3:



Example VI-3 was prepared by following a similar procedure as described in VI-1 by replacing (R)-1-phenylethanamine with VI-3c. LC-MS (ESI) *m/z*: 362.15$[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 8.87 (d, *J*=8.0 Hz, 1H), 8.35 (s, 1H), 8.31 (d, *J*=5.0 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 8.00 (dd, *J*=8.1, 1.8 Hz, 1H), 7.94 (d, *J*=5.2 Hz, 1H), 7.87 (d, *J*=1.1 Hz, 1H), 7.66 (dd, *J*=8.1, 7.6 Hz, 1H), 6.98 (d, *J*=7.4 Hz, 1H), 6.67 (d, *J*=8.3 Hz, 1H), 5.32 (s, 2H), 5.12 (quin, *J*=7.2 Hz, 1H), 3.87 (s, 3H), 1.52 (d, *J*=7.2 Hz, 3H); Analytical HPLC RT E: 1.12 min, F: 1.59 min.

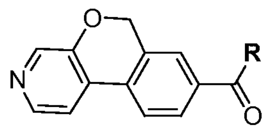
Example VI-4: N-((3S,4R)-4-Phenylpyrrolidin-3-yl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide

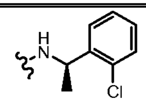
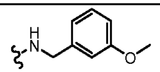


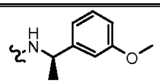
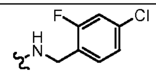
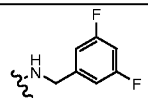
Amide coupling was carried out by following a similar procedure as described in Example VI-1 by replacing (R)-1-phenylethanamine with (3S,4R)-*tert*-butyl 3-amino-4-phenylpyrrolidine-1-carboxylate. Thus obtained intermediate was treated with TFA in DCM to provide Example VI-4 as white solid after reverse phase chromatography purification. LC-MS (ESI) *m/z*: 372.20 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 8.80 (d, *J*=8.0 Hz, 1H), 8.35 (s, 1H), 8.31 (d, *J*=5.0 Hz, 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.95 - 7.87 (m, 2H), 7.78 (s, 1H), 7.41 - 7.37 (m, 2H), 7.36 - 7.31 (m, 2H), 7.28 - 7.22 (m, 1H), 5.31 (s, 2H), 4.61 (quin, *J*=7.7 Hz, 1H), 3.61 - 3.56 (m, 1H), 3.47 (dd, *J*=17.6, 9.4 Hz, 1H), 3.08 (t, *J*=10.3 Hz, 1H), 2.98 (dd, *J*=11.1, 7.6 Hz, 1H); Analytical HPLC RT E: 0.92 min, F: 1.20 min.

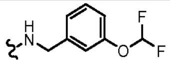
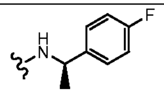
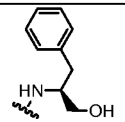
The compounds listed in Table VI were prepared by following the similar procedure as described in Example VI-1.

Table VI

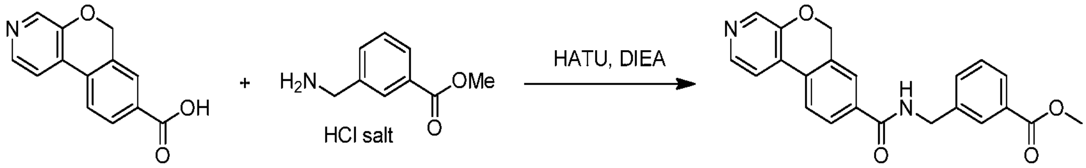


Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VI-5		(R)-N-(1-(2-chlorophenyl) ethyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	364.90	E:1.36 F:1.69	(500MHz, DMSO-d_6) 9.06 (d, *J*=7.2 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J*=4.7 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 1H), 7.93 (d, *J*=4.7 Hz, 1H), 7.85 (s, 1H), 7.55 (d, *J*=7.7 Hz, 1H), 7.43 (d, *J*=7.7 Hz, 1H), 7.34 (t, *J*=7.4 Hz, 1H), 7.30 - 7.23 (m, 1H), 5.50 - 5.41 (m, 1H), 5.32 (s, 2H), 1.46 (d, *J*=6.6 Hz, 3H)
VI-6		N-(3-methoxybenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	346.90	E:1.15 F:1.49	(500MHz, DMSO-d_6) 9.16 (br. s., 1H), 8.40 (br. s., 1H), 8.34 (br. s., 1H), 8.11 (d, *J*=8.3 Hz, 1H), 8.04 - 7.94 (m, 2H), 7.86 (s, 1H), 7.25 (t, *J*=7.7 Hz, 1H), 6.95 - 6.87 (m, 2H), 6.82 (d, *J*=8.3 Hz, 1H), 5.34 (s, 2H), 4.47 (d, *J*=5.0 Hz, 2H), 3.73 (s, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VI-7		(R)-N-(1-(3-methoxyphenyl) ethyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	361.20	E:1.26 F:1.56	(500MHz, DMSO-d_6) 8.89 (d, *J*=8.0 Hz, 1H), 8.35 (s, 1H), 8.32 (d, *J*=5.0 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.97 (dd, *J*=8.0, 1.7 Hz, 1H), 7.93 (d, *J*=5.2 Hz, 1H), 7.85 (d, *J*=0.8 Hz, 1H), 7.26 (t, *J*=8.0 Hz, 1H), 7.03 - 6.95 (m, 2H), 6.87 - 6.76 (m, 1H), 5.33 (s, 2H), 5.17 (quin, *J*=7.3 Hz, 1H), 3.76 (s, 3H), 1.49 (d, *J*=6.9 Hz, 3H)
VI-8		N-(4-chloro-2-fluorobenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	369.10	E:1.29 F:1.66	(500MHz, DMSO-d_6) 9.16 (t, *J*=5.8 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J*=5.0 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.96 (dd, *J*=8.3, 1.7 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.84 (s, 1H), 7.46 - 7.37 (m, 2H), 7.28 (dd, *J*=8.3, 1.9 Hz, 1H), 5.31 (s, 2H), 4.50 (d, *J*=5.8 Hz, 2H)
VI-9		N-(3,5-difluorobenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	353.15	E:1.08 F:1.64	(500MHz, DMSO-d_6) 9.23 (t, *J*=5.9 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J*=5.2 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.97 (dd, *J*=8.3, 1.4 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.86 (s, 1H), 7.17 - 7.08 (m, 1H), 7.08 - 7.00 (m, 2H), 5.32 (s, 2H), 4.51 (d, *J*=5.8 Hz, 2H)

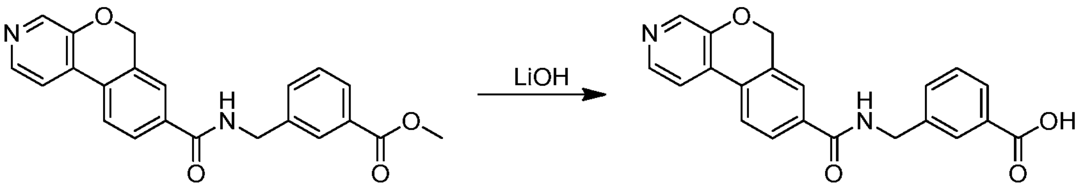
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VI-10		N-(3-(difluoromethoxy)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	383.15	E:1.23 F:1.57	(500MHz, DMSO-d_6) 9.21 (t, *J*=5.9 Hz, 1H), 8.34 (s, 1H), 8.30 (d, *J*=5.2 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.97 (dd, *J*=8.3, 1.4 Hz, 1H), 7.93 (d, *J*=5.0 Hz, 1H), 7.85 (s, 1H), 7.42 - 7.19 (m, 3H), 7.13 (s, 1H), 7.09 - 7.04 (m, 1H), 5.31 (s, 2H), 4.51 (d, *J*=5.8 Hz, 2H)
VI-11		(R)-N-(1-(4-fluorophenyl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	349.20	E:1.22 F:1.57	(500MHz, DMSO-d_6) 8.93 (d, *J*=8.0 Hz, 1H), 8.33 (s, 1H), 8.30 (d, *J*=5.0 Hz, 1H), 8.06 (d, *J*=8.3 Hz, 1H), 7.95 (dd, *J*=8.1, 1.2 Hz, 1H), 7.92 (d, *J*=5.0 Hz, 1H), 7.83 (s, 1H), 7.43 (dd, *J*=8.5, 5.8 Hz, 2H), 7.15 (t, *J*=8.8 Hz, 2H), 5.31 (s, 2H), 5.17 (quin, *J*=7.2 Hz, 1H), 1.48 (d, *J*=7.2 Hz, 3H)
VI-12		(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	361.20	E:1.03 F:1.31	(500MHz, DMSO-d_6) 8.36 - 8.27 (m, 3H), 8.04 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=5.0 Hz, 1H), 7.86 (d, *J*=8.0 Hz, 1H), 7.74 (s, 1H), 7.30 - 7.22 (m, 4H), 7.15 (br. s., 1H), 5.29 (s, 2H), 4.88 (t, *J*=5.4 Hz, 1H), 4.17 (d, *J*=5.5 Hz, 1H), 3.54 - 3.47 (m, 1H), 3.43 (dt, *J*=10.7, 5.5 Hz, 1H), 2.96 (dd, *J*=13.5, 5.0 Hz, 1H), 2.79 (dd, *J*=13.2, 9.4 Hz, 1H)

Example VII-1: Methyl 3-((6H-isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoate



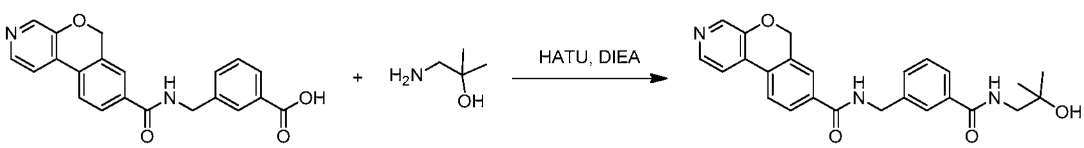
Example VII-1 was prepared by following a similar procedure as described in VI-1 by replacing (R)-1-phenylethanamine with methyl 3-(aminomethyl)benzoate, HCl salt. LC-MS (ESI) *m/z*: 375.20[M+H]$^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.25 (t, *J*=5.9 Hz, 1H), 8.40 (s, 1H), 8.35 (d, *J*=5.0 Hz, 1H), 8.11 (d, *J*=8.3 Hz, 1H), 8.01 (d, *J*=5.2 Hz, 1H), 7.98 (dd, *J*=8.0, 1.7 Hz, 1H), 7.94 (s, 1H), 7.88 - 7.83 (m, 2H), 7.62 (d, *J*=7.7 Hz, 1H), 7.53 - 7.47 (m, 1H), 5.35 (s, 2H), 4.56 (d, *J*=6.1 Hz, 2H), 3.85 (s, 3H). Analytical HPLC RT E: 1.19 min, F: 1.49 min.

Example VII-2: 3-((6H-Isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoic acid



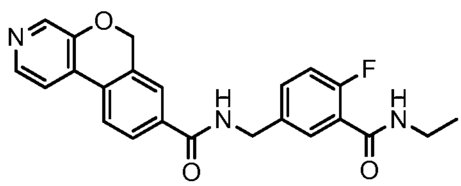
To a solution of Example VII-1 (220 mg, 0.588 mmol) in THF (5 mL) and H_2O (2 mL) was added LiOH (42.2 mg, 1.763 mmol) at rt. The reaction was stirred under argon at rt for 4 h. The solvent was removed. Reverse phase purification gave VII-2 as white solid (200 mg, 94%). LC-MS (ESI) *m/z*: 361.12 [M+H]$^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.22 (t, *J*=5.9 Hz, 1H), 8.33 (s, 1H), 8.30 (d, *J*=5.2 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 8.00 - 7.94 (m, 1H), 7.91 (d, *J*=3.9 Hz, 2H), 7.86 (s, 1H), 7.82 (d, *J*=7.7 Hz, 1H), 7.56 (d, *J*=7.7 Hz, 1H), 7.48 - 7.41 (m, 1H), 5.31 (s, 2H), 4.55 (d, *J*=5.8 Hz, 2H); Analytical HPLC RT E: 0.96 min, F: 0.96 min.

Example VII-3: N-(3-((2-Hydroxy-2-methylpropyl)carbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide



To a solution of VII-2 (30 mg, 0.083 mmol) in DMF (1.5 mL) were added 1-amino-2-methylpropan-2-ol (14.84 mg, 0.166 mmol), DIEA (0.044 mL, 0.250 mmol) and HATU (38.0 mg, 0.100 mmol) at rt. The reaction was stirred under argon at rt for 2 h. The crude product was purified by reverse phase chromatography to afford VII-3 as white solid (20.6 mg, 45%). LC-MS (ESI) *m/z*: 432.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.22 (t, *J*=5.9 Hz, 1H), 8.45 (s, 1H), 8.38 (d, *J*=5.3 Hz, 1H), 8.20 (t, *J*=5.9 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 8.09 (d, *J*=5.3 Hz, 1H), 8.00 (dd, *J*=8.1, 1.8 Hz, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.75 (d, *J*=7.7 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.46 - 7.40 (m, 1H), 5.37 (s, 2H), 4.55 (d, *J*=5.9 Hz, 2H), 3.25 (d, *J*=6.2 Hz, 2H), 1.10 (s, 6H); Analytical HPLC RT A: 3.56 min, B: 3.72 min.

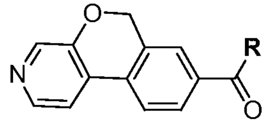
Example VII-4: N-(3-(Ethylcarbamoyl)-4-fluorobenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide

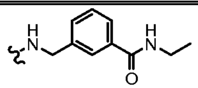
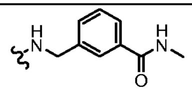


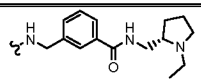
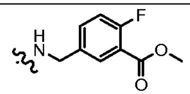
Example VII-4 was prepared by following a similar procedure as described in VII-1, VII-2 and VII-3 by replacing methyl 3-(aminomethyl)benzoate, HCl salt with Intermediate 9 in Example VII-1. LC-MS (ESI) *m/z*: 406.20 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.19 (t, *J*=5.9 Hz, 1H), 8.33 (s, 1H), 8.30 (d, *J*=5.0 Hz, 1H), 8.27 (br. s., 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.96 (d, *J*=8.0 Hz, 1H), 7.91 (d, *J*=5.0 Hz, 1H), 7.84 (s, 1H), 7.57 (dd, *J*=6.9, 2.2 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.23 (dd, *J*=10.3, 8.7 Hz, 1H), 5.31 (s, 2H), 4.49 (d, *J*=6.1 Hz, 2H), 3.28 - 3.23 (m, 2H), 1.10 (t, *J*=7.2 Hz, 3H); Analytical HPLC RT E: 1.06 min, F: 1.33 min.

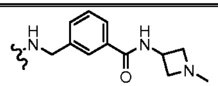
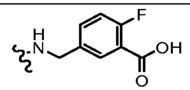
The compounds listed in Table VII were prepared by following the similar procedure as described in example Examples VII-1 to VII-4.

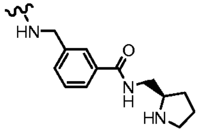
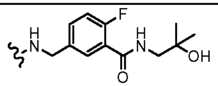
Table VII



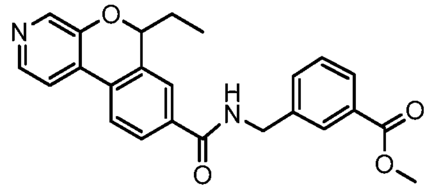
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VII-5		N-(3-(ethylcarbamoyl) benzyl)-6H-isochromeno [3,4-c]pyridine-8-carboxamide	388.1	A:6.01 B:6.24	(400MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.45 (s, 2H), 8.38 (d, *J*=5.3 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 8.09 (d, *J*=5.3 Hz, 1H), 8.00 (dd, *J*=8.1, 1.8 Hz, 1H), 7.87 (d, *J*=1.1 Hz, 1H), 7.81 (s, 1H), 7.71 (d, *J*=7.7 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.44 - 7.38 (m, 1H), 5.37 (s, 2H), 4.54 (d, *J*=5.9 Hz, 2H), 3.34 - 3.22 (m, 2H), 1.11 (t, *J*=7.2 Hz, 3H)
VII-6		N-(3-(methylcarbamoyl) benzyl)-6H-isochromeno [3,4-c]pyridine-8-carboxamide	374.15	E:0.89 F:1.18	(500MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.42 (s, 2H), 8.36 (d, *J*=5.2 Hz, 1H), 8.12 (d, *J*=8.0 Hz, 1H), 8.04 (d, *J*=5.2 Hz, 1H), 8.00 (s, 1H), 7.87 (s, 1H), 7.81 (s, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.42 (d, *J*=7.4 Hz, 1H), 5.35 (s, 2H), 4.57 - 4.52 (m, 2H), 2.77 (d, *J*=4.4 Hz, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VII-7		(S)-N-(3-((1-ethylpyrrolidin-2-yl) methylcarbamoyl)benzyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	471.30	E:0.91 F:1.15	(500MHz, DMSO-d_6) 9.21 (br. s., 1H), 8.35 (s, 1H), 8.32 (br. s., 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.99 (d, *J*=8.3 Hz, 1H), 7.94 (br. s., 1H), 7.87 (s, 1H), 7.82 (br. s., 1H), 7.73 (d, *J*=7.4 Hz, 1H), 7.51 (br. s., 1H), 7.46 (d, *J*=7.2 Hz, 1H), 5.33 (s, 2H), 4.57 (d, *J*=4.4 Hz, 2H), 3.76 - 2.98 (m, 7H), 1.69 (br. s., 4H), 1.27 - 0.92 (m, 3H)
VII-8		methyl 5-((6H-isochromeno [3,4-c]pyridine-8-carboxamido)methyl)-2-fluorobenzoate	393.0	A:4.89 B:5.37	(400MHz, DMSO-d_6) 9.24 (t, *J*=5.9 Hz, 1H), 8.45 (s, 1H), 8.38 (d, *J*=5.3 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 8.08 (d, *J*=5.3 Hz, 1H), 7.98 (dd, *J*=8.3, 1.7 Hz, 1H), 7.90 - 7.83 (m, 2H), 7.68 - 7.58 (m, 1H), 7.33 (dd, *J*=11.0, 8.6 Hz, 1H), 5.37 (s, 2H), 4.52 (d, *J*=5.7 Hz, 2H), 3.85 (s, 3H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VII-9		N-(3-(1-methylazetidin-3-ylcarbamoyl)benzyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	429.00	E:0.85 F:0.99	(500MHz, DMSO-d_6) 9.21 (t, *J*=6.1 Hz, 1H), 8.89 (d, *J*=6.6 Hz, 1H), 8.34 (s, 1H), 8.31 (d, *J*=5.2 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 7.98 (dd, *J*=8.1, 1.5 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.86 (s, 1H), 7.83 (s, 1H), 7.75 (d, *J*=7.7 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.48 - 7.43 (m, 1H), 5.32 (s, 2H), 4.56 (d, *J*=5.8 Hz, 4H), 3.95 - 3.81 (m, 2H), 3.46 (br. S., 2H)
VII-10		5-((6H-isochromeno[3,4-c] pyridine-8-carboxamido) methyl)-2-fluorobenzoic acid	379.15		(500MHz, DMSO-d_6) 9.22 (t, *J*=5.9 Hz, 1H), 8.38 (s, 1H), 8.33 (d, *J*=5.2 Hz, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 8.01 - 7.93 (m, 2H), 7.85 (d, *J*=1.1 Hz, 1H), 7.83 (dd, *J*=7.0, 2.3 Hz, 1H), 7.59 (ddd, *J*=8.5, 4.7, 2.5 Hz, 1H), 7.28 (dd, *J*=10.7, 8.5 Hz, 1H), 5.33 (s, 2H), 4.51 (d, *J*=5.8 Hz, 2H)

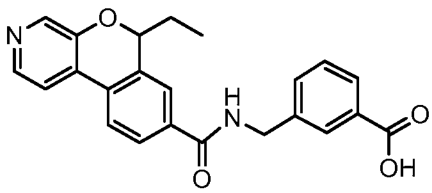
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VII-11		(R)-N-(3-(pyrrolidin-2-ylmethylcarbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	443.25	E:0.84 F:1.00	(500MHz, DMSO-d_6) 9.27 (t, *J*=5.9 Hz, 1H), 9.02 (br. s., 1H), 8.81 (t, *J*=5.6 Hz, 1H), 8.38 (s, 1H), 8.34 (d, *J*=5.2 Hz, 1H), 8.12 (d, *J*=8.3 Hz, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 7.97 (d, *J*=5.0 Hz, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.77 (d, *J*=7.7 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.45 (m, 1H), 5.34 (s, 2H), 4.57 (d, *J*=6.1 Hz, 2H), 3.66 - 3.49 (m, 3H), 3.25 (ddd, *J*=10.9, 7.3, 4.1 Hz, 1H), 3.19 - 3.10 (m, 1H), 2.11 - 2.02 (m, 1H), 1.98 - 1.82 (m, 2H), 1.68 (dq, *J*=12.9, 8.4 Hz, 1H)
VII-12		N-(4-fluoro-3-(2-hydroxy-2-methylpropylcarbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	450.25	E:0.95 F:1.21	(500MHz, DMSO-d_6) 9.22 (br. s., 1H), 8.35 (br. s., 1H), 8.31 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 8.01 (br. s., 1H), 7.97 (d, *J*=7.7 Hz, 1H), 7.93 (br. s., 1H), 7.85 (br. s., 1H), 7.63 (br. s., 1H), 7.49 (br. s., 1H), 7.27 (t, *J*=9.2 Hz, 1H), 5.32 (br. s., 2H), 4.58 (br. s., 1H), 4.51 (br. s., 2H), 3.25 (br. s., 2H), 1.13 (br. s., 6H)

Example VIII-1: Methyl 3-((6-ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoate



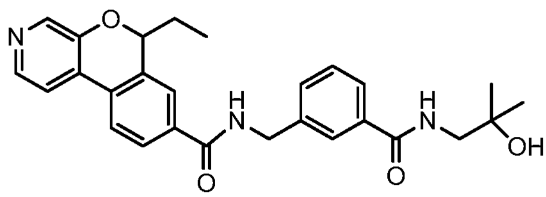
Example VIII-1 was prepared by following the similar procedure as described in Example III-1 using Intermediate 7 to replace Intermediate 1. LC-MS (ESI) *m/z*: 40.3.1[M+H]$^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.25 (s, 1H), 8.21 (d, *J*=5.1 Hz, 1H), 8.05 (s, 1H), 8.03 - 7.98 (m, 1H), 7.97 - 7.89 (m, 2H), 7.85 (d, *J*=5.1 Hz, 1H), 7.76 (s, 1H), 7.63 (d, *J*=7.7 Hz, 1H), 7.50 - 7.42 (m, 1H), 5.28 (dd, *J*=8.8, 4.6 Hz, 1H), 4.65 (s, 2H), 3.89 (s, 3H), 1.97 - 1.74 (m, 2H), 1.06 (t, *J*=7.4 Hz, 3H); Analytical HPLC RT A: 5.38 min, B: 5.91min.

Example VIII-2: 3-((6-Ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoic acid



Example VIII-2 was prepared by following the similar procedure as described in Example III-2 using Example VIII-1 to replace Example III-1. LC-MS (ESI) *m/z*: 389.0[M+H]$^+$; ^{1}H NMR (400MHz, CD_3OD) δ 8.57 (s, 1H), 8.43 (s, 2H), 8.20 (d, *J*=8.4 Hz, 1H), 8.07 - 8.00 (m, 2H), 7.97 - 7.90 (m, 1H), 7.85 (d, *J*=1.8 Hz, 1H), 7.62 (dd, *J*=7.7, 0.4 Hz, 1H), 7.51 - 7.41 (m, 1H), 5.54 (dd, *J*=8.6, 4.6 Hz, 1H), 4.66 (s, 2H), 2.08 - 1.82 (m, 2H), 1.09 (t, *J*=7.3 Hz, 3H); Analytical HPLC RT A: 4.49 min, B: 4.86 min.

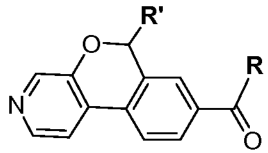
Example VIII-3: 6-Ethyl-N-(3-(2-hydroxy-2-methylpropylcarbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide

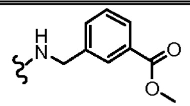
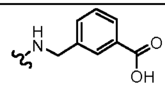


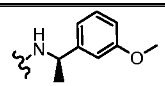
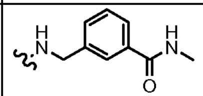
Example VIII-3 was prepared by following the similar procedure as described in Example III-3 using Example VIII-2 to replace Example III-2 to couple with 1-amino-2-methylpropan-2-ol. LC-MS (ESI) *m/z*: 460.1$[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.21 (t, *J*=5.8 Hz, 1H), 8.33 (s, 1H), 8.28 (d, *J*=5.2 Hz, 1H), 8.24 (t, *J*=5.9 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.97 (d, *J*=8.3 Hz, 1H), 7.92 (d, *J*=5.2 Hz, 1H), 7.83 (s, 2H), 7.75 (d, *J*=7.7 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.46 - 7.39 (m, 1H), 5.35 (dd, *J*=8.7, 4.5 Hz, 1H), 4.58 - 4.53 (m, 2H), 3.24 (d, *J*=6.1 Hz, 2H), 1.85 - 1.69 (m, 2H), 1.09 (s, 6H), 0.98 (t, *J*=7.3 Hz, 3H); Analytical HPLC RT E: 1.08 min, F: 1.42 min.

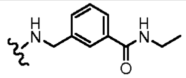
The compounds listed in Table VIII were prepared by following the similar procedure as described in Example VII-1-3, by using Intermediates 6, 7, 8, 9 and 10.

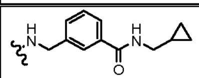
Table VIII

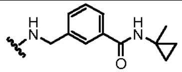
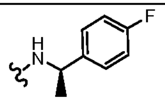


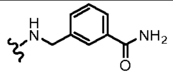
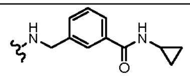
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-4	Me		methyl 3-((6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoate	389.0	A:5.27 B:5.62	(400MHz, CD_3OD) 8.21 (s, 1H), 8.19 (d, *J*=5.1 Hz, 1H), 8.03 (s, 1H), 7.99 - 7.86 (m, 3H), 7.81 (d, *J*=5.3 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.61 (d, *J*=7.7 Hz, 1H), 7.48 - 7.38 (m, 1H), 5.43 (q, *J*=6.5 Hz, 1H), 4.64 (s, 2H), 3.88 (s, 3H), 1.60 (d, *J*=6.6 Hz, 3H)
VIII-5	Me		3-((6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamido)methyl)benzoic acid	375.0	A:4.32 B:4.50	(400MHz, DMF-d_7) 9.24 (t, *J*=5.8 Hz, 1H), 8.39 (s, 1H), 8.37 (d, *J*=5.3 Hz, 1H), 8.20 - 8.06 (m, 4H), 8.05 - 7.98 (m, 2H), 7.93 (d, *J*=7.9 Hz, 1H), 7.68 (d, *J*=8.1 Hz, 1H), 7.56 - 7.45 (m, 1H), 5.59 (q, *J*=6.5 Hz, 1H), 4.70 (d, *J*=5.9 Hz, 2H), 1.64 (d, *J*=6.6 Hz, 3H)

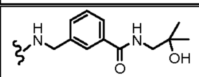
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-6	Me		N-((R)-1-(3-methoxyphenyl) ethyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	375.2	A:5.63 B:6.02	(400MHz, DMSO-d_6) 8.94 (d, *J*=7.3 Hz, 1H), 8.55 (s, 1H), 8.46 (d, *J*=5.5 Hz, 1H), 8.25 (d, *J*=5.5 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 8.02 (dt, *J*=8.0, 2.3 Hz, 1H), 7.87 (br. s., 1H), 7.26 (t, *J*=8.1 Hz, 1H), 7.04 - 6.94 (m, 2H), 6.85 - 6.76 (m, 1H), 5.77 - 5.62 (m, 1H), 5.18 (quin, *J*=7.3 Hz, 1H), 3.76 (s, 3H), 1.61 (dd, *J*=6.6, 2.4 Hz, 3H), 1.50 (d, *J*=6.6 Hz, 3H)
VIII-7	Me		6-methyl-N-(3-(methylcarbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	388.1	E:0.90 F:1.19	(500MHz, DMSO-d_6) 9.20 (br. s., 1H), 8.42 (br. s., 1H), 8.34 (s, 1H), 8.30 (d, *J*=4.7 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 1H), 8.02 - 7.94 (m, 2H), 7.86 (s, 1H), 7.81 (s, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.45 - 7.37 (m, 1H), 5.54 (q, *J*=6.2 Hz, 1H), 4.55 (br. s., 2H), 2.77 (d, *J*=1.9 Hz, 3H), 1.59 (d, *J*=6.3 Hz, 3H)

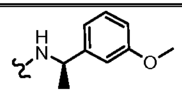
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-8	Me		N-(3-(ethylcarbamoyl)benzyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	402.1	E:0.97 F:1.27	(500MHz, DMSO-d_6) 9.20 (br. s., 1H), 8.45 (br. s., 1H), 8.33 (s, 1H), 8.29 (d, *J*=4.7 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.94 (d, *J*=6.3 Hz, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.71 (d, *J*=7.4 Hz, 1H), 7.50 - 7.44 (m, 1H), 7.44 - 7.35 (m, 1H), 5.54 (q, *J*=6.1 Hz, 1H), 4.55 (br. s., 2H), 3.27 (quin, *J*=6.6 Hz, 2H), 1.59 (d, *J*=6.6 Hz, 3H), 1.11 (t, *J*=7.0 Hz, 3H)

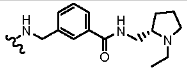
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-9	Me		N-(3-(cyclopropylmethylcarbamoyl)benzyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	428.1	E:1.08 F:1.41	(500MHz, DMSO-d_6) 8.98 (br. s., 1H), 8.32 (br. s., 1H), 8.12 (s, 1H), 8.08 (d, *J*=4.1 Hz, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.73 (br. s., 2H), 7.63 (d, *J*=13.8 Hz, 2H), 7.51 (d, *J*=7.4 Hz, 1H), 7.31 - 7.23 (m, 1H), 7.23 - 7.14 (m, 1H), 5.32 (q, *J*=6.0 Hz, 1H), 4.34 (br. s., 2H), 2.91 (t, *J*=5.6 Hz, 2H), 1.37 (d, *J*=6.3 Hz, 3H), 0.85 - 0.72 (m, 1H), 0.20 (d, *J*=7.2 Hz, 2H), 0.00 (d, *J*=2.2 Hz, 2H)

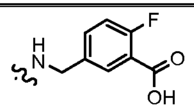
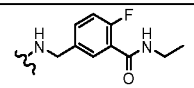
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-10	Me		6-methyl-N-(3-(1-methylcyclopropylcarbamoyl)benzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	428.1	E:1.14 F:1.48	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.63 (s, 1H), 8.35 (s, 1H), 8.31 (d, *J*=4.1 Hz, 1H), 8.10 (d, *J*=7.7 Hz, 1H), 8.03 - 7.97 (m, 2H), 7.86 (s, 1H), 7.79 (s, 1H), 7.68 (d, *J*=7.7 Hz, 1H), 7.46 (d, *J*=7.4 Hz, 1H), 7.42 - 7.34 (m, 1H), 5.55 (q, *J*=6.1 Hz, 1H), 4.54 (br. s., 2H), 1.59 (d, *J*=6.3 Hz, 3H), 1.35 (s, 3H), 0.72 (br. s., 2H), 0.59 (br. s., 2H)
VIII-11	Me		N-((R)-1-(4-fluorophenyl)ethyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	363.0	E:1.37 F:1.74	(500MHz, DMSO-d_6) 8.91 (d, *J*=7.7 Hz, 1H), 8.36 (s, 1H), 8.31 (d, *J*=4.4 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.98 (d, *J*=4.4 Hz, 2H), 7.82 (br. s., 1H), 7.44 (t, *J*=6.3 Hz, 2H), 7.16 (t, *J*=8.4 Hz, 2H), 5.56 (d, *J*=6.3 Hz, 1H), 5.19 (t, *J*=6.9 Hz, 1H), 1.58 (d, *J*=6.3 Hz, 3H), 1.50 (d, *J*=6.9 Hz, 3H)

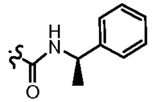
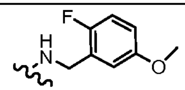
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-12	Me		N-(3-carbamoylbenzyl)-6-methyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	374.1	E:0.87 F:1.12	(500MHz, DMSO-d_6) 9.21 (br. s., 1H), 8.35 (s, 1H), 8.31 (br. s., 1H), 8.11 (d, *J*=8.3 Hz, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 7.88 (br. s., 2H), 7.77 (d, *J*=7.4 Hz, 1H), 7.50 (d, *J*=7.4 Hz, 1H), 7.46 - 7.39 (m, 1H), 7.35 (br. s., 1H), 5.56 (d, *J*=6.3 Hz, 1H), 4.57 (br. s., 2H), 1.60 (d, *J*=6.3 Hz, 3H)
VIII-13	Me		N-(3-(cyclopropylcarbamoyl) benzyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	414.1	E:0.97 F:1.27	(500MHz, DMSO-d_6) 9.19 (br. s., 1H), 8.42 (br. s., 1H), 8.33 (br. s., 1H), 8.29 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.98 (d, *J*=8.0 Hz, 1H), 7.85 (s, 1H), 7.79 (br. s., 1H), 7.68 (d, *J*=7.4 Hz, 1H), 7.47 (d, *J*=7.4 Hz, 1H), 7.43 - 7.37 (m, 1H), 5.54 (d, *J*=6.1 Hz, 1H), 4.54 (br. s., 2H), 2.86 - 2.79 (m, 1H), 1.58 (d, *J*=6.1 Hz, 3H), 0.72 - 0.64 (m, 2H), 0.56 (br. s., 2H)

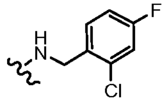
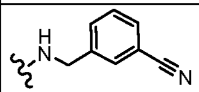
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-14	Me		N-(3-(2-hydroxy-2-methylpropylcarbamoyl) benzyl)-6-methyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	446.2	E:0.92 F:1.19	(500MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.33 (s, 1H), 8.29 (d, *J*=5.0 Hz, 1H), 8.20 (t, *J*=5.9 Hz, 1H), 8.09 (d, *J*=8.3 Hz, 1H), 8.01 - 7.97 (m, 1H), 7.93 (d, *J*=5.2 Hz, 1H), 7.85 (d, *J*=9.9 Hz, 2H), 7.75 (d, *J*=7.4 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.45 - 7.40 (m, 1H), 5.53 (q, *J*=6.5 Hz, 1H), 4.56 (dd, *J*=5.6, 2.3 Hz, 2H), 3.25 (d, *J*=6.3 Hz, 2H), 1.58 (d, *J*=6.6 Hz, 3H), 1.10 (s, 6H)

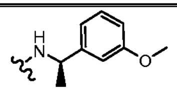
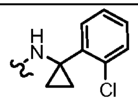
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-15	Et		6-ethyl-N-((R)-1-(3-methoxyphenyl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	389.1	E:1.43 F:1.81	(500MHz, DMSO-d_6) 8.89 (d, *J*=7.7 Hz, 1H), 8.44 (s, 1H), 8.36 (d, *J*=5.2 Hz, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=5.2 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.83 (dd, *J*=4.0, 1.5 Hz, 1H), 7.30 - 7.22 (m, 1H), 6.99 - 6.94 (m, 2H), 6.85 - 6.74 (m, 1H), 5.42 (dt, *J*=8.5, 4.0 Hz, 1H), 5.16 (quin, *J*=7.3 Hz, 1H), 3.73 (s, 3H), 1.88 - 1.70 (m, 2H), 1.49 (d, *J*=6.9 Hz, 3H), 1.00 (td, *J*=7.4, 1.5 Hz, 3H)

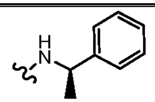
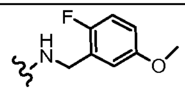
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-16	Me		N-(3-(((S)-1-ethylpyrrolidin-2-yl)methylcarbamoyl)benzyl)-6-methyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	485.2	E:0.92 F:1.20	(500MHz, DMSO-d_6) 9.20 (t, *J*=5.9 Hz, 1H), 8.38 - 8.31 (m, 2H), 8.29 (d, *J*=5.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.98 (dd, *J*=8.0, 1.7 Hz, 1H), 7.92 (d, *J*=5.0 Hz, 1H), 7.86 (d, *J*=1.4 Hz, 1H), 7.80 (s, 1H), 7.71 (d, *J*=7.7 Hz, 1H), 7.52 - 7.45 (m, 1H), 7.45 - 7.39 (m, 1H), 5.53 (q, *J*=6.5 Hz, 1H), 4.55 (dd, *J*=5.6, 2.9 Hz, 2H), 3.12 - 2.99 (m, 2H), 2.84 (dd, *J*=11.6, 7.2 Hz, 1H), 2.66 - 2.56 (m, 1H), 2.29 (br. s., 1H), 2.14 (br. s., 1H), 1.91 (s, 1H), 1.82 - 1.73 (m, 1H), 1.67 - 1.53 (m, 6H), 1.03 (t, *J*=7.2 Hz, 3H)

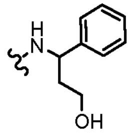
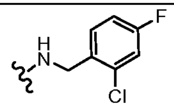
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-17	Et		5-((6-ethyl-6H-isochromeno [3,4-c]pyridine-8-carboxamido) methyl)-2-fluorobenzoic acid	407.1	A:4.50 B:4.80	(400MHz, CD_3OD) 8.59 (s, 1H), 8.50 - 8.42 (m, 2H), 8.21 (d, *J*=8.4 Hz, 1H), 8.03 (dd, *J*=8.1, 1.8 Hz, 1H), 7.97 (dd, *J*=6.8, 2.4 Hz, 1H), 7.85 (d, *J*=1.8 Hz, 1H), 7.62 (ddd, *J*=8.5, 4.5, 2.4 Hz, 1H), 7.19 (dd, *J*=10.7, 8.5 Hz, 1H), 5.56 (dd, *J*=8.6, 4.6 Hz, 1H), 4.62 (s, 2H), 2.03 - 1.85 (m, 2H), 1.10 (t, *J*=7.4 Hz, 3H)
VIII-18	Et		6-ethyl-N-(3-(ethylcarbamoyl)-4-fluorobenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	434.1	E:1.19 F:1.59	(500MHz, DMSO-d_6) δ 9.22 (t, *J*=5.8 Hz, 1H), 8.36 (s, 1H), 8.30 (d, *J*=5.0 Hz, 2H), 8.11 (d, *J*=8.3 Hz, 1H), 7.99 - 7.90 (m, 2H), 7.83 (s, 1H), 7.57 (d, *J*=6.6 Hz, 1H), 7.46 (br. s., 1H), 7.24 (t, *J*=9.4 Hz, 1H), 5.37 (dd, *J*=8.7, 4.5 Hz, 1H), 4.49 (d, *J*=5.5 Hz, 2H), 3.25 (quin, *J*=6.8 Hz, 3H), 1.87 - 1.68 (m, 2H), 1.09 (t, *J*=7.2 Hz, 3H), 0.98 (t, *J*=7.2 Hz, 3H)

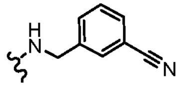
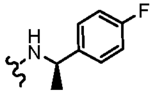
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-19	Et		6-ethyl-N-((R)-1-phenylethyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	359.1	E:1.41 F:1.85	(500MHz, DMSO-d_6) 8.94 (d, *J*=8.0 Hz, 1H), 8.45 (br. s., 1H), 8.36 (d, *J*=4.1 Hz, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 8.08 (d, *J*=4.7 Hz, 1H), 7.99 (d, *J*=7.4 Hz, 1H), 7.83 (d, *J*=6.1 Hz, 1H), 7.42 - 7.38 (m, 2H), 7.33 (t, *J*=7.3 Hz, 2H), 7.27 - 7.18 (m, 1H), 5.41 (d, *J*=4.4 Hz, 1H), 5.19 (quin, *J*=7.2 Hz, 1H), 1.85 - 1.70 (m, 2H), 1.50 (d, *J*=7.2 Hz, 3H), 0.99 (t, *J*=7.2 Hz, 3H)
VIII-20	Et		6-ethyl-N-(2-fluoro-5-methoxybenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	393.1	E:1.37 F:1.80	(500MHz, DMSO-d_6) 9.14 (t, *J*=5.2 Hz, 1H), 8.44 (s, 1H), 8.36 (d, *J*=4.7 Hz, 1H), 8.14 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=5.0 Hz, 1H), 7.98 (d, *J*=8.3 Hz, 1H), 7.85 (s, 1H), 7.12 (d, *J*=9.9 Hz, 1H), 6.91 (d, *J*=3.3 Hz, 1H), 6.89 - 6.81 (m, 1H), 5.42 (dd, *J*=8.4, 4.3 Hz, 1H), 4.50 (br. s., 2H), 3.72 (s, 3H), 1.89 - 1.66 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H)

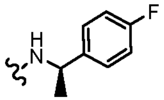
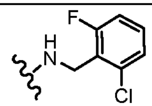
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-21	Et		N-(2-chloro-4-fluorobenzyl)-6-ethyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	397.0	E:1.50 F:1.95	(500MHz, DMSO-d_6) 9.18 (t, *J*=5.1 Hz, 1H), 8.45 (s, 1H), 8.36 (d, *J*=4.4 Hz, 1H), 8.15 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=5.0 Hz, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 7.86 (s, 1H), 7.51 - 7.40 (m, 2H), 7.22 (d, *J*=8.5 Hz, 1H), 5.42 (dd, *J*=8.3, 4.4 Hz, 1H), 4.54 (br. s., 2H), 1.90 - 1.69 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H)
VIII-22	Et		N-(3-cyanobenzyl)-6-ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	370.1	E:1.18 F:1.57	(500MHz, DMSO-d_6) 9.23 (t, *J*=5.4 Hz, 1H), 8.33 (s, 1H), 8.28 (d, *J*=5.0 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 1H), 7.97 (d, *J*=8.0 Hz, 1H), 7.92 (d, *J*=4.7 Hz, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.69 (d, *J*=7.7 Hz, 1H), 7.60 - 7.54 (m, 1H), 5.36 (dd, *J*=8.1, 4.5 Hz, 1H), 4.55 (d, *J*=5.2 Hz, 2H), 1.85 - 1.69 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H)

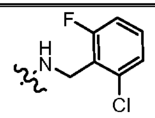
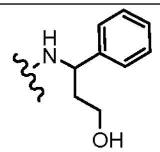
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-23	c-Propyl		6-cyclopropyl-N-((R)-1-(3-methoxyphenyl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	401.1	E:1.36 F:1.74	(500MHz, DMSO-d_6) 8.94 (d, *J*=7.4 Hz, 1H), 8.45 (s, 1H), 8.35 (d, *J*=5.0 Hz, 1H), 8.14 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=4.7 Hz, 1H), 8.05 - 7.99 (m, 1H), 7.91 (br. s., 1H), 7.25 (t, *J*=8.0 Hz, 1H), 6.97 (br. s., 2H), 6.81 (d, *J*=8.0 Hz, 1H), 5.16 (quin, *J*=6.9 Hz, 1H), 4.78 (d, *J*=9.1 Hz, 1H), 3.74 (s, 3H), 1.49 (d, *J*=6.9 Hz, 3H), 1.31 - 1.21 (m, 1H), 0.60 (br. s., 2H), 0.54 (d, *J*=3.0 Hz, 2H)
VIII-24	Et		N-(1-(2-chlorophenyl)cyclopropyl)-6-ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	405.1	E:1.48 F:1.92	(500MHz, DMSO-d_6) 9.16 (s, 1H), 8.48 (s, 1H), 8.37 (d, *J*=5.0 Hz, 1H), 8.11 (d, *J*=8.0 Hz, 2H), 7.89 (d, *J*=8.0 Hz, 1H), 7.78 - 7.71 (m, 2H), 7.39 (d, *J*=7.4 Hz, 1H), 7.33 - 7.22 (m, 2H), 5.39 (dd, *J*=8.3, 4.4 Hz, 1H), 1.86 - 1.67 (m, 2H), 1.27 (d, *J*=5.0 Hz, 2H), 1.16 (d, *J*=5.8 Hz, 2H), 0.97 (t, *J*=7.2 Hz, 3H)

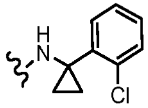
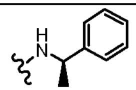
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-25	c-Propyl		6-cyclopropyl-N-((R)-1-phenylethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	371.2	E:1.40 F:1.84	(500MHz, DMSO-d_6) 8.94 (d, *J*=7.7 Hz, 1H), 8.35 (s, 1H), 8.28 (br. s., 1H), 8.09 (d, *J*=8.0 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.95 (br. s., 1H), 7.90 (d, *J*=4.4 Hz, 1H), 7.45 - 7.38 (m, 2H), 7.34 (t, *J*=7.2 Hz, 2H), 7.27 - 7.19 (m, 1H), 5.19 (t, *J*=7.0 Hz, 1H), 4.72 (d, *J*=9.1 Hz, 1H), 1.50 (d, *J*=6.6 Hz, 3H), 1.25 (br. s., 1H), 0.67 - 0.46 (m, 4H)
VIII-26	c-Propyl		6-cyclopropyl-N-(2-fluoro-5-methoxybenzyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	405.2	E:1.36 F:1.79	(500MHz, DMSO-d_6) 9.18 (br. s., 1H), 8.46 (s, 1H), 8.36 (br. s., 1H), 8.15 (d, *J*=8.0 Hz, 1H), 8.08 (d, *J*=3.3 Hz, 1H), 8.01 (d, *J*=8.0 Hz, 1H), 7.95 (s, 1H), 7.13 (t, *J*=9.2 Hz, 1H), 6.91 (d, *J*=3.0 Hz, 1H), 6.88 - 6.81 (m, 1H), 4.78 (d, *J*=9.1 Hz, 1H), 4.51 (br. s., 2H), 3.71 (s, 3H), 1.28 (d, *J*=5.0 Hz, 1H), 0.67 - 0.51 (m, 4H)

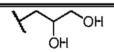
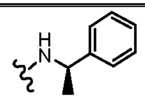
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-27	c-Propyl		6-cyclopropyl-N-(3-hydroxy-1-phenylpropyl)-6H-isochromeno [3,4-c]pyridine-8-carboxamide	401.2	E:1.18 F:1.58	(500MHz, DMSO-d_6) 8.96 - 8.84 (m, 1H), 8.35 (br. s., 1H), 8.28 (br. s., 1H), 8.09 (d, *J*=7.7 Hz, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.94 (br. s., 1H), 7.87 (s, 1H), 7.42 - 7.36 (m, 2H), 7.33 (t, *J*=7.3 Hz, 2H), 7.23 (d, *J*=6.9 Hz, 1H), 5.17 (d, *J*=6.9 Hz, 1H), 4.71 (d, *J*=8.8 Hz, 1H), 4.62 (br. s., 1H), 3.51 - 3.40 (m, 2H), 2.12 - 1.87 (m, 2H), 1.25 (br. s., 1H), 0.66 - 0.48 (m, 4H)
VIII-28	c-Propyl		N-(2-chloro-4-fluorobenzyl)-6-cyclopropyl-6H-isochromeno [3,4-c]pyridine-8-carboxamide	409.1	E:1.44 F:1.83	(500MHz, DMSO-d_6) 9.22 (br. s., 1H), 8.49 (s, 1H), 8.38 (d, *J*=4.1 Hz, 1H), 8.18 (d, *J*=8.0 Hz, 1H), 8.13 (d, *J*=4.1 Hz, 1H), 8.04 (d, *J*=8.0 Hz, 1H), 7.96 (s, 1H), 7.56 - 7.39 (m, 2H), 7.23 (t, *J*=8.5 Hz, 1H), 4.80 (d, *J*=9.1 Hz, 1H), 4.54 (br. s., 2H), 1.29 (d, *J*=5.2 Hz, 1H), 0.70 - 0.46 (m, 4H)

Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
VIII-29	c-Propyl		N-(3-cyanobenzyl)-6-cyclopropyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	382.1	E:1.20 F:1.55	(500MHz, DMSO-d_6) 9.28 (br. s., 1H), 8.37 (s, 1H), 8.30 (d, *J*=3.9 Hz, 1H), 8.13 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=8.0 Hz, 1H), 7.95 (br. s., 2H), 7.80 (s, 1H), 7.76 (d, *J*=7.4 Hz, 1H), 7.71 (d, *J*=7.7 Hz, 1H), 7.63 - 7.55 (m, 1H), 4.74 (d, *J*=9.1 Hz, 1H), 4.57 (br. s., 2H), 1.28 (d, *J*=5.0 Hz, 1H), 0.68 - 0.51 (m, 4H)
VIII-30	Et		6-ethyl-N-((R)-1-(4-fluorophenyl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	377.1	E:1.39 F:1.77	(500MHz, DMSO-d_6) 8.94 (d, *J*=7.4 Hz, 1H), 8.45 (s, 1H), 8.36 (br. s., 1H), 8.13 (d, *J*=8.0 Hz, 1H), 8.08 (br. s., 1H), 7.98 (d, *J*=8.0 Hz, 1H), 7.82 (d, *J*=5.0 Hz, 1H), 7.44 (t, *J*=5.9 Hz, 2H), 7.16 (t, *J*=8.3 Hz, 2H), 5.41 (d, *J*=4.1 Hz, 1H), 5.18 (t, *J*=7.0 Hz, 1H), 1.88 - 1.67 (m, 2H), 1.49 (d, *J*=6.6 Hz, 3H), 0.99 (t, *J*=7.0 Hz, 3H)

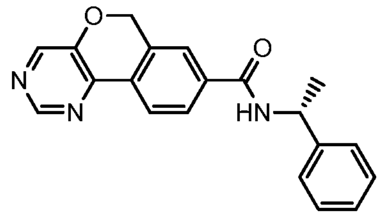
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-31	c-Propyl		6-cyclopropyl-N-((R)-1-(4-fluorophenyl)ethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	389.2	E:1.40 F:1.76	(500MHz, DMSO-d_6) 8.97 (d, *J*=7.4 Hz, 1H), 8.46 (s, 1H), 8.36 (br. s., 1H), 8.14 (d, *J*=8.0 Hz, 1H), 8.10 (d, *J*=3.3 Hz, 1H), 8.02 (t, *J*=6.3 Hz, 1H), 7.91 (br. s., 1H), 7.44 (t, *J*=5.9 Hz, 2H), 7.16 (t, *J*=8.3 Hz, 2H), 5.19 (t, *J*=7.0 Hz, 1H), 4.78 (d, *J*=8.8 Hz, 1H), 1.49 (d, *J*=6.9 Hz, 3H), 1.26 (d, *J*=6.6 Hz, 1H), 0.68 - 0.47 (m, 4H)
VIII-32	Et		N-(2-chloro-6-fluorobenzyl)-6-ethyl-6H-isochromeno[3,4-c]pyridine-8-carboxamide	397.1	E:1.36 F:1.77	(500MHz, DMSO-d_6) 8.88 (br. s., 1H), 8.32 (s, 1H), 8.26 (br. s., 1H), 8.05 (d, *J*=8.0 Hz, 1H), 7.96 - 7.87 (m, 2H), 7.77 (s, 1H), 7.45 - 7.32 (m, 2H), 7.26 (t, *J*=8.7 Hz, 1H), 5.38 - 5.28 (m, 1H), 4.61 (br. s., 2H), 1.85 - 1.64 (m, 2H), 0.97 (t, *J*=6.9 Hz, 3H)

Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-33	c-Propyl		N-(2-chloro-6-fluorobenzyl)-6-cyclopropyl-6H-isochromeno [3,4-c]pyridine-8-carboxamide	409.1	E:1.39 F:1.77	(500MHz, DMSO-d_6) 8.92 (br. s., 1H), 8.34 (s, 1H), 8.27 (d, *J*=3.3 Hz, 1H), 8.06 (d, *J*=8.3 Hz, 1H), 7.99 - 7.84 (m, 3H), 7.47 - 7.23 (m, 3H), 4.70 (d, *J*=9.1 Hz, 1H), 4.61 (br. s., 2H), 1.25 (d, *J*=5.2 Hz, 1H), 0.67 - 0.41 (m, 4H)
VIII-34	Et		6-ethyl-N-(3-hydroxy-1-phenylpropyl)-6H-isochromeno [3,4-c]pyridine-8-carboxamide	389.2	E:1.14 F:1.47	(500MHz, DMSO-d_6) 8.88 (d, *J*=7.4 Hz, 1H), 8.33 (s, 1H), 8.27 (br. s., 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.99 - 7.88 (m, 2H), 7.79 (br. s., 1H), 7.45 - 7.36 (m, 2H), 7.33 (t, *J*=7.0 Hz, 2H), 7.26 - 7.16 (m, 1H), 5.35 (br. s., 1H), 5.17 (d, *J*=7.2 Hz, 1H), 4.60 (br. s., 1H), 3.45 (m, 2H), 2.14 - 2.00 (m, 1H), 1.97 - 1.85 (m, 1H), 1.84 - 1.65 (m, 2H), 1.06 - 0.90 (m, 3H)

Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-35	c-Propyl		N-(1-(2-chlorophenyl) cyclopropyl)-6-cyclopropyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	417.1	E:1.51 F:1.90	(500MHz, DMSO-d_6) 9.17 (s, 1H), 8.44 (s, 1H), 8.34 (d, J=3.9 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 8.06 (d, J=3.6 Hz, 1H), 7.94 (br. s., 1H), 7.84 (s, 1H), 7.75 (d, J=7.2 Hz, 1H), 7.39 (d, J=7.2 Hz, 1H), 7.28 (quin, J=7.4 Hz, 2H), 4.71 (d, J=9.1 Hz, 1H), 1.34 - 1.21 (m, 4H), 1.17 (br. s., 2H), 0.65 - 0.48 (m, 4H)
VIII-36	allyl		6-allyl-N-((R)-1-phenylethyl)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	371.1	A:9.31 B:10.13	(400MHz, $CDCl_3$) 8.35 (s, 1H), 8.30 (d, J=5.1 Hz, 1H), 7.83 - 7.72 (m, 2H), 7.63 (br. s., 1H), 7.56 (d, J=5.1 Hz, 1H), 7.40 (q, J=7.9 Hz, 3H), 7.35 - 7.28 (m, 1H), 6.43 (d, J=7.5 Hz, 1H), 5.93 - 5.80 (m, 1H), 5.34 (dt, J=14.4, 7.1 Hz, 2H), 5.16 - 5.04 (m, 2H), 2.67 (dt, J=15.0, 7.7 Hz, 1H), 2.55 - 2.43 (m, 1H), 1.70 (s, 1H), 1.65 (d, J=6.8 Hz, 3H)

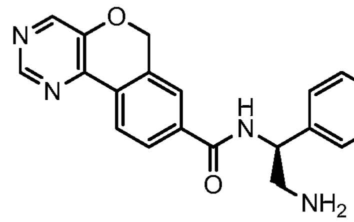
Ex. No.	R′	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
VIII-37			6-(2,3-dihydroxypropyl)-N-((R)-1-phenylethyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	405.2	E:1.07 F:1.26	(500MHz, DMSO-d_6) 8.92 (br. s., 1H), 8.30 (d, *J*=15.7 Hz, 2H), 8.07 (br. s., 1H), 8.01 - 7.90 (m, 2H), 7.81 (br. s., 1H), 7.40 (br. s., 2H), 7.33 (br. s., 2H), 7.23 (br. s., 1H), 5.68 - 5.54 (m, 1H), 5.19 (br. s., 1H), 5.02 - 4.34 (m, 2H), 3.79 (br. s., 1H), 3.30- 3.21 (m, 2H), 2.00-1.82 (m, 2H), 1.50 (br. s., 3H)

Example IX-1: (R)-N-(1-Phenylethyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide



Example IX-1 was prepared by following a similar procedure as described in I-1 by replacing Intermediate 1 with Intermediate 3. LC-MS (ESI) *m/z*: 332.10 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 8.99 (d, *J*=8.0 Hz, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.21 (d, *J*=8.0 Hz, 1H), 8.00 (d, *J*=8.0 Hz, 1H), 7.84 (s, 1H), 7.43 - 7.38 (m, 2H), 7.33 (t, *J*=7.6 Hz, 2H), 7.26 - 7.21 (m, 1H), 5.46 (s, 2H), 5.18 (quin, *J*=7.2 Hz, 1H), 1.49 (d, *J*=7.2 Hz, 3H); Analytical HPLC RT E: 1.53 min, F: 1.58 min.

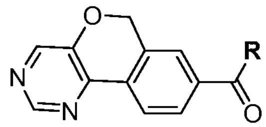
Example IX-2: (S)-N-(2-Amino-1-phenylethyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide

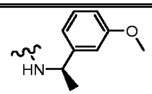
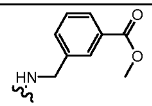


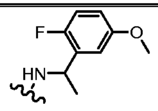
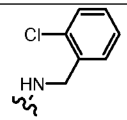
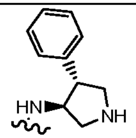
Example IX-2 was prepared by following a similar procedure as described in Example VI-2 by replacing Intermediate 2 with Intermediate 3 in VI-2d. LC-MS (ESI) *m/z*: 347.1$[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 8.85 (s, 1H), 8.47 (s, 1H), 8.35 (d, *J*=8.1 Hz, 1H), 8.03 (dd, *J*=8.0, 1.7 Hz, 1H), 7.82 (s, 1H), 7.53 - 7.43 (m, 4H), 7.42 - 7.38 (m, 1H), 5.51 (dd, *J*=9.2, 5.7 Hz, 1H), 5.45 (s, 2H), 3.51 - 3.45 (m, 2H); Analytical HPLC RT A: 7.06 min, F: 7.41 min.

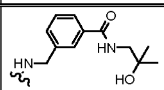
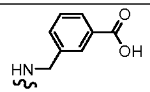
The compounds listed in Table IX were prepared by following the similar procedures as described in Examples IX-1 and IX-2.

Table IX

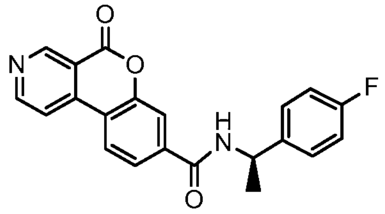


Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IX-3		(R)-N-(1-(3-methoxyphenyl)ethyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide	362.10	A:8.30 B:7.24	(400MHz, DMSO-d_6) 8.93 (d, J=8.1 Hz, 1H), 8.88 (s, 1H), 8.54 (s, 1H), 8.21 (d, J=8.1 Hz, 1H), 7.99 (dd, J=8.0, 1.7 Hz, 1H), 7.82 (d, J=0.9 Hz, 1H), 7.24 (t, J=8.1 Hz, 1H), 7.01 - 6.94 (m, 2H), 6.80 (ddd, J=8.2, 2.5, 1.0 Hz, 1H), 5.46 (s, 2H), 5.15 (quin, J=7.3 Hz, 1H), 3.74 (s, 3H), 1.48 (d, J=7.0 Hz, 3H)
IX-4		methyl 3-((6H-isochromeno[4,3-d] pyrimidine-8-carboxamido) methyl)benzoate	376.1	A:11.56 B:10.29	(400MHz, DMSO-d_6) 9.28 (t, J=5.9 Hz, 1H), 8.88 (s, 1H), 8.54 (s, 1H), 8.22 (d, J=8.1 Hz, 1H), 8.01 (dd, J=8.1, 1.5 Hz, 1H), 7.95 (s, 1H), 7.88 - 7.82 (m, 2H), 7.63 (d, J=7.9 Hz, 1H), 7.53 - 7.47 (m, 1H), 5.46 (s, 2H), 4.56 (d, J=5.9 Hz, 2H), 3.84 (s, 3H)

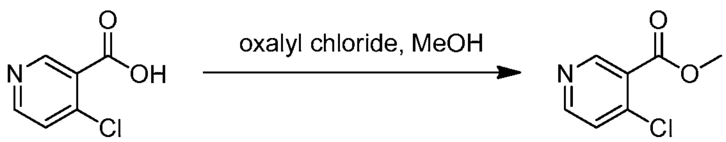
Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IX-5		(±)-N-(1-(2-fluoro-5-methoxyphenyl)ethyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide	380.10	E:1.60 F:1.65	(500MHz, DMSO-d_6) 9.01 (d, *J*=7.7 Hz, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.22 (d, *J*=8.3 Hz, 1H), 8.00 (d, *J*=8.3 Hz, 1H), 7.83 (s, 1H), 7.10 (t, *J*=9.4 Hz, 1H), 7.02 (dd, *J*=5.8, 2.8 Hz, 1H), 6.87 - 6.79 (m, 1H), 5.47 (s, 2H), 5.37 (quin, *J*=7.2 Hz, 1H), 3.71 (s, 3H), 1.46 (d, *J*=6.9 Hz, 3H)
IX-6		N-(2-chlorobenzyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide	352.10	E:1.59 F:1.64	(500MHz, DMSO-d_6) 9.21 (t, *J*=5.5 Hz, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.23 (d, *J*=8.3 Hz, 1H), 8.04 (d, *J*=8.3 Hz, 1H), 7.88 (s, 1H), 7.47 (d, *J*=7.4 Hz, 1H), 7.42 - 7.37 (m, 1H), 7.36 - 7.28 (m, 2H), 5.47 (s, 2H), 4.56 (d, *J*=5.5 Hz, 2H)
IX-7		N-((3S,4R)-4-phenylpyrrolidin-3-yl)-6H-isochromeno[4,3-d] pyrimidine-8-carboxamide	373.20	E:1.15 F:1.17	(500MHz, DMSO-d_6) 8.97 (d, *J*=8.0 Hz, 1H), 8.90 (s, 1H), 8.57 (s, 1H), 8.22 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=8.0 Hz, 1H), 7.77 (s, 1H), 7.46 - 7.41 (m, 2H), 7.38 (t, *J*=7.6 Hz, 2H), 7.33 - 7.27 (m, 1H), 5.46 (s, 2H), 4.79 (quin, *J*=8.5 Hz, 1H), 3.81 (br. s., 1H), 3.72 (br. s., 1H), 3.68 - 3.60 (m, 1H), 3.18 (br. s., 1H)

Ex. No.	R	Name	LCMS $(M+H)^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
IX-8		N-(3-(2-hydroxy-2-methylpropylcarbamoyl)benzyl)-6H-isochromeno[4,3-d]pyrimidine-8-carboxamide	433.25	E:1.12 F:1.14	(500MHz, DMSO-d_6) 9.26 (t, *J*=5.5 Hz, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.28 - 8.19 (m, 2H), 8.01 (d, *J*=8.0 Hz, 1H), 7.86 (s, 1H), 7.83 (s, 1H), 7.75 (d, *J*=7.4 Hz, 1H), 7.51 - 7.46 (m, 1H), 7.45 - 7.39 (m, 1H), 5.46 (s, 2H), 4.60 - 4.51 (m, 3H), 3.24 (d, *J*=5.8 Hz, 2H), 1.09 (s, 6H)
IX-9		3-((6H-isochromeno[4,3-d]pyrimidine-8-carboxamido)methyl)benzoic acid	362.15	E:1.16 F:0.93	(500MHz, DMSO-d_6) 9.30 (t, *J*=5.6 Hz, 1H), 8.89 (s, 1H), 8.55 (s, 1H), 8.22 (d, *J*=8.0 Hz, 1H), 8.01 (d, *J*=8.0 Hz, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.83 (d, *J*=7.7 Hz, 1H), 7.59 (d, *J*=7.7 Hz, 1H), 7.51 - 7.43 (m, 1H), 5.47 (s, 2H), 4.55 (d, *J*=5.8 Hz, 2H)

Example X-1: (R)-N-(1-(4-Fluorophenyl)ethyl)-5-oxo-5H-chromeno[3,4-c]pyridine-8-carboxamide

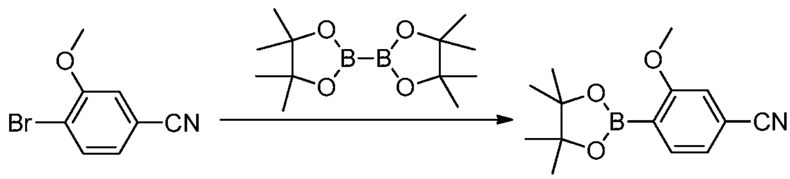


Example X-1a: Methyl 4-chloronicotinate



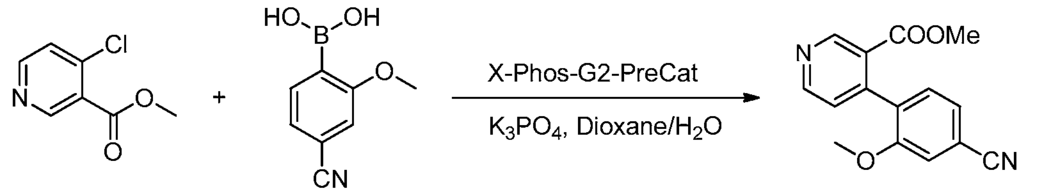
To a suspension of the 4-chloronicotinic acid (1.12g, 7.11 mmol) in DCM (10 mL) at rt was added oxalyl chloride (2M in DCM, 8.89 mL, 17.77 mmol) followed by addition of DMF (0.250 mL) dropwise. After stirred for 45 min at rt, the reaction was cooled to 0 °C and quenched with methanol. The crude oil was triturated with EtOAc, and the solid was collected by filtration, which was further washed with hexane and dried to afford X-a as white solid (1.2 g, 98%). LC-MS (ESI) *m/z*: 171.9$[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.70 (d, *J*=5.5 Hz, 1H), 7.72 (d, *J*=5.5 Hz, 1H), 3.91 (s, 3H).

Example X-1b: 3-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



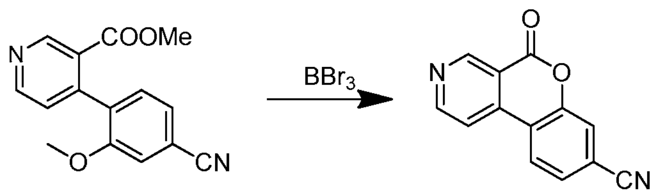
A mixture of 4-bromo-3-methoxybenzonitrile(1g, 4.72 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (1.796 g, 7.07 mmol), K_3PO_4 (1.157 g, 11.79 mmol) and $PdCl_2$(dppf) CH_2Cl_2 adduct (0.207 g, 0.283 mmol) in dioxane (12 mL) was degassed and then heated at 90 °C for 3 h. The reaction was cooled to rt and was filtered through a pad of CELITE®. The solvent was removed. Normal phase chromatography afforded X-1b as brown oil (1.7 g, 5.76 mmol, 100%). LC-MS (ESI) of the boronic acid *m/z*: 178.0 $[M+H]^+$.

Example X-1c: Methyl 4-(4-cyano-2-methoxyphenyl)nicotinate



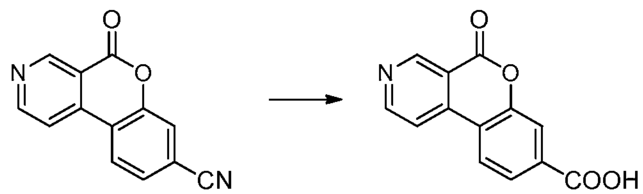
To a solution of X-1a (1.12g, 6.53 mmol) in dioxane (10 mL) and H_2O (2.5 mL) were added X-1b (1.733 g, 7.83 mmol), K_3PO_4 (3.05 g, 14.36 mmol) and XPhos-G2-PreCat (0.206 g, 0.261 mmol) at rt. The reaction was heated with microwave at 140 °C for 10 min. The solvent was removed. Normal phase chromatography afforded X-1c as pale solid (0.84 g, 48.0%) LC-MS (ESI) *m/z*: 269.0$[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.80 (d, *J*=5.1 Hz, 1H), 7.45 - 7.37 (m, 1H), 7.35 - 7.30 (m, 1H), 7.22 (d, *J*=5.1 Hz, 1H), 7.16 (d, *J*=1.3 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H).

Example X-1d: 5-Oxo-5H-chromeno[3,4-c]pyridine-8-carbonitrile



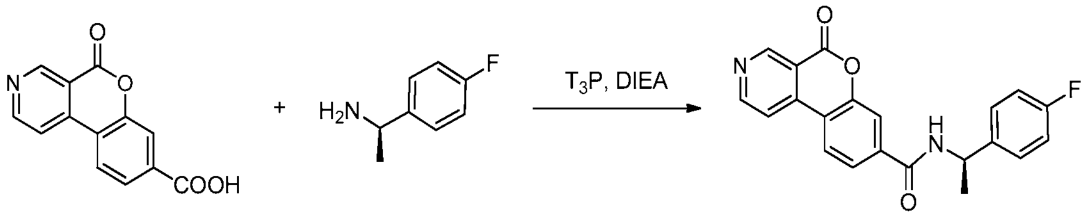
To a solution of X-1c (123 mg, 0.458 mmol) in DCM (3 mL) at 0 °C was added BBr_3 (1M in heptane, 2.751 mL, 2.75 mmol) dropwise. The solution was warmed to rt and stirred overnight. The solvent was removed. Purification by reverse phase chromatography afforded X-1d. LC-MS (ESI) *m/z*: 223.0$[M+H]^+$.

Example X-1e: 5-Oxo-5H-chromeno[3,4-c]pyridine-8-carboxylic acid



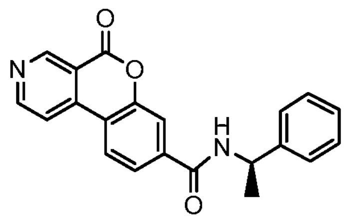
A suspension of X-1d (14 mg, 0.042 mmol) in HCl (aq. 7N, 0.297 ml, 2.082 mmol) was heated at 100 °C in a sealed vial for 8 h. The solvent was removed to afford X-1e as solid (10.4 mg, 90%). LC-MS (ESI) *m/z*: 242.0$[M+H]^+$.

Example X-1:



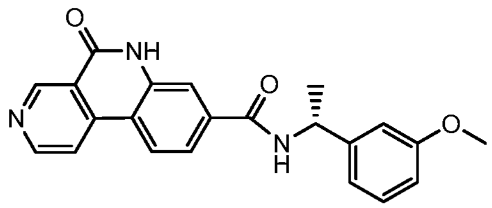
To a suspension of X-1e (10 mg, 0.036 mmol) in DCM (1 mL) were added (R)-1-(4-fluorophenyl)ethanamine, HCl salt (6.96 mg, 0.040 mmol), DIEA (0.044 mL, 0.252 mmol) and T_3P (0.060 mL, 0.101 mmol) at rt. The reaction was stirred under argon at rt for 1.5 h and then sat over weekend. Purification by reverse phase chromatography afforded Example X-1 as white solid (7.2 mg, 51%). LC-MS (ESI) *m/z*: 363.0$[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.11 - 9.02 (m, 2H), 8.55 (d, *J*=8.0 Hz, 1H), 8.43 (d, *J*=5.0 Hz, 1H), 7.98 - 7.92 (m, 2H), 7.45 (t, *J*=6.3 Hz, 2H), 7.16 (t, *J*=8.3 Hz, 2H), 5.20 (t, *J*=7.0 Hz, 1H), 1.51 (d, *J*=6.9 Hz, 3H); Analytical HPLC RT E: 1.50 min, F: 1.59 min.

Example X-2: (R)-5-Oxo-N-(1-phenylethyl)-5H-chromeno[3,4-c]pyridine-8-carboxamide

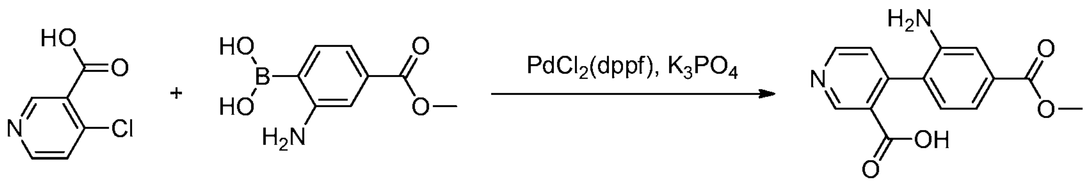


Example X-2 was prepared by following the similar procedure as described in Example X-1. LC-MS (ESI) *m/z*: 345.0$[M+H]^+$; ^1H NMR (400MHz, CD_3OD) δ 9.47 (s, 1H), 8.99 (d, *J*=5.5 Hz, 1H), 8.44 (d, *J*=8.1 Hz, 1H), 8.36 (d, *J*=5.5 Hz, 1H), 7.99 - 7.84 (m, 2H), 7.50 - 7.40 (m, 2H), 7.35 (t, *J*=7.7 Hz, 2H), 7.30 - 7.21 (m, 1H), 5.37 - 5.21 (m, 1H), 1.61 (d, *J*=7.0 Hz, 3H); Analytical HPLC RT A: 5.67 min, F: 5.48 min.

Example X-3: (R)-N-(1-(3-Methoxyphenyl)ethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide

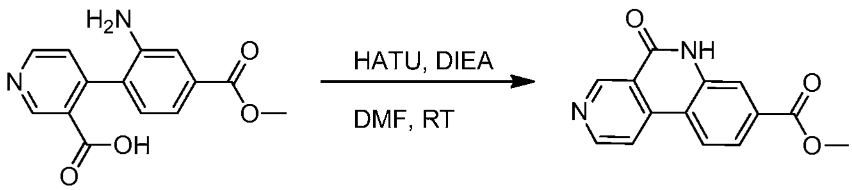


Example X-3a: 4-(2-Amino-4-(methoxycarbonyl)phenyl)nicotinic acid



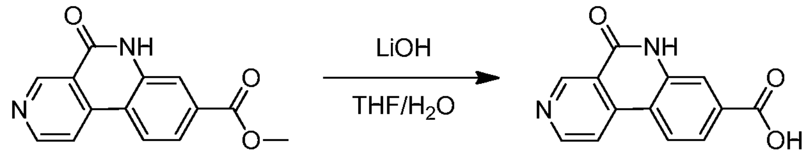
To a solution of 4-chloronicotinic acid (110 mg, 0.698 mmol) in dioxane (3 mL) were added (2-amino-4-(methoxycarbonyl)phenyl)boronic acid, HCl salt (194 mg, 0.838 mmol), K_3PO_4 (1.745 mL, 1.745 mmol) and $Pd(Ph_3P)_4$ (40.3 mg, 0.035 mmol) at rt. The reaction was heated with microwave at 150 °C for 15 min. The solvent was removed. Purified by reverse phase chromatography afforded X-3a as white solid (85 mg, 24%). LC-MS (ESI) *m/z*: 273.0$[M+H]^+$.

Example X-3b: Methyl 5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylate



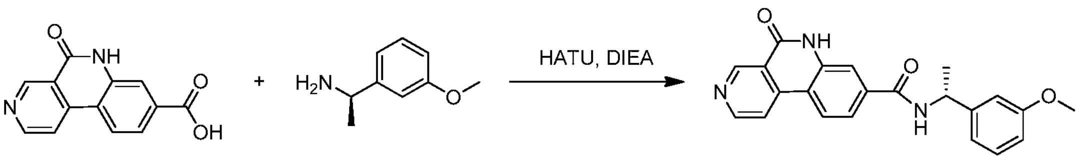
To a solution of X-3a (20 mg, 0.040 mmol) in DMF (1.5 mL) were added DIEA (0.035 mL, 0.200 mmol) and HATU (15.20 mg, 0.040 mmol) at rt. The reaction was stirred under argon at RT for 1.5 h. The crude product was purified by reverse phase chromatography to afford X-3b as light yellow solid (9 mg, 61%). LC-MS (ESI) *m/z*: 255.0$[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 9.59 (s, 1H), 8.95 (d, *J*=5.9 Hz, 1H), 8.58 (d, *J*=5.9 Hz, 1H), 8.54 (d, *J*=8.6 Hz, 1H), 8.06 (d, *J*=1.3 Hz, 1H), 7.99 (dd, *J*=8.4, 1.5 Hz, 1H), 3.99 (s, 3H).

Example X-3c: 5-Oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid



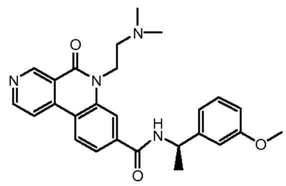
To a solution of X-3b (9 mg, 0.024 mmol) in THF (1.5 mL) and H_2O (0.5 mL) was added LiOH (5.85 mg, 0.244 mmol) at rt. The reaction was stirred under argon for 2 h. the solvent was removed to afford X-3c as light yellow solid (5.87 mg, 100%). LC-MS (ESI) *m/z*: 241.1$[M+H]^+$.

Example X-3:

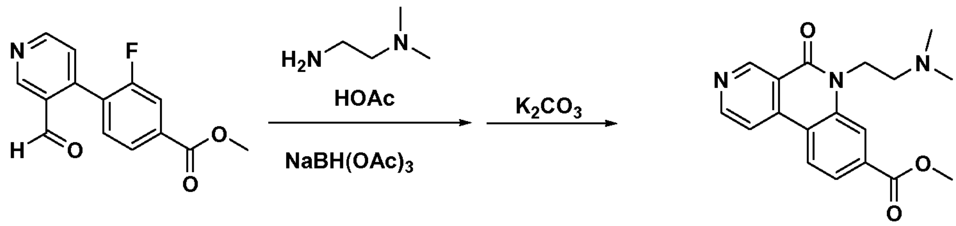


To a solution of X-3c (6 mg, 0.025 mmol) in DMF (1 mL) were added (R)-1-(3-methoxyphenyl)ethanamine (18.88 mg, 0.125 mmol), DIEA (0.044 mL, 0.250 mmol) and HATU (18.99 mg, 0.050 mmol). The reaction was stirred under argon at rt for 1 h. Purification by reverse phase chromatography afforded X-3 as white solid (2.5 mg, 26%). LC-MS (ESI) *m/z*: 374.20 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 12.04 (s, 1H), 9.03 (d, *J*=8.0 Hz, 1H), 8.57 (d, *J*=8.3 Hz, 1H), 8.54 (br. s., 1H), 7.83 (s, 1H), 7.80 (dd, *J*=8.5, 1.4 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.01 - 6.95 (m, 2H), 6.81 (dd, *J*=8.1, 1.8 Hz, 1H), 5.16 (quin, *J*=7.3 Hz, 1H), 3.75 (s, 3H), 1.48 (d, *J*=7.2 Hz, 3H); Analytical HPLC RT E: 1.12 min, F: 1.29 min.

Example X-4: (R)-6-(2-(Dimethylamino)ethyl)-N-(1-(3-methoxyphenyl)ethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide

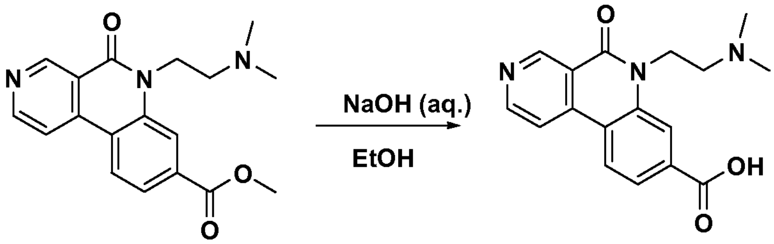


Example X-4a: Methyl 6-(2-(dimethylamino)ethyl)-5-oxo-5,6-dihydrobenzo[c][2,7] naphthyridine-8-carboxylate



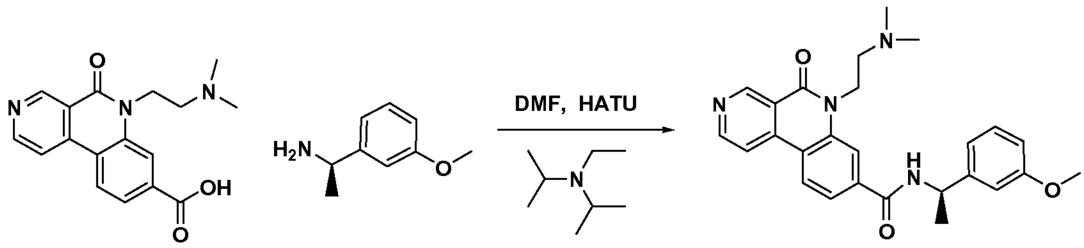
To a solution of Intermediate 4a (54 mg, 0.208 mmol) in DCE (1.5 mL) were added N1,N1-dimethylethane-1,2-diamine (0.046 mL, 0.417 mmol) and acetic acid (0.036 mL, 0.625 mmol). The reaction was stirred under argon at rt for 1 h. and followed by addition of sodium triacetoxyborohydride (93 mg, 0.417 mmol). After stirring at rt for 1.5 h, it was heated at 50 °C for 4 h, and then cooled to rt. To the reaction mixture was added potassium carbonate (17.27 mg, 0.125 mmol) and the mixture was stirred at rt for 1.5 h. LCMS showed the reaction was completed. The solvent was removed. The residue was dissolved in DMF/MeOH/water and purified by reverse phase chromatography to afford X-4a as TFA salt (42.8mg, 37.1%). LCMS (ESI) *m/z*: 326.1 $[M+H]^+$.

Example X-4b: 6-(2-(Dimethylamino)ethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid



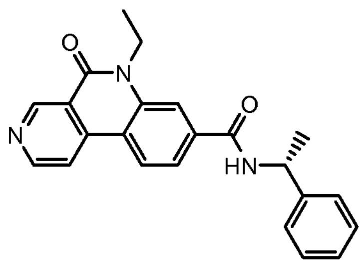
To a solution of X-4a (42.8 mg, 0.132 mmol) in EtOH (2mL) was added NaOH (1N aq.) (0.527 mL, 0.527 mmol). The reaction was stirred under argon at rt for 2 h. To the reaction mixture was added HCl ((3.7N) (0.214 mL, 0.790 mmol) to adjust the PH~8. Purification by reverse phase chromatography afforded X-4b as TFA salt (41 mg, 57.7% yield). LC-MS (ESI) *m/z*: 312.1 $[M+H]^+$

Example X-4:

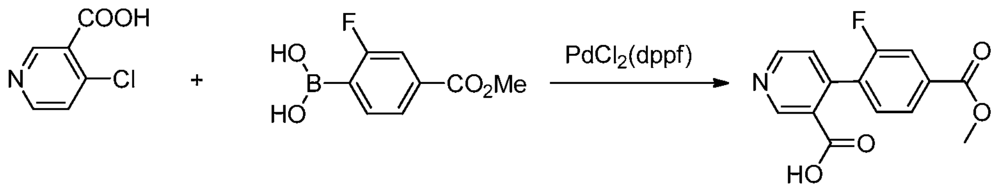


To a solution of X-4b (17 mg, 0.032 mmol) in DMF (1 mL) were added (R)-1-(3-methoxyphenyl)ethanamine hydrochloride (17.74 mg, 0.095 mmol), DIEA (0.055 mL, 0.315 mmol), and HATU (21.57 mg, 0.057 mmol) at rt. The reaction was stirred under argon at rt overnight. Purification by reverse phase chromatography afforded X-4 as TFA salt (3.0 mg, 4.22 μmol, 13.39% yield). LC-MS (ESI) *m/z*: 445.1$[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 9.53 (s, 1H), 9.29 (br. s., 1H), 9.07 (d, *J*=7.9 Hz, 1H), 9.00 (d, *J*=5.7 Hz, 1H), 8.74 (d, *J*=8.6 Hz, 1H), 8.56 (d, *J*=5.7 Hz, 1H), 8.02 - 7.93 (m, 2H), 7.27 (t, *J*=8.1 Hz, 1H), 7.01 (d, *J*=4.2 Hz, 2H), 6.88 - 6.79 (m, 1H), 5.21 (t, *J*=7.3 Hz, 1H), 4.82 (t, *J*=5.8 Hz, 2H), 3.76 (s, 3H), 3.52 (d, *J*=5.3 Hz, 2H), 2.97 (d, *J*=4.2 Hz, 6H), 1.54 (d, *J*=7.0 Hz, 3H); Analytical HPLC RT A: 7.13 min, B: 7.88 min.

Example X-5: (R)-6-Ethyl-5-oxo-N-(1-phenylethyl)-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide

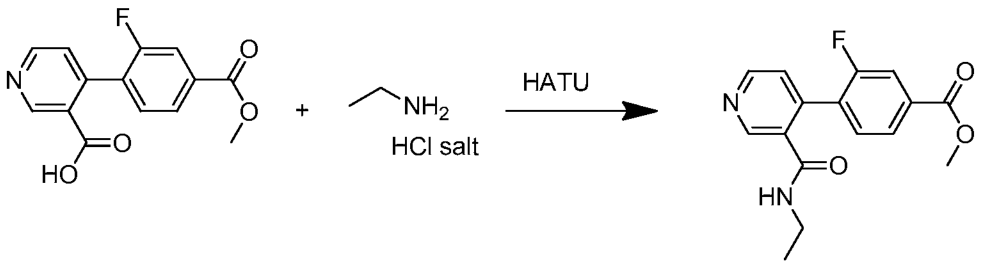


Example X-5a: 4-(2-Fluoro-4-(methoxycarbonyl)phenyl)nicotinic acid



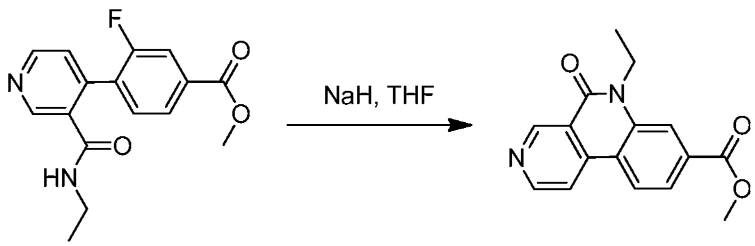
To a solution of 4-chloronicotinic acid (580 mg, 3.68 mmol) in dioxane (20 mL) and water (5 mL) were added (2-fluoro-4-(methoxycarbonyl)phenyl)boronic acid (802 mg, 4.05 mmol), K_3PO_4 (1954 mg, 9.20 mmol) and $PdCl_2$(dppf) (135 mg, 0.184 mmol) at rt. The reaction was stirred under argon at 90 °C for 2 h. The reaction mixture was diluted with EtOAc, washed with H_2O. Solvent was removed. Purification by reverse phase chromatography afforded X-5a as white solid (150 mg, 15%). LC-MS (ESI) *m/z*: 276.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 13.34 (br. s., 1H), 9.07 (d, *J*=0.7 Hz, 1H), 8.85 (d, *J*=5.1 Hz, 1H), 7.89 (dd, *J*=7.9, 1.5 Hz, 1H), 7.75 (dd, *J*=10.6, 1.5 Hz, 1H), 7.60 (t, *J*=7.7 Hz, 1H), 7.49 (dd, *J*=5.1, 0.7 Hz, 1H), 3.90 (s, 3H).

Example X-5b: Methyl 4-(3-(ethylcarbamoyl)pyridin-4-yl)-3-fluorobenzoate



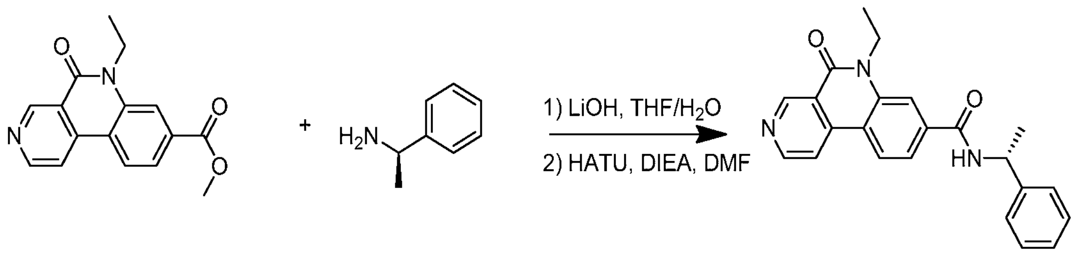
To a solution of X-5a (20 mg, 0.073 mmol) in DMF (1.5 mL) were added ethanamine, HCl (11.85 mg, 0.145 mmol), HATU (41.4 mg, 0.109 mmol) and DIEA (0.1 mL) at rt. The reaction was stirred under argon at rt for 1 hr. Purification by reverse phase chromatography afforded X-5b as white solid (29 mg, 96%). LC-MS (ESI) *m/z*: 303.1$[M+H]^+$; ^1H NMR (400MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.83 (d, *J*=5.5 Hz, 1H), 7.98 (dd, *J*=7.9, 1.5 Hz, 1H), 7.86 (dd, *J*=10.5, 1.4 Hz, 1H), 7.78 (d, *J*=5.7 Hz, 1H), 7.50 (t, *J*=7.6 Hz, 1H), 6.75 (br. s., 1H), 3.97 (s, 3H), 3.44 - 3.32 (m, 2H), 1.14 (t, *J*=7.3 Hz, 3H).

Example X-5c: Methyl 6-ethyl-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylate



To a solution of X-5b (29 mg, 0.070 mmol) in THF (3 mL) was added NaH (13.93 mg, 0.348 mmol) at 0 °C. The reaction was stirred under argon at 0 °C for 1hr. The reaction was quenched by adding citric acid solution. The reaction mixture was diluted with EtOAc, washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to give X-5c as white solid (17 mg, 86%). LC-MS (ESI) *m/z*: 283.1[M+H]$^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.94 (d, *J*=5.5 Hz, 1H), 8.35 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=1.1 Hz, 1H), 8.06 (d, *J*=5.5 Hz, 1H), 7.99 (dd, *J*=8.3, 1.4 Hz, 1H), 4.51 (q, *J*=7.3 Hz, 2H), 4.02 (s, 3H), 1.46 (t, *J*=7.2 Hz, 3H).

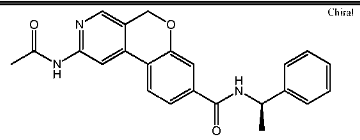
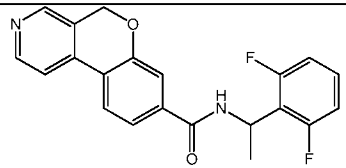
Example X-5d, Example X-5:

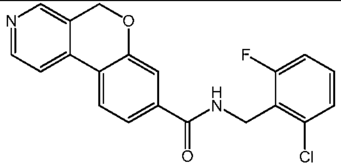
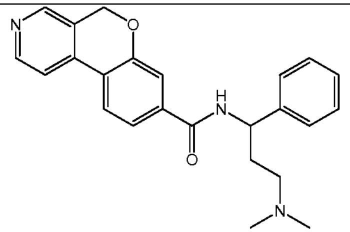
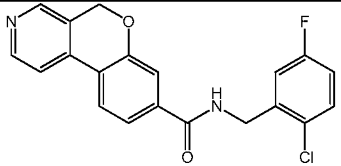


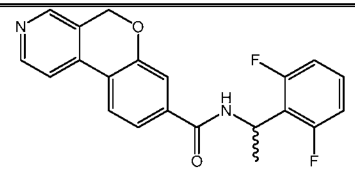
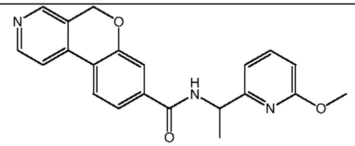
To a solution of X-5c (17 mg, 0.060 mmol) in THF (2 mL) and water (0.5 mL) was added LiOH (7.21 mg, 0.301 mmol) at rt. The reaction was stirred under argon for 1hr. Solvent was removed to give white solid. To this solid were added (R)-1-phenylethanamine (21.68 mg, 0.179 mmol), DIEA (0.052 mL, 0.298 mmol) and HATU (34.0 mg, 0.089 mmol) at rt. The reaction was stirred under argon for 2 h. Purification by reverse phase chromatography afforded X-5 as white solid (17.4 mg, 78%). LC-MS (ESI) *m/z*: 372.20[M+H]$^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.52 (br. s., 1H), 9.15 (d, *J*=7.4 Hz, 1H), 8.97 (br. s., 1H), 8.70 (d, *J*=8.0 Hz, 1H), 8.52 (br. s., 1H), 8.04 (br. s., 1H), 7.95 (d, *J*=7.4 Hz, 1H), 7.45 (d, *J*=6.9 Hz, 2H), 7.37 (br. s., 2H), 7.30 - 7.24 (m, *J*=6.6 Hz, 1H), 5.32 - 5.21 (m, *J*=6.5, 6.5 Hz, 1H), 4.47 (d, *J*=5.8 Hz, 2H), 1.56 (d, *J*=6.1 Hz, 3H), 1.33 (br. s., 3H); Analytical HPLC RT E: 1.31 min, F: 1.50 min.

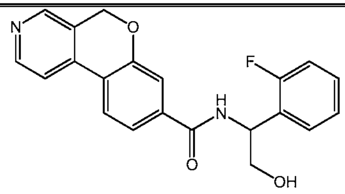
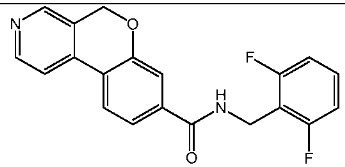
Compounds listed in Table XI were prepared by following procedures similar to those described for Example I-1 and Example VIII-3 using the appropriate intermediates described or purchased from commercial sources. Other coupling reagents than the one described, such as HATU, T_3P, BOP, PyBop, and EDC/HOBt, could be used.

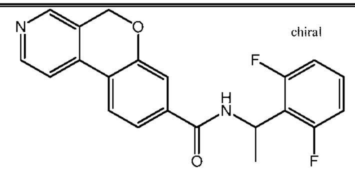
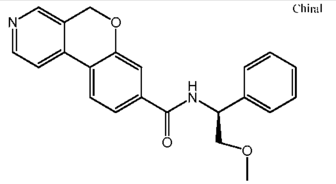
Table XI

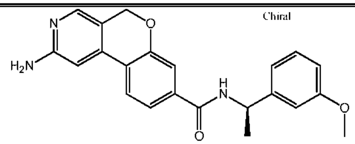
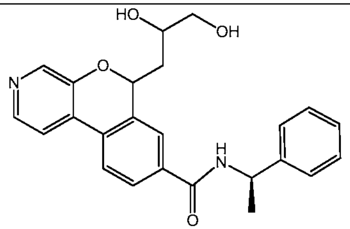
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-1		2-acetamido-N-[(1R)-1-phenylethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	388.1	E:1.27 F:1.51	(500MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.97 (d, J = 7.9 Hz, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.45 (s, 1H), 7.38 - 7.25 (m, 4H), 7.23 - 7.14 (m, 1H), 5.14 (s, 2H), 5.09 (t, J = 7.3 Hz, 1H), 2.10 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H)
XI-2		N-[1-(2,6-difluorophenyl)ethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	367.1	E:1.18 F:1.57	(500MHz, DMSO-d_6) δ 9.00 (d, J = 6.4 Hz, 1H), 8.61 (d, J = 5.0 Hz, 1H), 8.52 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.40 - 7.20 (m, 1H), 7.04 (t, J = 8.1 Hz, 2H), 5.36 (t, J = 6.9 Hz, 1H), 5.26 (s, 2H), 1.56 (d, J = 7.1 Hz, 3H)

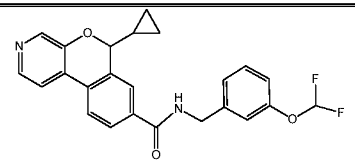
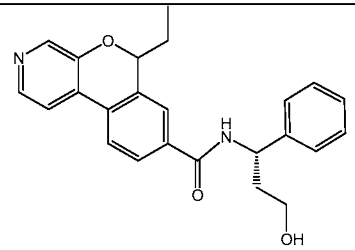
Ex. No.	Structure	Name	LCMS [M+H]$^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-3		N-[(2-chloro-6-fluorophenyl)methyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	369.0	E:1.14 F:1.17	(500MHz, DMSO-d$_6$) δ 8.90 (br. s., 1H), 8.60 (d, *J* = 5.0 Hz, 1H), 8.52 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 5.0 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.42 - 7.31 (m, 2H), 7.23 (t, *J* = 8.9 Hz, 1H), 5.25 (s, 2H), 4.58 (d, *J* = 4.0 Hz, 2H)
XI-4		N-[3-(dimethylamino)-1-phenylpropyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	388.1	E:0.88 F:1.11	(500MHz, DMSO-d$_6$) δ 9.05 (d, *J* = 7.6 Hz, 1H), 8.59 (br. s., 1H), 8.51 (s, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.84 (br. s., 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.49 (br. s., 1H), 7.40 - 7.28 (m, 4H), 7.22 (br. s., 1H), 5.25 (s, 2H), 5.04 (br. s., 1H), 2.29 (br. s., 2H), 2.17 (br. s., 6H), 1.89 (m,2H)
XI-5		N-[(2-chloro-5-fluorophenyl)methyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	369.0	E:1.19 F:1.59	(500MHz, DMSO-d$_6$) δ 9.21 (t, *J* = 5.6 Hz, 1H), 8.67 (d, *J* = 5.0 Hz, 1H), 8.59 (s, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.62 - 7.43 (m, 2H), 7.22 - 7.09 (m, 2H), 5.30 (s, 2H), 4.52 (d, *J* = 5.4 Hz, 2H)

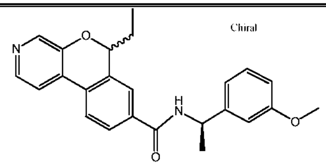
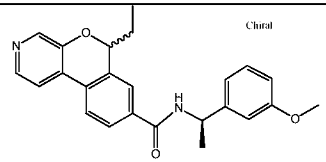
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-6		N-[1-(2,6-difluorophenyl)ethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	367.1	E:1.18 F:1.57	(500MHz, DMSO-d_6) δ 9.04 (d, *J* = 6.1 Hz, 1H), 8.71 (br. s., 1H), 8.64 (br. s., 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.07 (d, *J* = 5.4 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.54 (s, 1H), 7.37 - 7.27 (m, 1H), 7.04 (t, *J* = 8.1 Hz, 2H), 5.36 (t, *J* = 6.9 Hz, 1H), 5.31 (s, 2H), 1.57 (d, *J* = 7.1 Hz, 3H)
XI-7		N-[1-(6-methoxypyridin-2-yl)ethyl]-5H-chromeno [3,4-c]pyridine-8-carboxamide	362.1	E:0.95 F:1.41	(500MHz, DMSO-d_6) δ 8.89 (d, *J* = 7.7 Hz, 1H), 8.61 (d, *J* = 5.0 Hz, 1H), 8.53 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 5.0 Hz, 1H), 7.70 - 7.62 (m, 2H), 7.57 (s, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 5.27 (s, 2H), 5.09 (quin, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 1.51 (d, *J* = 7.1 Hz, 3H)

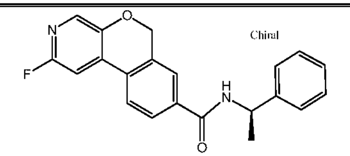
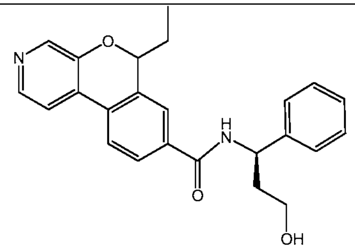
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-8		N-[1-(2-fluorophenyl)-2-hydroxyethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	365.1	E:0.81 F:1.12	(500MHz, DMSO-d_6) δ 8.87 (d, *J* = 7.7 Hz, 1H), 8.62 (d, *J* = 5.0 Hz, 1H), 8.54 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 5.0 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.58 (s, 1H), 7.49 (t, *J* = 7.1 Hz, 1H), 7.35 - 7.24 (m, 1H), 7.22 - 7.11 (m, 2H), 5.45 - 5.32 (m, 1H), 5.28 (s, 2H), 3.78 - 3.59 (m, 2H)
XI-9		N-[(2,6-difluorophenyl) methyl]-5H-chromeno [3,4-c]pyridine-8-carboxamide	353.0	E:0.96 F:1.41	(500MHz, DMSO-d_6) δ 9.00 (br. s., 1H), 8.61 (d, *J* = 5.0 Hz, 1H), 8.52 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 5.4 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.40 (quin, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 2H), 5.25 (s, 2H), 4.52 (d, *J* = 5.0 Hz, 2H)

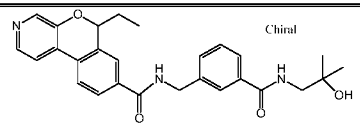
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-10		N-[1-(2,6-difluorophenyl)ethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	367.1	E:1.19 F:1.57	(500MHz, DMSO-d_6) δ 8.99 (d, *J* = 6.4 Hz, 1H), 8.63 (d, *J* = 4.4 Hz, 1H), 8.55 (br. s., 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 5.0 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.32 (t, *J* = 6.7 Hz, 1H), 7.08 - 6.98 (m, 2H), 5.36 (t, *J* = 6.9 Hz, 1H), 5.27 (s, 2H), 1.57 (d, *J* = 7.4 Hz, 3H)
XI-11		N-[(1S)-2-methoxy-1-phenylethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	361.1	E:1.14 F:1.48	(500MHz, DMSO-d_6) δ 8.96 (d, *J* = 7.9 Hz, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 8.51 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 5.2 Hz, 1H), 7.65 - 7.58 (m, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 - 7.20 (m, 1H), 5.25 (s, 2H), 5.24 - 5.20 (m, 1H), 3.75-3.53 (m, 5H)

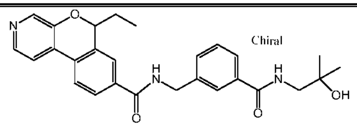
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-12		2-amino-N-[(1R)-1-(3-methoxyphenyl)ethyl]-5H-chromeno[3,4-c] pyridine-8-carboxamide	376.1	E:1.24 F:1.46	(500MHz, DMSO-d_6) δ 8.86 (d, J = 8.2 Hz, 1H), 7.88 - 7.78 (m, 2H), 7.57 (d, J = 7.9 Hz, 1H), 7.48 (s, 1H), 7.23 (t, J = 8.1 Hz, 1H), 6.98 - 6.91 (m, 2H), 6.85 (s, 1H), 6.81 - 6.73 (m, 1H), 5.15 - 5.07 (m, 1H), 5.02 (s, 2H), 3.72 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H)
XI-13		6-(2,3-dihydroxypropyl)-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	405.1	E:1.07 F:1.26	(500MHz, DMSO-d_6) δ 8.92 (br. s., 1H), 8.30 (d, J = 15.7 Hz, 2H), 8.07 (br. s., 1H), 8.01 - 7.90 (m, 2H), 7.81 (br. s., 1H), 7.40 (br. s., 2H), 7.33 (br. s., 2H), 7.23 (br. s., 1H), 5.68 - 5.54 (m, 1H), 5.19 (br. s., 1H), 5.02 - 4.34 (m, 2H), 3.79 (br. s., 1H), 3.30-3.21 (m, 2H), 2.00-1.82 (m, 2H), 1.50 (br. s., 3H)

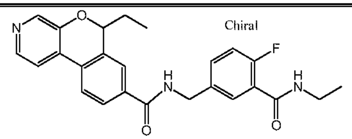
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-14		6-cyclopropyl-N-{[3-(difluoromethoxy)phenyl]methyl}-6H-isochromeno[3,4-c]pyridine-8-carboxamide	423.1	E:1.39 F:1.81	(500MHz, DMSO-d_6) δ 9.23 (br. s., 1H), 8.46 (br. s., 1H), 8.36 (br. s., 1H), 8.15 (d, J = 7.7 Hz, 1H), 8.07 (br. s., 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.95 (br. s., 1H), 7.45 - 7.34 (m, 1H), 7.26 - 7.19 (m, 1H), 7.14 (br. s., 1H), 7.11 - 7.04 (m, 2H), 4.78 (d, J = 8.8 Hz, 1H), 4.53 (br. s., 2H), 1.28 (br. s., 1H), 0.62 (br. s., 2H), 0.56 (br. s., 2H)
XI-15		6-ethyl-N-[(1S)-3-hydroxy-1-phenylpropyl]-6H-isochromeno[3,4-c]pyridine-8-carboxamide	389.1	E:1.11 F:1.45	(500MHz, DMSO-d_6) δ 8.85 (dd, J = 8.0, 3.0 Hz, 1H), 8.33 (s, 1H), 8.28 (d, J = 5.0 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.99 - 7.83 (m, 1H), 7.91 (d, J = 5.0 Hz, 1H), 7.79 (s, 1H), 7.45 - 7.36 (m, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.27 - 7.15 (m, 1H), 5.35 (dd, J = 8.3, 4.1 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.57 (t, J = 4.8 Hz, 1H), 3.53 - 3.38 (m, 2H), 2.12 - 2.00 (m, 1H), 1.92 (dq, J = 13.4, 6.5 Hz, 1H), 1.86 - 1.66 (m, 2H), 0.99 (td, J = 7.2, 4.5 Hz, 3H)

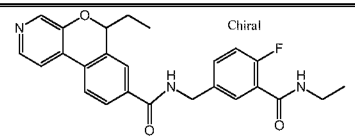
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-16		6-ethyl-N-[(1R)-1-(3-methoxyphenyl)ethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	389.1	A:8.99 B:9.93	(400MHz, methanol-d_4) δ 8.57-8.23 (br, 2H), 8.08 - 7.98 (m, 1H), 7.92 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.32 - 7.24 (m, 1H), 7.08 - 6.96 (m, 2H), 6.86 - 6.74 (m, 1H), 5.31 (dd, *J* = 8.8, 4.6 Hz, 1H), 5.27 - 5.17 (m, 1H), 3.80 (s, 3H), 2.03 - 1.74 (m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H)
XI-17		6-ethyl-N-[(1R)-1-(3-methoxyphenyl)ethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	389.1	A:9.05 B:9.97	(400MHz, methanol-d_4) δ 8.26 (s, 1H), 8.23 (d, *J* = 5.1 Hz, 1H), 8.04 - 8.00 (m, 1H), 7.96 - 7.90 (m, 1H), 7.86 (d, *J* = 5.1 Hz, 1H), 7.74 (d, *J* = 1.5 Hz, 1H), 7.30 - 7.22 (m, 1H), 7.04 - 6.95 (m, 2H), 6.85 - 6.78 (m, 1H), 5.31 (dd, *J* = 8.8, 4.6 Hz, 1H), 5.24 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 1.99 - 1.76 (m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H)

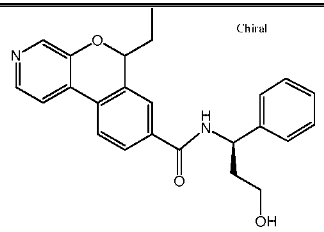
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-18		2-fluoro-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	349.0	E:1.68 F:1.69	(500MHz, DMSO-d_6) δ 8.93 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.01 - 7.96 (m, 2H), 7.86 (s, 1H), 7.79 (s, 1H), 7.46 - 7.38 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 - 7.16 (m, 1H), 5.30 (s, 2H), 5.18 (quin, *J* = 7.2 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H)
XI-19		6-ethyl-N-[(1R)-3-hydroxy-1-phenylpropyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	389.2	E:1.11 F:1.45	(500MHz, DMSO-d_6) δ 8.85 (dd, *J* = 8.0, 2.8 Hz, 1H), 8.33 (s, 1H), 8.27 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 5.2 Hz, 1H), 7.79 (s, 1H), 7.44 - 7.37 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 5.35 (dd, *J* = 8.4, 4.3 Hz, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.58 (t, *J* = 4.7 Hz, 1H), 3.51 - 3.39 (m, 2H), 2.11 - 2.00 (m, 1H), 1.97 - 1.88 (m, 1H), 1.85 - 1.67 (m, 2H), 1.04 - 0.94 (m, 3H)

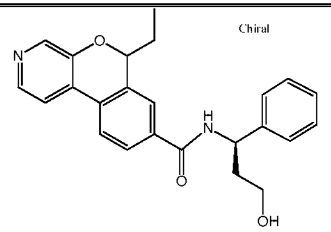
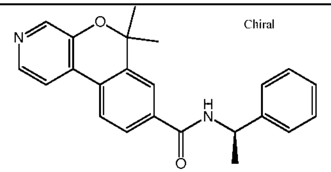
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-20		6-ethyl-N-({3-[(2-hydroxy-2-methylpropyl)carbamoyl]phenyl}methyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	460.2	A:4.30 B:4.69	(400MHz, DMSO-d_6) δ 9.18 (t, J = 5.8 Hz, 1H), 8.34 (s, 1H), 8.28 (d, J = 4.8 Hz, 1H), 8.21 (t, J = 6.1 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.98 (dd, J = 8.1, 1.5 Hz, 1H), 7.92 (d, J = 5.1 Hz, 1H), 7.84 (s, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.57 - 7.47 (m, 1H), 7.46 - 7.38 (m, 1H), 5.36 (dd, J = 8.6, 4.6 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 3.25 (d, J = 6.2 Hz, 3H), 1.90 - 1.64 (m, 2H), 1.10 (s, 6H), 0.99 (t, J = 7.3 Hz, 3H)

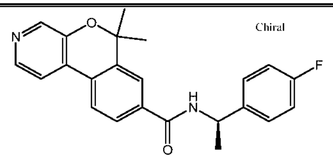
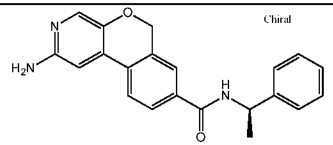
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-21		6-ethyl-N-({3-[(2-hydroxy-2-methylpropyl)carbamoyl]phenyl}methyl)-6H-isochromeno[3,4-c]pyridine-8-carboxamide	460.2	A:4.11 B:4.38	(400MHz, DMSO-d_6) δ 9.18 (t, J = 5.8 Hz, 1H), 8.46 - 8.25 (m, 2H), 8.20 (t, J = 6.1 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.97 (dd, J = 8.1, 1.8 Hz, 1H), 7.92 (d, J = 4.8 Hz, 1H), 7.84 (s, 2H), 7.75 (d, J = 7.7 Hz, 1H), 7.55 - 7.47 (m, 1H), 7.46 - 7.38 (m, 1H), 5.35 (dd, J = 8.6, 4.6 Hz, 1H), 4.55 (d, J = 5.9 Hz, 2H), 3.25 (d, J = 6.2 Hz, 3H), 2.02 - 1.65 (m, 2H), 1.10 (s, 6H), 0.99 (t, J = 7.4 Hz, 3H)

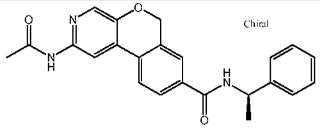
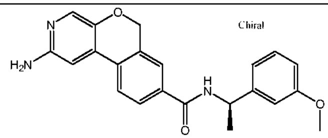
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-22		6-ethyl-N-{[3-(ethylcarbamoyl)-4-fluorophenyl]methyl}-6H-isochromeno[3,4-c]pyridine-8-carboxamide	434.2	A:4.69 B:5.11	(400MHz, DMSO-d_6) δ 9.18 (t, *J* = 5.9 Hz, 1H), 8.33 (s, 1H), 8.28 (d, *J* = 5.1 Hz, 2H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.96 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.91 (d, *J* = 5.1 Hz, 1H), 7.82 (d, *J* = 1.3 Hz, 1H), 7.57 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.50 - 7.41 (m, 1H), 7.24 (dd, *J* = 10.3, 8.6 Hz, 1H), 5.35 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.50 (d, *J* = 5.9 Hz, 2H), 3.26 (dd, *J* = 7.3, 5.7 Hz, 2H), 1.87 - 1.68 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H)

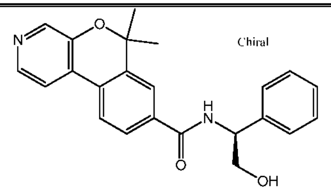
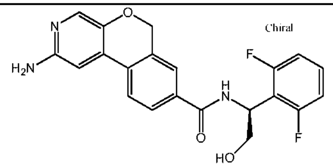
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-23		6-ethyl-N-{[3-(ethylcarbamoyl)-4-fluorophenyl]methyl}-6H-isochromeno[3,4-c]pyridine-8-carboxamide	434.2	A:4.68 B:5.11	(400MHz, DMSO-d_6) δ 9.18 (t, J = 5.9 Hz, 1H), 8.41 - 8.21 (m, 3H), 8.09 (d, J = 8.1 Hz, 1H), 7.96 (dd, J = 8.0, 1.7 Hz, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.82 (d, J = 1.1 Hz, 1H), 7.57 (dd, J = 7.0, 2.2 Hz, 1H), 7.51 - 7.40 (m, 1H), 7.24 (dd, J = 10.3, 8.6 Hz, 1H), 5.35 (dd, J = 8.6, 4.6 Hz, 1H), 4.50 (d, J = 5.9 Hz, 2H), 3.28 - 3.19 (m, 2H), 1.90 - 1.65 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H)

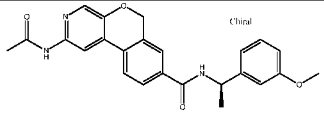
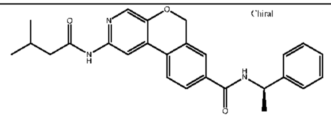
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-24		6-ethyl-N-[(1R)-3-hydroxy-1-phenylpropyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	389.2	A:4.68 B:5.07	(400MHz, DMSO-d_6) δ 8.85 (d, J = 8.1 Hz, 1H), 8.33 (s, 1H), 8.28 (d, J = 5.1 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.95 (dd, J = 8.0, 1.7 Hz, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.79 (s, 1H), 7.44 - 7.37 (m, 2H), 7.36 - 7.28 (m, 2H), 7.27 - 7.15 (m, 1H), 5.36 (dd, J = 8.6, 4.6 Hz, 1H), 5.24 - 5.10 (m, 1H), 4.57 (t, J = 4.8 Hz, 1H), 3.45 (qd, J = 11.0, 4.7 Hz, 2H), 2.14 - 1.99 (m, 1H), 1.92 (dq, J = 13.3, 6.6 Hz, 1H), 1.85 - 1.65 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H)

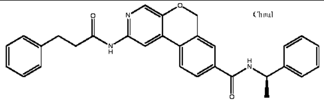
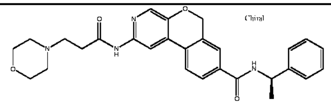
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-25		6-ethyl-N-[(1R)-3-hydroxy-1-phenylpropyl]-6H-isochromeno[3,4-c]pyridine-8-carboxamide	389.1	A:4.67 B:5.05	(400MHz, DMSO-d_6) δ 8.84 (d, *J* = 8.1 Hz, 1H), 8.33 (s, 1H), 8.28 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.91 (d, *J* = 5.1 Hz, 1H), 7.79 (s, 1H), 7.46 - 7.37 (m, 2H), 7.36 - 7.28 (m, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 5.35 (dd, *J* = 8.7, 4.7 Hz, 1H), 5.25 - 5.08 (m, 1H), 4.56 (t, *J* = 5.0 Hz, 1H), 3.55 - 3.38 (m, 2H), 2.13 - 2.00 (m, 1H), 1.98 - 1.86 (m, 1H), 1.85 - 1.68 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H)
XI-26		6,6-dimethyl-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c]pyridine-8-carboxamide	359.1	A:5.76 B:6.27	(400MHz, CD_3OD) δ 8.82 (d, J = 7.3 Hz, 1H), 8.16 (br. s., 2H), 7.95 (d, J = 7.9 Hz, 1H), 7.89 - 7.81 (m, 2H), 7.79 (s, 1H), 7.36 - 7.29 (m, 2H), 7.24 (t, J = 7.7 Hz, 2H), 7.18 - 7.10 (m, 1H), 5.18 (t, J = 7.3 Hz, 1H), 1.62 (s, 6H), 1.50 (d, J = 7.0 Hz, 3H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-27		N-[(1R)-1-(4-fluorophenyl)ethyl]-6,6-dimethyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	377.1	A:5.80 B:6.52	(400MHz, CD_3OD) δ 8.98 (d, *J* = 7.3 Hz, 1H), 8.48 (s, 1H), 8.41 (d, *J* = 5.5 Hz, 1H), 8.36 (d, *J* = 5.9 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 7.44 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.07 (t, *J* = 8.8 Hz, 2H), 5.27 (quin, *J* = 7.2 Hz, 1H), 1.78 (s, 6H), 1.60 (d, *J* = 7.0 Hz, 3H)
XI-28		2-amino-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	346.1	E:1.22 F:1.47	(500MHz, DMSO-d_6) δ 9.01 (d, *J* = 7.3 Hz, 1H), 7.97 (br. s., 2H), 7.83 (br. s., 1H), 7.50 - 7.28 (m, 6H), 7.25 - 7.17 (m, 1H), 5.20 (s, 2H), 5.17 - 5.07 (m, 1H), 1.47 (d, *J* = 6.4 Hz, 3H)

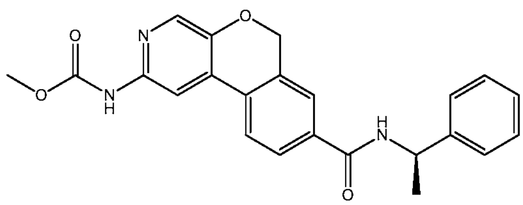
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-29		2-acetamido-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	388.2	E:1.35 F:1.51	(500MHz, DMSO-d_6) δ 10.43 (br. s., 1H), 8.95 (d, *J* = 7.7 Hz, 1H), 8.03 - 7.91 (m, 2H), 7.89 - 7.75 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.25 - 7.18 (m, 1H), 5.25 (s, 2H), 5.17 (t, *J* = 7.2 Hz, 1H), 2.12 (br. s., 3H), 1.48 (d, *J* = 6.7 Hz, 3H)
XI-30		2-amino-N-[(1R)-1-(3-methoxyphenyl)ethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	376.1	E:1.31 F:1.37	(500MHz, DMSO-d_6) δ 8.98 (d, *J* = 7.7 Hz, 1H), 8.05 - 7.96 (m, 2H), 7.87 (d, *J* = 14.8 Hz, 2H), 7.39 (s, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.01 - 6.94 (m, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 5.24 (s, 2H), 5.14 (t, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 1.47 (d, *J* = 7.1 Hz, 3H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-31		N-[(1S)-2-hydroxy-1-phenylethyl]-6,6-dimethyl-6H-isochromeno[3,4-c] pyridine-8-carboxamide	375.3	E:0.96 F:1.30	(500MHz, DMSO-d_6) δ 8.87 (d, *J* = 8.1 Hz, 1H), 8.33 - 8.23 (m, 2H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.97 - 7.89 (m, 2H), 7.41 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 - 7.21 (m, 1H), 5.11 (d, *J* = 6.1 Hz, 1H), 5.04 (t, *J* = 5.6 Hz, 1H), 3.81 - 3.62 (m, 2H), 1.70 - 1.66 (m, 3H), 1.66 (s, 3H)
XI-32		2-amino-N-[(1S)-1-(2,6-difluorophenyl)-2-hydroxyethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	398.1	E:0.91 F:1.22	(500MHz, DMSO-d_6) δ 8.79 (d, *J* = 7.1 Hz, 1H), 7.99 - 7.69 (m, 4H), 7.34 (t, *J* = 7.1 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 2H), 6.92 (s, 1H), 5.37 (d, *J* = 6.7 Hz, 1H), 5.07 (s, 2H), 3.89 (d, *J* = 6.4 Hz, 1H), 3.77 (d, *J* = 5.4 Hz, 1H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XI-33		2-acetamido-N-[(1R)-1-(3-methoxyphenyl) ethyl]-6H-isochromeno [3,4-c]pyridine-8-carboxamide	418.0	E:1.31 F:1.46	(500MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.94 (d, *J* = 8.1 Hz, 1H), 8.50 (s, 1H), 8.10 (s, 1H), 8.00 - 7.93 (m, 1H), 7.91 - 7.80 (m, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.02 - 6.91 (m, 2H), 6.81 (d, *J* = 9.1 Hz, 1H), 5.26 (s, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 2.11 (s, 3H), 1.49 (d, 3H)
XI-34		2-(3-methylbutanamido)-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	430.3	E:1.57 F:1.78	(500MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.96 (d, *J* = 8.1 Hz, 1H), 8.56 (s, 1H), 8.11 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 15.8 Hz, 2H), 7.45 - 7.38 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 - 7.18 (m, 1H), 5.26 (s, 2H), 5.20 (t, *J* = 7.2 Hz, 1H), 2.29 (d, *J* = 7.1 Hz, 2H), 2.17 - 2.05 (m, 1H), 1.50 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 6H)

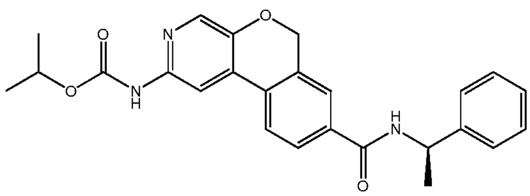
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XI-35		N-[(1R)-1-phenylethyl]-2-(3-phenylpropanamido)-6H-isochromeno[3,4-c] pyridine-8-carboxamide	478.1	E:1.76 F:1.92	(500MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.97 (d, *J* = 8.1 Hz, 1H), 8.54 (s, 1H), 8.10 (s, 1H), 8.03 - 7.93 (m, 2H), 7.87 (d, *J* = 17.5 Hz, 2H), 7.43 - 7.38 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 (m., 6H), 7.20 (d, *J* = 6.7 Hz, 1H), 5.26 (s, 2H), 5.19 (t, *J* = 7.2 Hz, 1H), 2.97 - 2.91 (m, 2H), 2.77 - 2.70 (m, 2H), 1.50 (d, *J* = 6.7 Hz, 3H)
XI-36		2-[3-(morpholin-4-yl) propanamido]-N-[(1R)-1-phenylethyl]-6H-isochromeno[3,4-c] pyridine-8-carboxamide	487.0	E:1.16 F:1.51	(500MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.96 (d, *J* = 8.1 Hz, 1H), 8.55 (s, 1H), 8.12 (s, 1H), 8.02 - 7.94 (m, 1H), 7.90 - 7.84 (m, 2H), 7.44 - 7.39 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 - 7.21 (m, 1H), 5.26 (s, 2H), 5.19 (t, *J* = 7.2 Hz, 1H), 3.59 (br. s., 4H), 2.64 (d, *J* = 6.4 Hz, 2H), 2.58 (d, *J* = 6.4 Hz, 2H), 2.43 (br. s., 4H), 1.50 (d, *J* = 7.1 Hz, 3H)

Example XI-37: Methyl N-(8-{[(1R)-1-phenylethyl]carbamoyl}-6H-isochromeno[3,4-c]pyridin-2-yl)carbamate



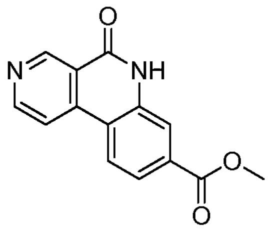
Example XI-28 (9.3 mg, 0.020 mmol) was suspended in 2 mL of CH_2Cl_2 and was cooled in an ice bath. To this mixture was added methyl carbonochloridate (7.82 µl, 0.101 mmol) and DIEA (0.035 mL, 0.202 mmol). The mixture was stirred at 0 °C for 10 minutes. The solvent was removed. The residue was dissolved in DMF, filtered, and purified by reverse phase HPLC (2.1 mg, 25%). LC-MS (ESI) *m/z*:404.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.51 (s, 1H), 9.09 (d, *J* = 7.9 Hz, 1H), 8.96 (d, *J* = 5.2 Hz, 1H), 8.66 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 5.8 Hz, 1H), 7.95 - 7.81 (m, 2H), 7.45 (dd, *J* = 8.2, 5.8 Hz, 2H), 7.19 - 7.10 (m, 2H), 6.08 - 5.94 (m, 1H), 5.30 - 5.14 (m, 2H), 5.06 (d, *J* = 15.3 Hz, 3H), 1.52 (d, *J* = 7.0 Hz, 3H).

Example XI-38: Propan-2-yl N-(8-{[(1R)-1-phenylethyl]carbamoyl}-6H-isochromeno[3,4-c]pyridin-2-yl)carbamate

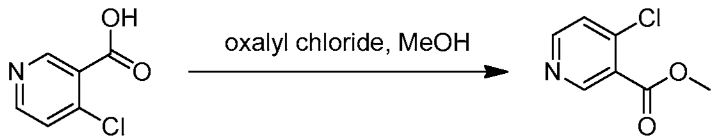


Example XI-38 was prepared according to the procedures described for Example XI-37. LC-MS (ESI) *m/z*: 432.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.96 (d, *J* = 8.1 Hz, 1H), 8.23 (s, 1H), 8.06 (s, 1H), 8.01 - 7.95 (m, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.86 (s, 1H), 7.45 - 7.39 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 - 7.17 (m, 1H), 5.19 (t, *J* = 7.2 Hz, 1H), 4.94 (dt, *J* = 12.3, 6.3 Hz, 1H), 2.90 (s, 1H), 2.74 (s, 1H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 6H)

Intermediate 18: Methyl 5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylate

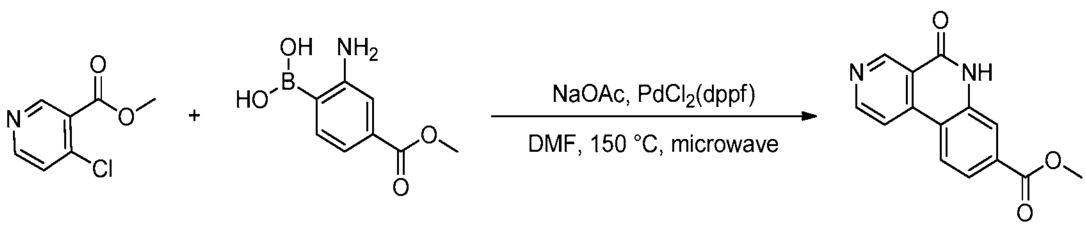


Intermediate 18A: Methyl 4-chloronicotinate



To a suspension of 4-chloronicotinic acid (1.1 g, 7.1 mmol) in DCM (10 mL), was added oxalyl chloride (2 M in DCM) (8.9 mL, 18 mmol) followed by addition of DMF (0.25 mL), dropwise. The reaction mixture was stirred at rt for 45 min, cooled to 0 ºC, and was quenched with methanol. The solvent was removed. The residue was suspended in EtOAc. White precipitate was filtered, washed with hexane and EtOAc, and dried to afford Intermediate 18A (1.2 g, 98%) as off-white solid. LC-MS (ESI) *m/z*: 172.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.70 (d, *J* = 5.5 Hz, 1H), 7.72 (d, *J* = 5.5 Hz, 1H), 3.91 (s, 3H).

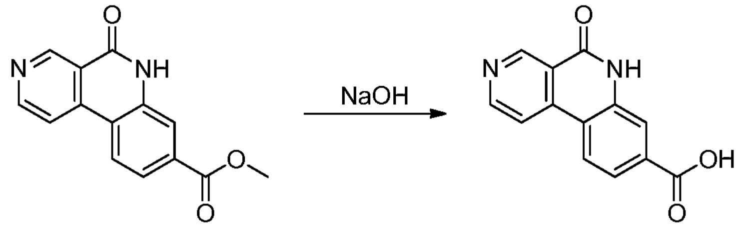
Intermediate 18:



To a solution of Intermediate 18A (780 mg, 3.9 mmol) in DMF (10 mL), were added (2-amino-4-(methoxycarbonyl)phenyl)boronic acid (750 mg, 3.9 mmol), sodium acetate (1300 mg, 16 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (250 mg, 0.31 mmol). The reaction was purged with nitrogen and then was heated in a microwave reactor at 150 ºC for 10 min. The reaction mixture was cooled to rt and water (70 mL) was added. The solid formed was filtered, washed with water (3x), ether (5x), and was dried to afford Intermediate 18 (540 mg, 55%) as a tan solid. LC-MS (ESI) *m/z*: 255.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 12.06 (br. s., 1H), 9.46 (s, 1H), 8.96 (d, *J* = 5.3 Hz, 1H), 8.59 (d,

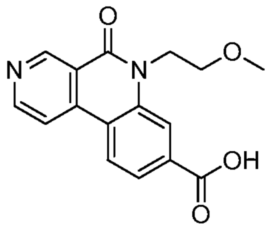
J = 8.1 Hz, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.00 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H).

Intermediate 19: 5-Oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid

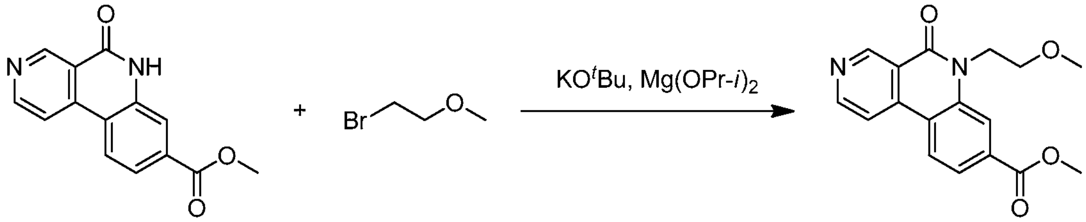


To a suspension of Intermediate 18 (40 mg, 0.13 mmol) in EtOH (1.5 mL), was added NaOH (1 N, 0.38 mL, 0.38 mmol). The reaction mixture was stirred under argon at rt for 1.5 h. To the mixture was added HCl (3.7 N, 0.07 mL, 0.25 mmol) to adjust the pH to ~8. Purification by reverse phase chromatography afforded Intermediate 19 (30 mg, 67%) as a brown solid. LC-MS (ESI) *m/z*: 241.1 $[M+H]^+$.

Intermediate 20: 6-(2-Methoxyethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid

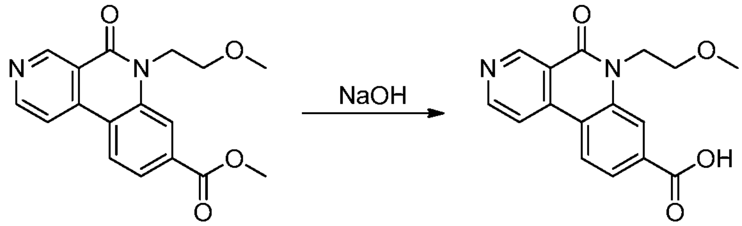


Intermediate 20A: Methyl 6-(2-methoxyethyl)-5-oxo-5,6-dihydrobenzo[c][2,7] naphthyridine-8-carboxylate



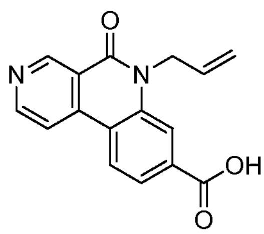
To a solution of 18 (70 mg, 0.28 mmol) and 1-bromo-2-methoxyethane (120 mg, 0.83 mmol) in THF (2.5 mL), were added potassium *tert*-butoxide (1 M, 0.29 mL, 0.29 mmol) and magnesium isopropyloxide (94 mg, 0.55 mmol). The reaction was stirred at rt in a sealed tube for 1 h, and then was heated at 70 ºC for 6 h. The solvent was removed. The residue was purified by reverse phase chromatography to afford Intermediate 20A (35 mg, 30%) as a yellowish solid. LC-MS (ESI) *m/z*: 313.1 $[M+H]^+$; ^{1}H NMR (400MHz, CD_3OD) δ 9.61 (s, 1H), 8.94 (d, *J* = 5.9 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.57 (d, *J* = 5.9 Hz, 1H), 8.41 (d, *J* = 1.1 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.3 Hz, 1H), 4.69 (t, *J* = 5.6 Hz, 2H), 4.01 (s, 3H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.37 (s, 3H).

Intermediate 20:

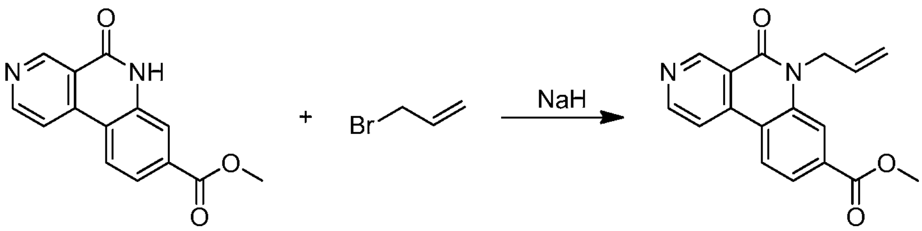


To a solution of 20A (35 mg, 0.080 mmol) in EtOH (2 mL), was added NaOH (1N, 0.49 mL, 0.49 mmol). The reaction mixture was stirred under argon at rt for 1.5 h. Aqueous HCl (3.7 N) (0.09 mL, 0.33 mmol) was added to adjust the pH to ~8. Purification by reverse chromatography afforded Intermediate 20 (31mg, 90%) as yellow solid. LC-MS (ESI) *m/z*: 299.1 $[M+H]^+$.

Intermediate 21: 6-Allyl-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid

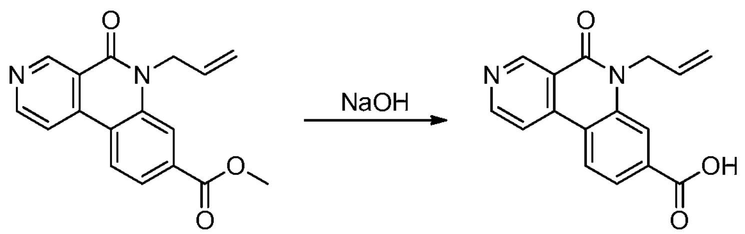


Intermediate 21A: Methyl 6-allyl-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylate



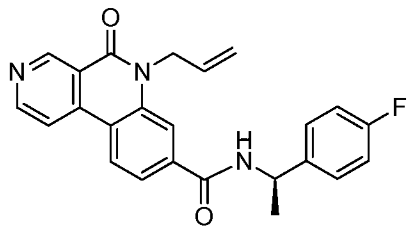
NaH (60% suspension, 320 mg, 7.9 mmol) was added to a solution of Intermediate 18 (500 mg, 1.6 mmol) in DMF (10 mL) at 0 ºC, portionwise. The reaction temperature was stirred at 0 ºC for 10 min. Allyl bromide (1.4 mL, 16 mmol) was then added dropwise. The ice bath was removed, and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred at rt for 1 h. It was cooled with an ice bath, diluted with EtOAc, and was slowly quenched with water. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and concentrated. Purification by normal phase chromatography afforded Intermediate 21A (120 mg, 25%) as an orange solid. LC-MS (ESI) *m/z*: 295.1 $[M+H]^+$;^{1}H NMR (400MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.97 (d, *J* = 5.5 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 1.3 Hz, 1H), 8.08 (d, *J* = 5.5 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.03 (ddt, *J* = 17.2, 10.5, 5.1 Hz, 1H), 5.31 (dd, *J* = 10.5, 0.8 Hz, 1H), 5.23 (dd, *J* = 17.3, 0.8 Hz, 1H), 5.13 - 5.00 (m, 2H), 4.00 (s, 3H).

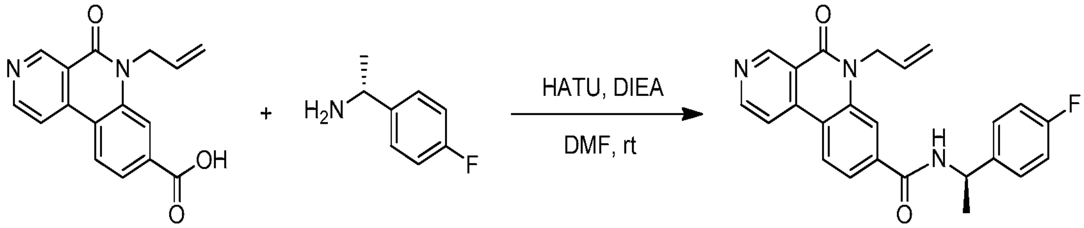
Intermediate 21: 6-Allyl-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxylic acid



To a suspension of Intermediate 21A (150 mg, 0.50 mmol) in EtOH (3 mL), was added NaOH (1 N, 1.0 mL, 1.0 mmol). The reaction was stirred under argon at rt for 1.5 h. Aqueous HCl (3.7 N) (0.14 mL, 0.51 mmol) was added to adjust the pH to ~8. Purification by reverse chromatography afforded Intermediate 21 (120 mg, 85%) as yellow solid. LC-MS (ESI) *m/z*: 281.0 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.98 (d, *J* = 5.5 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.00 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 6.14 - 5.97 (m, 1H), 5.20 (d, *J* = 10.6 Hz, 1H), 5.09 - 4.97 (m, 3H).

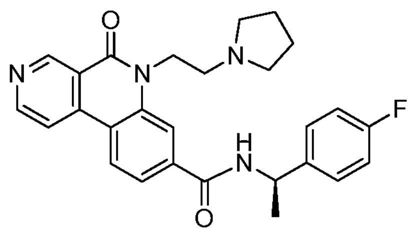
Example XII-1: (R)-6-Allyl-N-(1-(4-fluorophenyl)ethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide



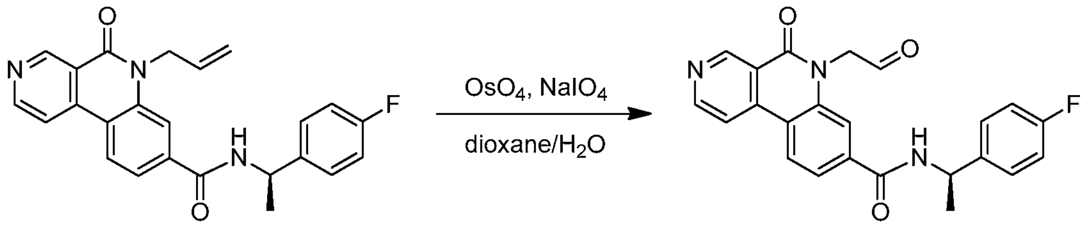


To a solution of Intermediate 21 (110 mg, 0.39 mmol) in DMF (3 mL) were added (R)-1-(4-fluorophenyl)ethanamine (110 mg, 0.78 mmol), HATU (250 mg, 0.67 mmol), and DIEA (0.34 mL, 1.9 mmol). The reaction mixture was stirred under argon at rt for 2 h. The reaction was partitioned between EtOAc and water. The organic layer was dried over sodium sulfate, and purified by normal phase chromatography to afford Example XII-1 (210 mg, 91%) as a foam. LC-MS (ESI) *m/z*: 402.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.51 (s, 1H), 9.09 (d, *J* = 7.9 Hz, 1H), 8.96 (d, *J* = 5.2 Hz, 1H), 8.66 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 5.8 Hz, 1H), 7.95 - 7.81 (m, 2H), 7.45 (dd, *J* = 8.2, 5.8 Hz, 2H), 7.19 - 7.10 (m, 2H), 6.08 - 5.94 (m, 1H), 5.30 - 5.14 (m, 2H), 5.06 (d, *J* = 15.3 Hz, 3H), 1.52 (d, *J* = 7.0 Hz, 3H).

Example XII-2: (R)-N-(1-(4-Fluorophenyl)ethyl)-5-oxo-6-(2-(pyrrolidin-1-yl)ethyl)-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide

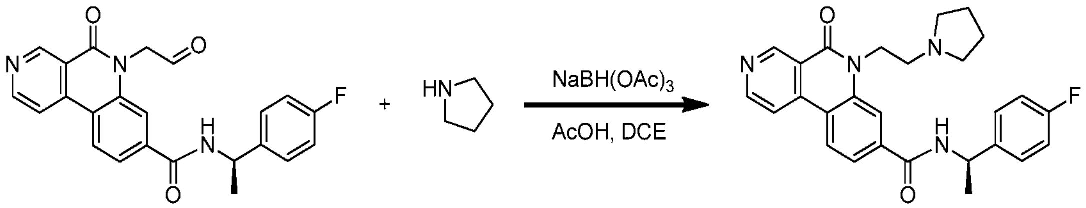


Intermediate XII-2A: (R)-N-(1-(4-Fluorophenyl)ethyl)-5-oxo-6-(2-oxoethyl)-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide



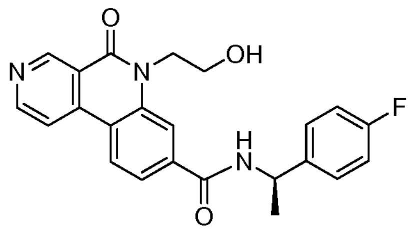
To a solution of Example XII-1 (50 mg, 0.13 mmol) in dioxane (5 mL) and water (0.5 mL), were added sodium periodate (80 mg, 0.37 mmol) and osmium tetroxide (4% in water, 0.016 mL, 2.5 µmol). The reaction was stirred under argon at rt overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over sodium sulfate and concentrated. Purification by normal phase chromatography afforded Intermediate XII-2A (23 mg, 46%) as film of solid. LC-MS (ESI) *m/z*: 404.1 $[M+H]^+$.

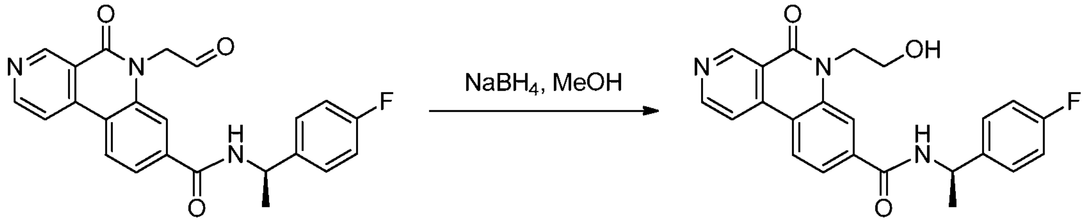
Example XII-2:



To a suspension of Intermediate XII-2A (23 mg, 0.06 mmol) in DCE (3 mL), were added pyrrolidine (20 mg, 0.28 mmol) and AcOH (0.07 mL, 1.1 mmol). The reaction mixture was stirred at rt for 20 min, and then sodium triacetoxyborohydride (85 mg, 0.40 mmol) was added in portions. The reaction was stirred under argon at rt for 30 min. The solvent was removed. The residue was dissolved in MeOH, and was purified by reverse chromatography to afford Example XII-2 (5.1 mg, 19%) as a solid. LC-MS (ESI) *m/z*: 459.2 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ 9.50 (br. s., 1H), 9.13 (d, *J* = 7.3 Hz, 1H), 8.96 (d, *J* = 4.6 Hz, 1H), 8.68 (d, *J* = 8.2 Hz, 1H), 8.50 (d, *J* = 4.6 Hz, 1H), 7.96 - 7.90 (m,1H), 7.47 (br. s., 2H), 7.27 - 7.12 (m, 3H), 6.64 (br. s., 1H), 5.39 - 5.27 (m, 2H), 5.25 - 5.17 (m, 1H), 3.06 (m, 2H),.2.04 - 1.77 (m, 10H), 1.53 (d, *J* = 6.7 Hz, 3H).

Example XII-3: (R)-N-(1-(4-Fluorophenyl)ethyl)-6-(2-hydroxyethyl)-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-8-carboxamide

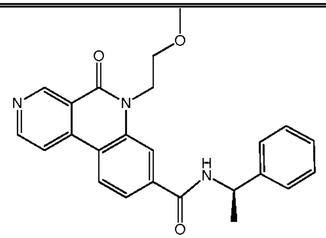
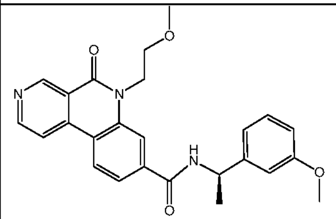


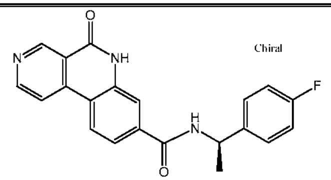


To a solution of Intermediate XII-2A (10 mg, 0.03 mmol) in MeOH (2 mL), was added $NaBH_4$ (9.4 mg, 0.25 mmol). The reaction mixture was stirred under argon at rt for 50 min. Purification by reverse phase chromatography afforded Example XII-3. LC-MS (ESI) *m/z*: 406.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ 9.45 (br. s., 1H), 9.13 (d, *J* = 7.6 Hz, 1H), 8.90 (br. s., 1H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.42 (d, *J* = 4.9 Hz, 1H), 8.10 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 6.6 Hz, 2H), 7.14 (t, *J* = 8.7 Hz, 2H), 5.19 (t, *J* = 7.0 Hz, 1H), 4.47 (br. s., 2H), 3.70 - 3.60 (m, 3H), 1.51 (d, *J* = 6.7 Hz, 3H).

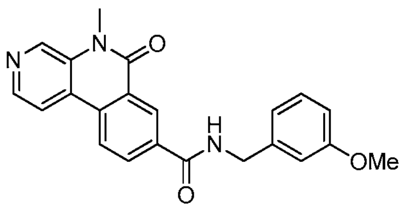
Compounds listed in Table XII were prepared by following procedures similar to those described for Example XII-1 using the appropriate intermediates described or purchased from commercial sources. Other coupling reagents, such as HATU, T_3P, BOP, PyBop, and EDC/HOBt, could be instead of the one described.

Table XII

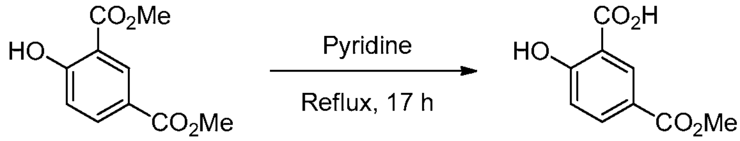
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XII-4		6-(2-methoxyethyl)-5-oxo-N-[(1R)-1-phenylethyl]-5H,6H-benzo[c]2,7-naphthyridine-8-carboxamide	402.1	E:1.26 F:1.46	(500MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.10 (d, *J* = 7.7 Hz, 1H), 8.95 (d, *J* = 5.2 Hz, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.50 (d, *J* = 5.8 Hz, 1H), 8.13 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 - 7.19 (m, 1H), 5.24 (t, *J* = 7.2 Hz, 1H), 4.63 (t, *J* = 5.8 Hz, 2H), 3.71 (t, *J* = 5.9 Hz, 2H), 3.27 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H)
XII-5		6-(2-methoxyethyl)-N-[(1R)-1-(3-methoxyphenyl)ethyl]-5-oxo-5H,6H-benzo[c]2,7-naphthyridine-8-carboxamide	432.2	E:1.83 F:2.11	(500MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.08 (d, *J* = 8.2 Hz, 1H), 8.95 (d, *J* = 5.2 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.12 (s, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 6.99 (br. s., 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 5.21 (t, *J* = 6.9 Hz, 1H), 4.63 (br. s., 2H), 3.75 (s, 3H), 3.71 (br. s., 2H), 3.27 (s, 3H), 1.52 (d, *J* = 6.7 Hz, 3H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XII-6		N-[(1R)-1-(4-fluorophenyl) ethyl]-5-oxo-5H,6H-benzo[c]2,7-naphthyridine-8-carboxamide	362.2	E:1.12 F:1.31	(500MHz, DMSO-d_6) δ 9.43 (s, 1H), 9.05 (d, *J* = 7.9 Hz, 1H), 8.93 (d, *J* = 5.5 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.44 (d, *J* = 5.5 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.48 - 7.38 (m, 2H), 7.14 (t, *J* = 8.5 Hz, 2H), 5.29 - 5.05 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 3H)

Example XIII-1: N-(3-Methoxybenzyl)-5-methyl-6-oxo-5,6-dihydrobenzo[c][1,7]naphthyridine-8-carboxamide

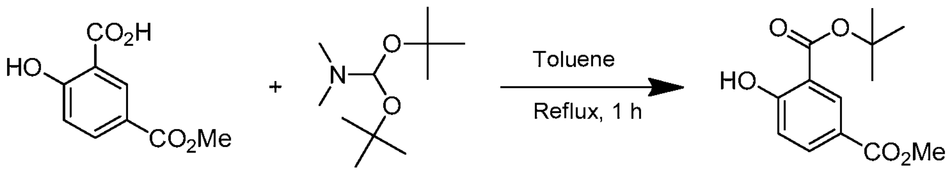


Example XIII-1A: 2-Hydroxy-5-(methoxycarbonyl)benzoic acid



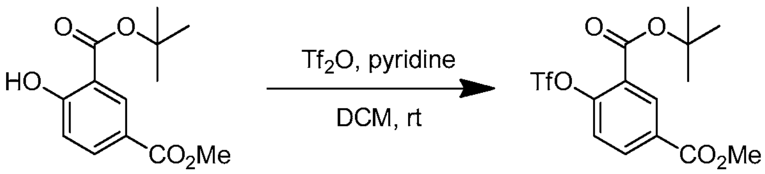
Pyridine (140 ml, 1700 mmol) was added to dimethyl 4-hydroxyisophthalate (10 g, 48mmol) and the mixture was refluxed for 17 h. The mixture was then concentrated *in vacuo*, and the residue was acidified with 1.5 N HCl/H_2O (1:1) (120 mL). The resulting precipitate was collected by filtration, washed with water (3 x 20 mL), and dried *in vacuo* to give a brown solid, which was azeotroped with toluene to give Example XIII-1A as brown solid (9.0 g. 92%). LC-MS (ESI) *m/z*: 194.9 $[M-H]^-$.

Example XIII-1B: 3-*tert*-Butyl 1-methyl 4-hydroxyisophthalate



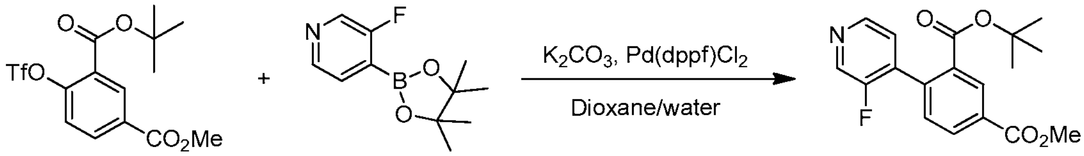
To a solution of Example XIII-1A (5.0 g, 26 mmol) in toluene (100 mL), was added 1,1-di-*tert*-butoxyltrimethylamine (25 mL, 100 mmol). The reaction was refluxed for 1.5 h. The reaction was cooled to rt, diluted with toluene (30 mL), washed with 10% percent citric acid solution (2 x 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a yellow liquid, which was purified by normal phase chromatography to give Example XIII-1B as a white solid (3.2 g, 48%). LC-MS (ESI) *m/z*: 251.0 $[M-H]^-$.

Example XIII-1C: 3-*tert*-Butyl 1-methyl 4-(((trifluoromethyl)sulfonyl)oxy)isophthalate



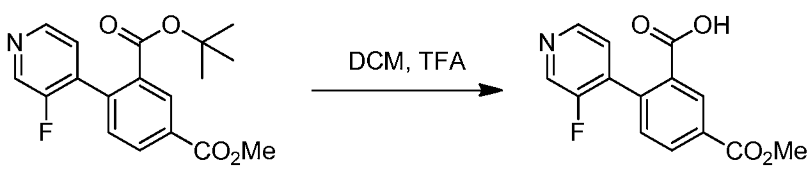
To a solution of Example XIII-1B (3.2 g, 13mmol) and pyridine (5.2 mL, 64 mmol) in DCM (70 mL), was added Tf_2O (4.3 mL, 25 mmol). The reaction mixture was stirred at rt for 2.5 h. The reaction was quenched with water (50 mL), extracted with DCM (3 x 50 mL). The combined DCM layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by normal phase chromatography to give Example XIII-1C as a colorless viscous liquid (3.5 g, 70%). LC-MS (ESI) *m/z*: 402.0 $[M+H+NH_2]^+$.

Example XIII-1D: 3-*tert*-Butyl 1-methyl 4-(3-fluoropyridin-4-yl)isophthalate



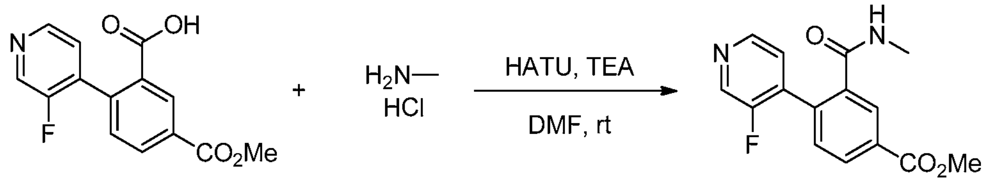
A solution of Example XIII-1C (3.5 g, 9.1 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.0 g, 9.1 mmol) and K_2CO_3 (3.8 g, 27 mmol) in dioxane (60 mL) and water (10 mL) was purged with nitrogen for 10 minutes, and then was added $PdCl_2$(dppf) (0.40 g, 0.55 mmol). The reaction was heated at 80 ºC for 2 h and then it was cooled to rt. The reaction was diluted with ethyl acetate (50 mL), washed with brine solution (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by normal phase chromatography to give Example XIII-1D as a brown solid (2.7 g, 89%). LC-MS (ESI) *m/z*: 332.1 $[M+H]^+$.

Example XIII-1E: 2-(3-Fluoropyridin-4-yl)-5-(methoxycarbonyl)benzoic acid



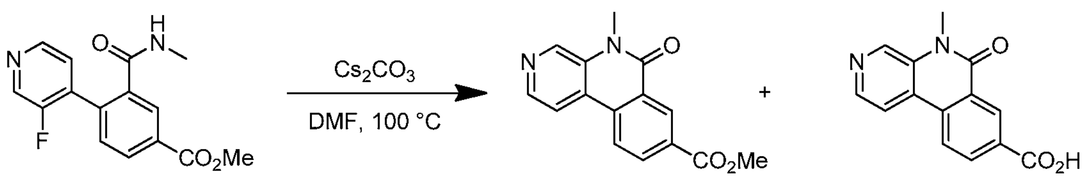
To the solution of Example XIII-1D (2.7 g, 8.2 mmol) in DCM (25 mL) was added TFA (6 mL, 78 mmol). The reaction was stirred at rt for 18 h. The solvent was removed to give brown solid. It was washed with petroleum ether (2 x 25 mL), diethyl ether (2 x 15 mL) and dried *in vacuo* to give Example XIII-1E as an off-white solid (2.2 g, 68%). LC-MS (ESI) *m/z*: 276.0 $[M+H]^+$.

Example XIII-1F: Methyl 4-(3-fluoropyridin-4-yl)-3-(methylcarbamoyl)benzoate



To the solution of Example XIII-1E (800 mg, 2.9 mmol) and methylamine HCl salt (290 mg, 4.4 mmol) in DMF (5 mL) at 0 °C, were added TEA (2.0 mL, 15 mmol) and HATU (1100 mg, 2.9 mmol). The reaction was warmed to rt and stirred overnight. The solvent was removed to give brown solid, which was partitioned between water (15 mL) and ethyl acetate (25 mL). The organic solution was extracted with ethyl acetate (3 x 25 mL). The combined ethyl acetate layers were washed with brine solution, dried over Na_2SO_4, filtered and concentrated. Purification by normal phase chromatography gave an off-white solid. The solid was dissolved in DCM (4 mL) and reprecipitated by adding petroleum ether, and filtered to give Example XIII-1F as white solid (400 mg, 46%). LC-MS (ESI) *m/z*: 289.1 $[M+H]^+$.

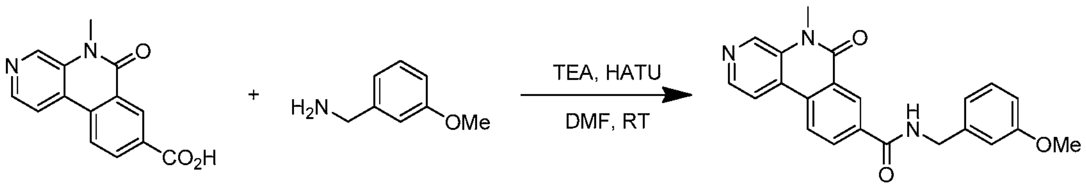
Example XIII-1G: Methyl 5-methyl-6-oxo-5,6-dihydrobenzo[c][1,7]naphthyridine-8-carboxylate, and
Example XIII-1H: 5-Methyl-6-oxo-5,6-dihydrobenzo[c][1,7]naphthyridine-8-carboxylic acid



To the suspension of methyl 4-(3-fluoropyridin-4-yl)-3-(methylcarbamoyl) benzoate (440 mg, 1.5 mmol) in DMF (10 mL), was added Cs_2CO_3 (1200 mg, 3.8 mmol). The reaction was refluxed at 85 °C overnight. The solvent was removed to give a yellow residue, which was dissolved in ethyl acetate (40 mL) and water (15 mL). Two layers were separated. The aqueous layer was saturated with NaCl and extracted with ethyl acetate (4 x 20 mL). The combined ethyl acetate layers were washed with brine solution

(1 x 5 mL), dried over Na_2SO_4, filtered and concentrated to give Example XIII-1G as an off-white solid (100 mg, 24%). LC-MS (ESI) *m/z*: 269.0 $[M+H]^+$. The aqueous layer was acidified to pH 5 and solid was precipitated, which was filtered and dried *in vacuo* to give Example XIII-1H as an off-white solid (240 mg, 58%). LC-MS (ESI) *m/z*: 253.0 $[M+H]^+$.

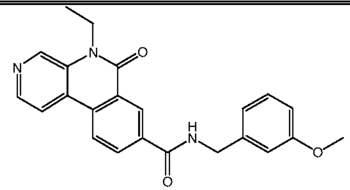
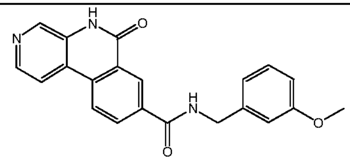
Example XIII-1:

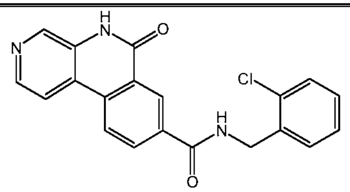
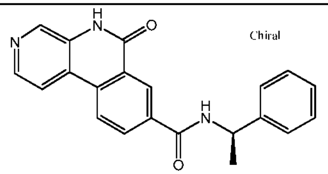


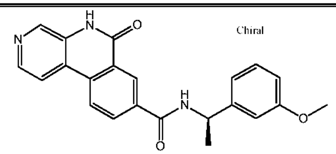
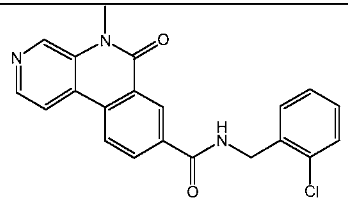
To the suspension of Example XIII-1H (120 mg, 0.47 mmol) and (3-methoxyphenyl)methanamine (65 mg, 0.47 mmol) in DMF (4 mL) were added TEA (0.33 mL, 2.4 mmol) and HATU (270 mg, 0.71 mmol). The reaction was stirred at rt for overnight. Reaction was diluted with water (40 mL), and precipitated solid was collected and further purified by normal phase chromatography to give Example XIII-1 as a white solid (25 mg, 13%). LC-MS (ESI) *m/z*: 374.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (t, J = 5.96 Hz, 1 H) 8.93 - 9.02 (m, 2 H) 8.77 (d, J = 8.47 Hz, 1 H) 8.55 - 8.60 (m, 1 H) 8.47 (d, J = 5.21 Hz, 1 H) 8.39 (dd, J = 8.44, 1.98 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.82 - 6.87 (m, 1 H) 4.52 (d, J = 5.90 Hz, 2 H) 3.83 (s, 3 H) 3.75 (s, 3 H); Analytical HPLC RT A: 6.34 min, B: 6.39 min.

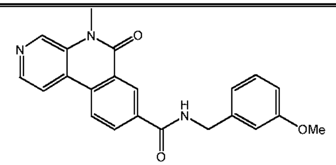
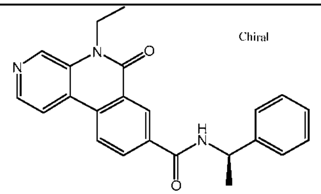
Compounds listed in Table XIII were prepared by following a similar procedure to that described for Example XIII-1.

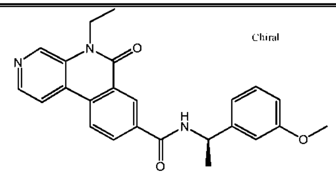
Table XIII

Ex. No.	Structure	Name	LCMS [M+H]+	HPLC Method, RT (min.)	1H NMR (δ, ppm)
XIII-2		5-ethyl-N-[(3-methoxyphenyl)methyl]-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	388.2	A:6.83 B:6.93	(400 MHz, DMSO-d_6) 9.46 (t, *J* = 6.02 Hz, 1 H) 9.04 (s, 1 H) 8.96 (d, *J* = 2.01 Hz, 1 H) 8.77 (d, *J* = 8.53 Hz, 1 H) 8.57 (d, *J* = 5.02 Hz, 1 H) 8.46 - 8.51 (m, 1 H) 8.39 (dd, *J* = 8.53, 2.01 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.81 - 6.87 (m, 1 H) 4.46 - 4.56 (m, 4 H) 3.75 (s, 3 H) 1.33 (t, *J* = 7.03 Hz, 3 H)
XIII-3		N-[(3-methoxyphenyl) methyl]-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	360.2	A:5.85 B:6.09	(400 MHz, DMSO-d_6) 12.02 (br. s., 1 H) 9.45 (t, *J* = 6.02 Hz, 1 H) 8.91 (d, *J* = 2.01 Hz, 1 H) 8.70 - 8.75 (m, 2 H) 8.44 - 8.47 (m, 1 H) 8.35 - 8.41 (m, 2 H) 7.24 - 7.29 (m, 1 H) 6.92 - 6.96 (m, 2 H) 6.81 - 6.86 (m, 1 H) 4.52 (d, *J* = 5.52 Hz, 2 H) 3.74 - 3.76 (s, 3 H)

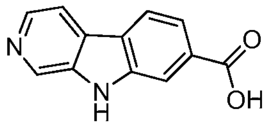
Ex. No.	Structure	Name	LCMS [M+H]+	HPLC Method, RT (min.)	1H NMR (δ, ppm)
XIII-4		N-[(2-chlorophenyl)methyl]-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	364.0	A:6.46 B:6.67	(400 MHz, DMSO-d_6) 12.02 (br. s., 1 H) 9.47 (t, J = 5.77 Hz, 1 H) 8.94 (d, J = 2.01 Hz, 1 H) 8.71 - 8.77 (m, 2 H) 8.46 (d, J = 5.52 Hz, 1 H) 8.41 (dd, J = 8.53, 2.01 Hz, 1 H) 8.38 (d, J = 5.52 Hz, 1 H) 7.46 - 7.51 (m, 1 H) 7.41 - 7.45 (m, 1 H) 7.29 - 7.38 (m, 2 H) 4.62 (d, J = 5.52 Hz, 2 H)
XIII-5		6-oxo-N-[(1R)-1-phenylethyl]-5H,6H-benzo[c] 1,7-naphthyridine-8-carboxamide	344.2	A:6.19 B:6.25	(400 MHz, DMSO-d_6) 9.28 (d, J = 7.97 Hz, 1 H) 8.93 (d, J = 1.76 Hz, 1 H) 8.70 - 8.74 (m, 2 H) 8.46 (d, J = 5.33 Hz, 1 H) 8.36 - 8.40 (m, 2 H) 7.42 - 7.47 (m, 2 H) 7.33 - 7.38 (m, 2 H) 7.22 - 7.28 (m, 1 H) 5.25 (t, J = 7.37 Hz, 1 H) 1.54 (d, J = 7.09 Hz, 3 H)

Ex. No.	Structure	Name	LCMS [M+H]+	HPLC Method, RT (min.)	1H NMR (δ, ppm)
XIII-6		N-[(1R)-1-(3-methoxyphenyl)ethyl]-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	374.2	A:6.22 B:6.33	(400 MHz, DMSO-d_6) δ ppm 12.03 (br.s, 1 H) 9.24 (d, J = 8.09 Hz, 1 H) 8.92 (d, J = 1.82 Hz, 1 H) 8.69 - 8.74 (m, 2 H) 8.45 (d, J = 5.33 Hz, 1 H) 8.35 - 8.40 (m, 2 H) 7.24 - 7.29 (m, 1 H) 6.99 - 7.03 (m, 2 H) 6.80 - 6.84 (m, 1 H) 5.21 (quin, J = 7.17 Hz, 1 H) 3.76 (s, 3 H) 1.53 (d, J = 7.09 Hz, 3 H)
XIII-7		N-[(2-chlorophenyl)methyl]-5-methyl-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	378.2	A:6.98 B:7.00	(400 MHz, DMSO-d_6) 9.48 (t, J = 5.68 Hz, 1 H) 8.97 - 9.01 (m, 2 H) 8.78 (d, J = 8.41 Hz, 1 H) 8.55 - 8.61 (m, 1 H) 8.48 (d, J = 5.15 Hz, 1 H) 8.41 (dd, J = 8.41, 1.95 Hz, 1 H) 7.47 - 7.51 (m, 1 H) 7.41 - 7.46 (m, 1 H) 7.30 - 7.39 (m, 2 H) 4.62 (d, J = 5.71 Hz, 2 H) 3.83 (s, 3 H)

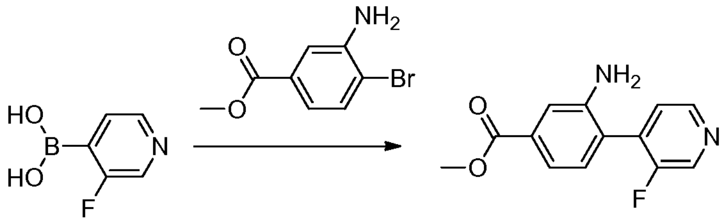
Ex. No.	Structure	Name	LCMS [M+H]+	HPLC Method, RT (min.)	1H NMR (δ, ppm)
XIII-8		N-[(3-methoxyphenyl) methyl]-5-methyl-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	374.2.	A:6.34 B:6.39	(400 MHz, DMSO-d_6) ppm 9.46 (t, J = 5.96 Hz, 1 H) 8.93 - 9.02 (m, 2 H) 8.77 (d, J = 8.47 Hz, 1 H) 8.55 - 8.60 (m, 1 H) 8.47 (d, J = 5.21 Hz, 1 H) 8.39 (dd, J = 8.44, 1.98 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.82 - 6.87 (m, 1 H) 4.52 (d, J = 5.90 Hz, 2 H) 3.83 (s, 3 H) 3.75 (s, 3 H)
XIII-9		5-ethyl-6-oxo-N-[(1R)-1-phenylethyl]-5H,6H-benzo[c] 1,7-naphthyridine-8-carboxamide	372.2	G:13.81 H:18.58	(400 MHz, DMSO-d_6) 9.28 (d, J = 7.97 Hz, 1 H) 9.04 (s, 1 H) 8.96 (d, J = 1.82 Hz, 1 H) 8.75 (d, J = 8.47 Hz, 1 H) 8.56 (d, J = 5.27 Hz, 1 H) 8.49 (d, J = 5.33 Hz, 1 H) 8.38 (dd, J = 8.44, 1.91 Hz, 1 H) 7.45 (d, J = 7.22 Hz, 2 H) 7.33 - 7.39 (m, 2 H) 7.22 - 7.28 (m, 1 H) 5.24 (quin, J = 7.28 Hz, 1 H) 4.50 (q, J = 7.01 Hz, 2 H) 1.54 (d, J = 7.09 Hz, 3 H) 1.33 (t, J = 7.03 Hz, 3 H)

Ex. No.	Structure	Name	LCMS [M+H]+	HPLC Method, RT (min.)	1H NMR (δ, ppm)
XIII-10		5-ethyl-N-[(1R)-1-(3-methoxyphenyl)ethyl]-6-oxo-5H,6H-benzo[c]1,7-naphthyridine-8-carboxamide	402.2	G:13.96 H:18.65	(400 MHz, DMSO-d_6) 9.28 (d, *J* = 7.97 Hz, 1 H) 9.04 (s, 1 H) 8.96 (d, *J* = 1.82 Hz, 1 H) 8.75 (d, *J* = 8.47 Hz, 1 H) 8.56 (d, *J* = 5.27 Hz, 1 H) 8.49 (d, *J* = 5.33 Hz, 1 H) 8.38 (dd, *J* = 8.44, 1.91 Hz, 1 H) 7.45 (d, *J* = 7.22 Hz, 2 H) 7.33 - 7.39 (m, 2 H) 7.22 - 7.28 (m, 1 H) 5.24 (quin, *J* = 7.28 Hz, 1 H) 4.50 (q, *J* = 7.01 Hz, 2 H) 1.54 (d, *J* = 7.09 Hz, 3 H) 1.33 (t, *J* = 7.03 Hz, 3 H)

Intermediate 22: 9*H*-Pyrido[3,4-*b*]indole-7-carboxylic acid

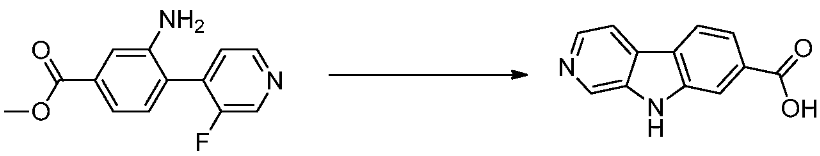


Intermediate 22A: Methyl 3-amino-4-(3-fluoropyridin-4-yl)benzoate



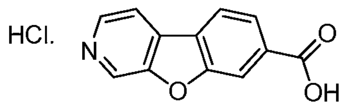
Methyl 3-amino-4-bromobenzoate (4 g, 17.39 mmol), (3-fluoropyridin-4-yl)boronic acid (5.5 g, 39.0 mmol), dioxane (10 mL), water (2 mL) and potassium carbonate (8.41 g, 60.9 mmol) were taken in a dried two neck RB (25mL) and purged with nitrogen for 10 minutes. To this mixture was added $PdCl_2$(dppf) (1.27 g, 1.74 mmol) at 50 °C. The mixture was flushed with nitrogen and heated at 80 °C for 8 h. The reaction mixture was cooled to room temperature, then was diluted with the DCM. The organic phase was washed with the water, dried over sodium sulfate. The crude compound was purified by silica gel chromatography (gradient elution, 30-65% ethyl acetate in petroleum ether) to afford 2.9 g (68%) of the title compound. LC-MS (ESI) *m/z*: 241.0 $[M+H]^+$; ^1H NMR (400 MHz, chloroform-d) δ ppm 8.60 (d, *J* = 1.57 Hz, 1 H) 8.52 (dd, *J* = 4.86, 1.10 Hz, 1H) 7.48 - 7.52 (m, 2 H) 7.35 - 7.39 (m, 1H) 7.19 (d, *J* = 7.78 Hz, 1H) 3.93 (s, 3 H) 3.79 - 3.84 (m, 2 H).

Intermediate 22:

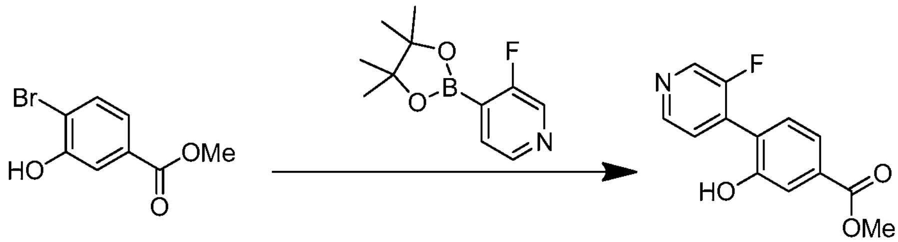


To pyridine hydrochloride (1.5 g, 12.98 mmol) at 150 °C, was added Intermediate 22A (1g, 4.06 mmol) under nitrogen atmosphere. The mixture was heated to 170 °C for 2 h, then was allowed to cool to rt. The reaction mixture was quenched with aq. NaOH and stirred for 3 h. the reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The crude mass was treated with water and the solid was collected by filtration and dried to afford Intermediate 22 (450 mg, 52%). The material was used without further purification. LC-MS (ESI) *m/z*: 241.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.79 (bs, 1 H) 8.97 (s, 1 H) 8.37 (d, *J* = 5.27 Hz, 1 H) 8.11 - 8.29 (m, 3 H) 7.83 (d, *J* = 8.28 Hz, 1 H).

Intermediate 23: Benzofuro[2,3-c]pyridine-7-carboxylic acid, HCl salt



Intermediate 23A: Methyl 4-(3-fluoropyridin-4-yl)-3-hydroxybenzoate

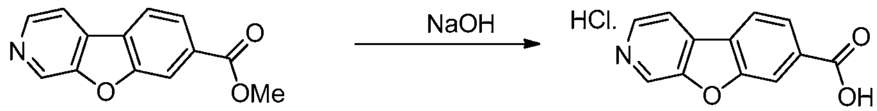


To a solution of methyl 4-bromo-3-hydroxybenzoate (1.0 g, 4.3 mmol) in dioxane (20 mL) and water (2 mL), was added K_2CO_3 (1.80 g, 13.0 mmol) and 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.16 g, 5.19 mmol). The reaction mixture was degassed by bubbling with N_2 for 5 mins. $PdCl_2$(dppf) (0.317 g, 0.433 mmol) was added to the reaction, which was degassed again. The mixture was then heated to 90 ºC for 6 h. The reaction mixture was diluted with water (30 mL) and was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated to give crude product which was purified by flash chromatography (gradient elution, 0-60% EtOAc/Hex) to afford Intermediate 23A (0.65 g, 61% yield) as an off-white solid. LC-MS (ESI) *m/z*: 248.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.36 (s, 1 H), 8.64 (d, *J* = 1.88 Hz, 1 H), 8.50 (dd, *J* = 4.86, 1.10 Hz, 1 H), 7.60 (d, *J* = 1.51 Hz, 1 H), 7.49 - 7.54 (m, 2 H), 7.42 (d, *J* = 7.97 Hz, 1 H), 3.88 (s, 3 H); ^{19}F NMR: (400 MHz, DMSO-d_6) : -128.57.

Intermediate 23B: Methyl benzofuro[2,3-c]pyridine-7-carboxylate

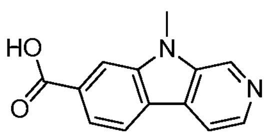
To a solution of Intermediate 23A (0.450 g, 1.820 mmol) in DMF (5 mL), was added K_2CO_3 (0.755 g, 5.46 mmol). The mixture was stirred at 100 ºC for 2 hr. The DMF was evaporated and the mixture was diluted with water (50 mL). The obtained solid was filtered and washed with 50 ml of water and diethyl ether (10 ml) to afford Intermediate 23B (210 mg, 51%) as an off-white solid. LC-MS (ESI) *m/z*: 228.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (s, 1 H), 8.67 (d, *J* = 5.08 Hz, 1 H), 8.44 (d, *J* = 8.09 Hz, 1 H), 8.34 (s, 1 H), 8.30 (d, *J* = 5.02 Hz, 1 H), 8.10 (dd, *J* = 8.16, 1.25 Hz, 1 H), 3.94 (s, 3 H).

Intermediate 23:

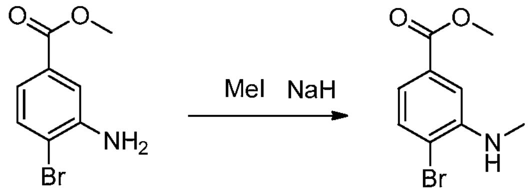


To a solution of Intermediate 23B (0.090 g, 0.40 mmol) in MeOH (3 mL) and water (1 mL), was added sodium hydroxide (0.024 g, 0.59 mmol). The reaction mixture was stirred at rt for 1 hr, then the solvent was evaporated. The crude mass was washed with diethyl ether (10 mL), and then the residue was treated with 4M HCl in dioxane for 30 min. The solvent was evaporated to give Intermediate 23 (0.10 g, 100%) as a white solid. LC-MS (ESI) *m/z*: 214.0 $[M+H]^+$.

Intermediate 24: 9-Methyl-9H-pyrido[3,4-b]indole-7-carboxylic acid

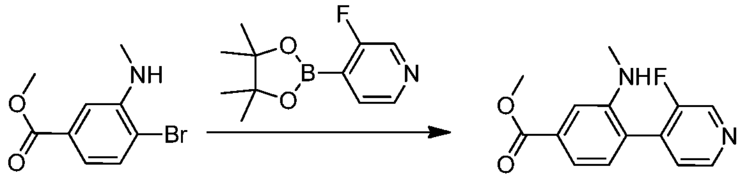


Intermediate 24A: Methyl 4-bromo-3-(methylamino)benzoate



To a solution of methyl 3-amino-4-bromobenzoate (1.5 g, 6.52 mmol) in THF (30 mL) at 0 °C, was added NaH (0.203 g, 8.48 mmol). The mixture was stirred for 10 min, then iodomethane (1.11 g, 7.82 mmol) was added. The reaction mixture was stirred for 5 hr, then was quenched with addition of sat. ammonium chloride solution. The mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated. The crude compound was purified by flash chromatography (5 to 80% gradient of ethyl acetate in pet. ether) to afford 0.75 g (47%) of Intermediate 24A. LC-MS (ESI) *m/z*: 244.0 $[M+H]^+$; ^1H NMR (400 MHz, chloroform-d) δ ppm 7.48 (d, *J* = 8.16 Hz, 1 H) 7.26 - 7.27 (m, 1 H) 7.24 (d, *J* = 2.01 Hz, 1 H) 7.22 (d, *J* = 2.01 Hz, 1 H) 3.90 (s, 3 H) 2.95 (d, *J* = 5.21 Hz, 3 H).

Intermediate 24B: Methyl 4-(3-fluoropyridin-4-yl)-3-(methylamino)benzoate

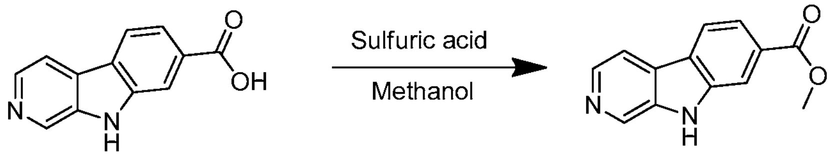


To a degassed solution of Intermediate 24A (700 mg, 2.87 mmol) in dioxane (20 mL) and water (3 mL), were added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.02 g, 4.59 mmol), potassium carbonate (1.39 g, 10.0 mmol) and $PdCl_2$(dppf) (210 mg, 0.287 mmol) at rt. The reaction was stirred under argon at 90 °C for 6 h. The reaction mixture was cooled to rt, then was diluted with the DCM. The organic phase was washed with the water, dried over sodium sulfate and concentrated. The crude compound was purified by silica gel chromatography (30-60% ethyl acetate gradient in pet. ether) to afford Intermediate 24B (400 mg, 51%). LC-MS (ESI) *m/z*: 246.0 $[M+H]^+$; ^1H NMR (400 MHz, chloroform-d) δ ppm 8.59 (d, *J* = 1.51 Hz, 2 H) 8.50 (dd, *J* = 4.83, 1.00 Hz, 2 H) 7.46 (dd, *J* = 7.81, 1.60 Hz, 2 H) 7.39 (d, *J* = 1.51 Hz, 2 H) 7.33 (s, 1 H) 7.14 (d, *J* = 7.78 Hz, 1 H) 3.94 (s, 3 H) 3.66 - 3.73 (m, 1 H) 2.89 (d, *J* = 5.15 Hz, 3H).

Intermediate 24:

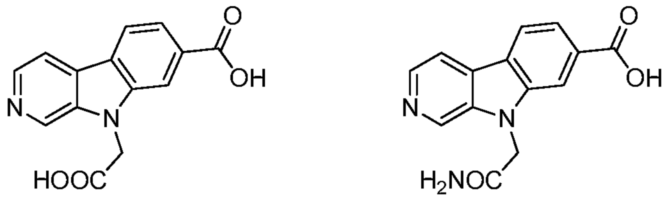
To pyridine hydrochloride (250 mg, 2.16 mmol) at 150 °C, was add added Intermediate 24B (250 mg, 0.961 mmol). The mixture was heated at 175 °C for 2 h, then was cooled to rt. To the crude reaction mixture, was added 50% NaOH solution and the mixture was stirred for 2h. The reaction mixture was concentrated, then was neutralized with the addition of acetic acid. The mixture was concentrated *in vacuo*, then was treated with water and the solid was collected by filtration and dried to afford Intermediate 24 (90 mg, 41%). LC-MS (ESI) *m/z*: 227.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (s, 1 H) 8.44 (d, *J* = 5.27 Hz, 1 H) 8.38 (d, *J* = 8.09 Hz, 1 H) 8.28 (s, 1 H) 8.21 (dd, *J* = 5.21, 1.00 Hz, 1 H) 7.88 (dd, *J* = 8.16, 1.32 Hz, 1 H) 4.05 (s, 3 H).

Intermediate 25: Methyl 9H-pyrido[3,4-b]indole-7-carboxylate

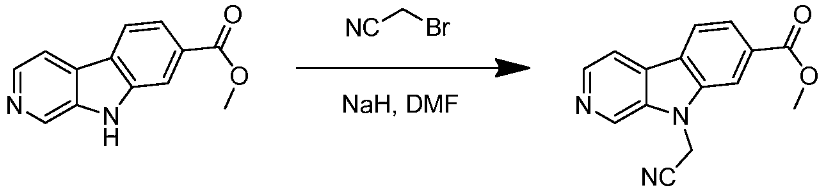


To a suspension of Intermediate 22 (3.1 g, 10.81 mmol) in methanol (75 mL), was added sulfuric acid (4.0 ml, 75 mmol). The mixture was heated at 68 °C for 3 h, then was concentrated. The crude material was basified with 10% $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic fraction was again washed with 10% $NaHCO_3$, followed by brine solution. The organic layer was dried with Na_2SO_4, filtered and concentrated to afford Intermediate 25 (0.721 g, 3.19 mmol, 29.5% yield) as a pale yellow solid. LC-MS (ESI) *m/z*: 227.0 $[M+H]^+$; ^1H NMR (300MHz, DMSO-d_6) δ 11.89 (s, 1H), 9.01 (s, 1H), 8.48 - 8.31 (m, 2H), 8.25 - 8.13 (m, 2H), 7.84 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.92 (s, 3H).

Intermediate 26: 9-(2-Amino-2-oxoethyl)-9H-pyrido[3,4-b]indole-7-carboxylic acid compound with 9-(carboxymethyl)-9H-pyrido[3,4-b]indole-7-carboxylic acid (1:1)

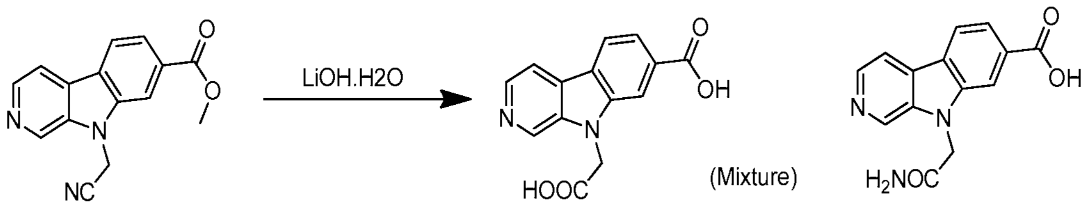


Intermediate 26A: Methyl 9-(cyanomethyl)-9H-pyrido[3,4-b]indole-7-carboxylate



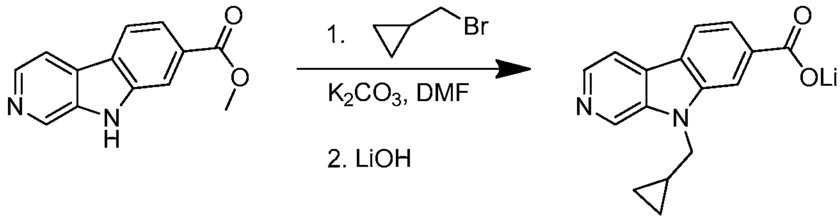
To the solution of Intermediate 25 (0.225 g, 0.995 mmol) in DMF (6 mL) at 0 ºC, sodium hydride (0.119 g, 2.98 mmol) was added. The mixture was stirred at rt for 15 min. 2-Bromoacetonitrile (0.139 mL, 1.989 mmol) was added to the reaction mixture and stirred at rt for 2 h. Water was added to the reaction mixture, which was then extracted with EtOAc (2 x 60 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (0-4% gradient MeOH/$CHCl_3$) to afford Intermediate 26A (0.29 g) as a dark yellow solid. LC-MS (ESI) *m/z*: 266.0 $[M+H]^+$; ^1H NMR (300MHz, DMSO-d_6) δ 9.27 (s, 1 H), 8.59 - 8.43 (m, 3 H), 8.34 - 8.25 (m, 1 H), 7.98 - 7.92 (m, 1 H), 6.04 - 6.00 (m, 2 H), 3.96 (s, 3 H).

Intermediate 26:



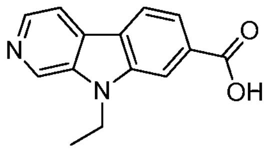
To the solution of Intermediate 26A (0.35 g, 1.32 mmol) in a mixture of MeOH (4 mL), water (4 mL) and THF (2 mL), lithium hydroxide hydrate (0.166 g, 3.96 mmol) was added and stirred at RT for 1.5 h. The reaction mixture was concentrated under reduced pressure. The crude product was acidified by slow addition of 1.5 N HCl at 0 ºC. The resultant precipitate was collected by filtration and the residue was washed with ether to afford the mixture of products Intermediate 26 (0.102 g) as a yellow solid. MS (ESI) *m/z*: 270.1 and 271.0 $[M+H]^+$.

Intermediate 27: Lithium 9-(cyclopropylmethyl)-9H-pyrido[3,4-b]indole-7-carboxylate

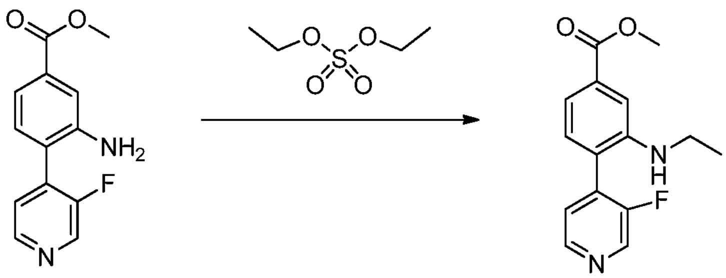


To a solution of Intermediate 25 (0.050 g, 0.22 mmol) in DMF (2 mL), were added K_2CO_3 (0.061 g, 0.44 mmol) and (bromomethyl)cyclopropane (0.060 g, 0.442 mmol). The mixture was heated at 80 °C for 3 h. Water was added to the reaction mixture, which was extracted with EtOAc (2x). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (0-4% MeOH gradient in $CHCl_3$) to afford 9-(cyclopropylmethyl)-9H-pyrido[3,4-b]indole-7-carboxylic acid. LC-MS (ESI) *m/z*: 281.1 $[M+H]^+$. The material was dissolved in THF (4 mL) and water (2 mL), then lithium hydroxide hydrate (0.040 g, 0.95 mmol) was added and the mixture was stirred at RT overnight. The reaction mixture was concentrated under reduced pressure to dryness. Then the crude was washed with ether for several times to get Intermediate 27 (0.085) as a yellow solid. MS (ESI) *m/z*: 267 $[M+H]^+$.

Intermediate 28: 9-Ethyl-9H-pyrido[3,4-b]indole-7-carboxylic acid

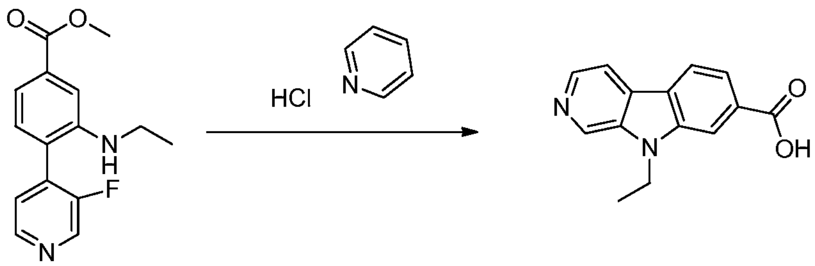


Intermediate 28A: Methyl 3-(ethylamino)-4-(3-fluoropyridin-4-yl)benzoate



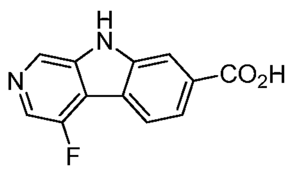
To a solution of Intermediate 22A (800 mg, 3.25 mmol) in DMF (5 mL), was added potassium carbonate (674 mg, 4.87 mmol). The mixture was stirred at 50 ºC for 10 min, then was cooled to RT. To this mixture, diethyl sulfate (751 mg, 4.87 mmol) was added, then the mixture was heated for 5 h at 120 ºC. The reaction mixture was cooled to room temperature, diluted with the DCM, washed with water, dried over sodium sulfate and concentrated. The crude compound was purified by silica gel chromatography (30-80% gradient of ethyl acetate in pet. ether) to afford Intermediate 28A (300 mg, 34%). MS (ESI) *m/z*: 241.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (d, *J* = 1.63 Hz, 1 H) 8.50 (dd, *J* = 4.86, 1.04 Hz, 1 H) 7.45 (dd, *J* = 6.37, 4.86 Hz, 1 H) 7.22 - 7.27 (m, 2 H) 7.15 (d, *J* = 7.72 Hz, 1 H) 5.13 (t, *J* = 5.6 Hz, 1 H) 3.86 (s, 3 H) 3.13 (dd, *J* = 6.93, 5.80 Hz, 2 H) 1.10 (t, *J* = 7.09 Hz, 3 H).

Intermediate 28:

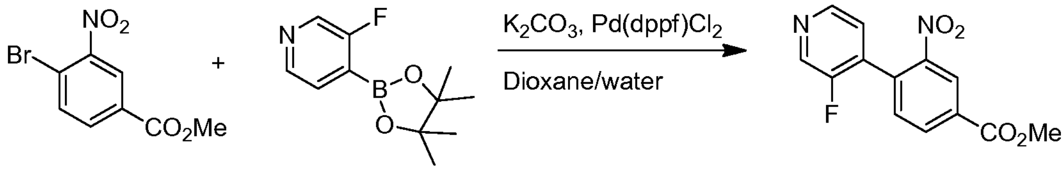


To melted pyridine hydrochloride (379 mg, 3.28 mmol) at 150 ºC, was added Intermediate 28A (300 mg, 1.09 mmol). The mixture was heated at 175 ºC for 2 h. To the crude reaction mixture was added 50% NaOH solution to reach pH 11. The reaction mixture was stirred for 3 h, then was concentrated. The reaction mixture was neutralized with acetic acid. Excess acetic acid was evaporated and the mixture was treated with water and the solid was collected to afford Intermediate 28 (250 mg, 95%). LC-MS (ESI) *m/z*: 241.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.14 (s, 1 H) 8.43 (d, *J* = 5.27 Hz, 1 H) 8.36 (d, *J* = 8.16 Hz, 1 H) 8.27 (s, 1 H) 8.21 (dd, *J* = 5.21, 0.88 Hz, 1 H) 7.87 (dd, *J* = 8.19, 1.22 Hz, 1 H) 4.63 (q, *J* = 7.13 Hz, 2 H) 1.38 (t, *J* = 7.12 Hz, 3 H).

Intermediate 29: 4-Fluoro-9H-pyrido[3,4-b]indole-7-carboxylic acid

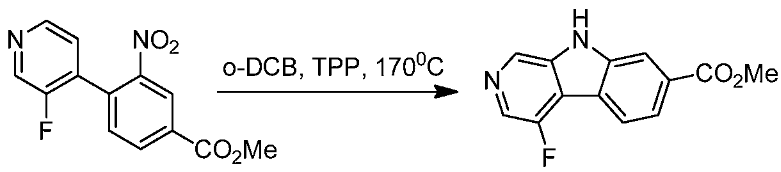


Intermediate 29A: Methyl 4-(3-fluoropyridin-4-yl)-3-nitrobenzoate



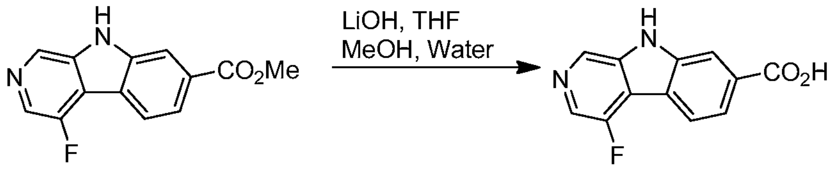
A solution of methyl 4-bromo-3-nitrobenzoate (0.8 g, 3.1 mmol) and K_2CO_3 (1.276 g, 9.23 mmol) in dioxane (10 mL) and water (2 mL) was bubbled with nitrogen for 10 min. To this solution was added 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.686 g, 3.08 mmol) and $PdCl_2$(dppf) (0.135 g, 0.185 mmol). The mixture was heated at 80 °C overnight. The mixture was diluted with ethyl acetate (30 mL), washed with brine (2x), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex) to afford Intermediate 29A (0.58 g, 68% yield). LC-MS (ESI) *m/z*: 277.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1 H) 8.60 - 8.64 (m, 2 H) 8.41 (d, *J* = 7.97 Hz, 1 H) 7.85 (d, *J* = 7.91 Hz, 1 H) 7.67 (t, *J* = 5.65 Hz, 1 H) 3.96 (s, 3 H).

Intermediate 29B: Methyl 4-fluoro-9H-pyrido[3,4-b]indole-7-carboxylate



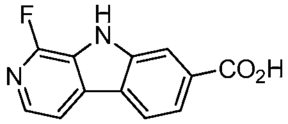
To a solution of Intermediate 29A (580 mg, 2.1 mmol) in 1,2-dichlorobenzene (6 mL) was added triphenylphosphine (1.38 g, 5.25 mmol). The mixture was heated at 170 °C for 4 h. To the cooled reaction mixture was added pet. ether (50 mL). The precipitate was filtered and washed with pet. ether (2x). The crude product was purified by flash chromatography (0-100% EtOAc/Hex). The solid was further purified by suspension in DCM (5 mL) and pet. ether (30 mL). The precipitate was collected by filtration to afford Intermediate 29B as a light brown solid (105 mg, 19%). LC-MS (ESI) *m/z*: 245.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.26 (s, 1 H) 8.91 (d, *J* = 2.64 Hz, 1 H) 8.37 (d, *J* = 1.19 Hz, 1 H) 8.26 - 8.30 (m, 2 H) 7.90 - 7.94 (m, 1 H) 3.94 (s, 3 H).

Intermediate 29:

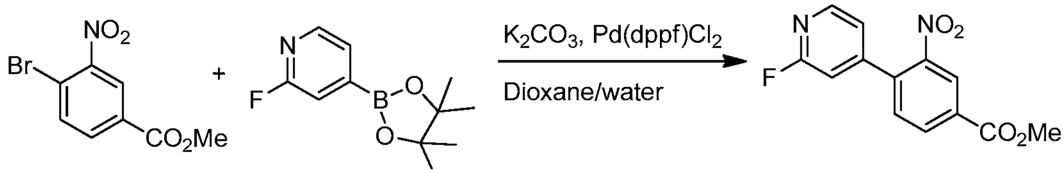


To a suspension of Intermediate 29B (105 mg, 0.430 mmol) in THF (3 mL) and water (1 mL), was added LiOH (25.7 mg, 1.08 mmol). The resultant clear yellow solution was stirred overnight. The reaction mixture was concentrated, then the residue was dissolved in THF (1.5 mL) and water (0.5 mL). To this mixture was added LiOH (25.7 mg, 1.075 mmol). The mixture was stirred overnight, then was concentrated. The residue was dissolved in water, then was acidified to pH 3 with 1.5 N HCl. The precipitated solid was collected by filtration, washed with water and hexane, and dried *in vacuo* to afford Intermediate 29 as a brown solid (75 mg). LC-MS (ESI) *m/z*: 231.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.23 (s, 1 H) 8.89 (d, *J* = 2.64 Hz, 1 H) 8.37 (d, *J* = 1.44 Hz, 1 H) 8.24 - 8.27 (m, 2 H) 7.89 - 7.92 (m, 1 H).

Intermediate 30: 1-Fluoro-9H-pyrido[3,4-b]indole-7-carboxylic acid

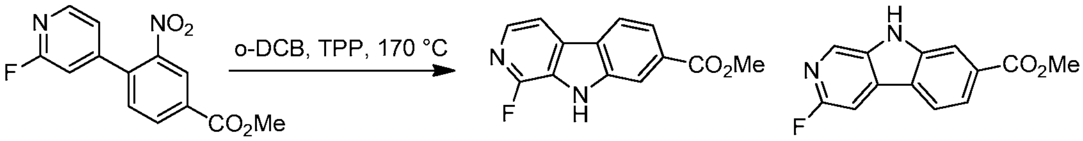


Intermediate 30A: Methyl 4-(2-fluoropyridin-4-yl)-3-nitrobenzoate



A solution of methyl 4-bromo-3-nitrobenzoate (1.0 g, 3.85 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.858 g, 3.85 mmol) and K_2CO_3 (1.59 g, 11.5 mmol) in dioxane (20 mL) and water (4 mL) was bubbled with nitrogen for 10 minutes. To this mixture were added 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.858 g, 3.85 mmol) and $PdCl_2(dppf)-CH_2Cl_2$ adduct (0.188 g, 0.231 mmol). The mixture was heated at 80 °C for 4 h, then was diluted with EtOAc. The organic phase was washed with brine (2x), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (0-100% gradient of EtOAc/Hex.) to afford Intermediate 30A as a yellow solid (0.8 g, 73%). LC-MS (ESI) *m/z*: 277.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J* = 1.63 Hz, 1 H) 8.34 - 8.38 (m, 2 H) 7.80 (d, *J* = 7.97 Hz, 1 H) 7.38 - 7.46 (m, 2 H) 3.96 (s, 3 H).

Intermediate 30B: Methyl 1-fluoro-9H-pyrido[3,4-b]indole-7-carboxylate
Intermediate 30C: Methyl 3-fluoro-9H-pyrido[3,4-b]indole-7-carboxylate

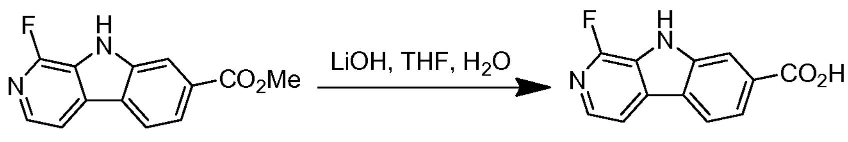


To a solution of Intermediate 30A (800 mg, 2.90 mmol) in 1,2-dichlorobenzene (8 mL), was added triphenylphosphine (1.9 g, 7.24 mmol). The mixture was heated at 170 °C overnight, then was concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/Hex.) to afford Intermediate 30B (240 mg) as a yellow solid and Intermediate 30C, which was repurified by flash chromatography (0-100% EtOAc/Hex.) to afford 55 mg.

Intermediate 30B: LC-MS (ESI) *m/z*: 245.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.43 (s, 1 H) 8.41 (d, *J* = 8.34 Hz, 1 H) 8.23 (dd, *J* = 1.44, 0.69 Hz, 1 H) 8.18 (dd, *J* = 5.36, 3.17 Hz, 1 H) 7.96 (dd, *J* = 5.36, 1.85 Hz, 1 H) 7.89 (dd, *J* = 8.31, 1.47 Hz, 1 H) 3.94 (s, 3 H).

Intermediate 30C: LC-MS (ESI) *m/z*: 245.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.88 (s, 1 H) 8.60 (dd, *J* = 1.51, 0.94 Hz, 1 H) 8.40 (d, *J* = 8.28 Hz, 1 H) 8.21 (dd, *J* = 1.38, 0.69 Hz, 1 H) 7.99 (d, *J* = 2.20 Hz, 1 H) 7.83 (dd, *J* = 8.28, 1.51 Hz, 1 H) 3.92 - 3.95 (m, 3 H).

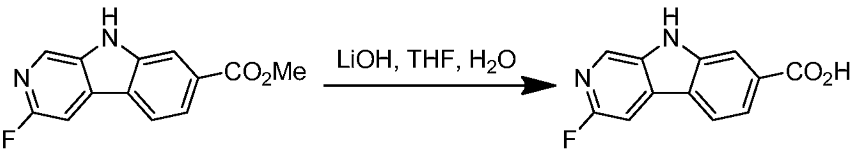
Intermediate 30:



To a suspension of Intermediate 30B (230 mg, 0.942 mmol) in THF (2 mL) and water (0.5 mL), was added LiOH (67.7 mg, 2.83 mmol). The yellow solution was allowed to stir at rt overnight. The reaction mixture was concentrated to gave yellow residue, which was dissolved in water (8 mL) and acidified with 1.5 N HCl to pH 3. The precipitated solid was filtered and washed with water, hexane, and dried to afford

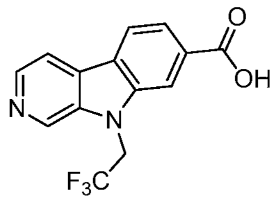
Intermediate 30 (190 mg, 64%) as a brown solid. LC-MS (ESI) *m/z*: 231.0 $[M+H]^+$; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 13.11 (s, 1 H) 12.39 (s, 1 H) 8.38 (d, *J* = 8.17 Hz, 1 H) 8.14 - 8.22 (m, 2 H) 7.94 (d, *J* = 5.15 Hz, 1 H) 7.87 (d, *J* = 8.26 Hz, 1 H).

Intermediate 31: 3-Fluoro-9H-pyrido[3,4-b]indole-7-carboxylic acid

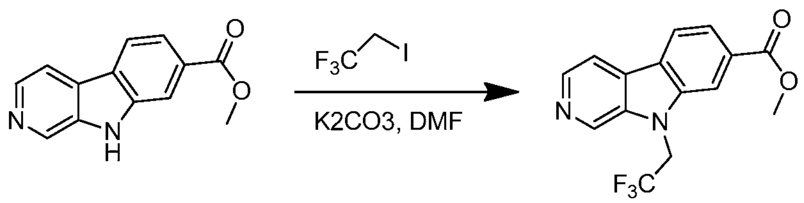


To a suspension of Intermediate 30C (55 mg, 0.23 mmol) in THF (2 mL) and water (0.5 mL), was added LiOH (16.2 mg, 0.676 mmol). The resultant yellow solution was allowed to stir at rt overnight. The reaction mixture was concentrated to gave yellow residue, which was dissolved in water (8 mL) and acidified with 1.5 N HCl to pH 3. The precipitated solid was filtered and washed with water and hexane, and dried to afford Intermediate 31(42 mg, 57%) as a brown solid. LC-MS (ESI) *m/z*: 231.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.86 (s, 1 H) 8.58 (s, 1 H) 8.37 (d, *J* = 8.28 Hz, 1 H) 8.19 (d, *J* = 0.63 Hz, 1 H) 7.97 (d, *J* = 2.13 Hz, 1 H) 7.82 (dd, *J* = 8.28, 1.38 Hz, 1 H).

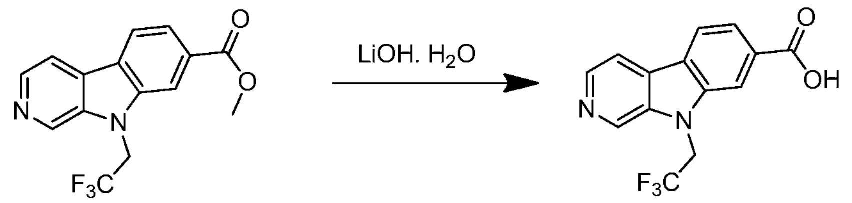
Intermediate 32: 9-(2,2,2-Trifluoroethyl)-9H-pyrido[3,4-b]indole-7-carboxylic acid



Intermediate 32A: Methyl 9-(2,2,2-trifluoroethyl)-9H-pyrido[3,4-b]indole-7-carboxylate

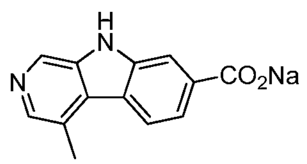


To a suspension of Intermediate 22 (0.20 g, 0.88 mmol) in DMF (5 mL), was added K_2CO_3 (0.611 g, 4.42 mmol), followed by the addition of 1,1,1-trifluoro-2-iodoethane (0.436 mL, 4.42 mmol). The mixture was heated at 100 ºC overnight. Water was added to the reaction mixture, which was then extracted with EtOAc (2x). The combined organic phase was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (0-4% MeOH/$CHCl_3$) to afford Intermediate 32A (0.14 g, 22% yield) as yellow semi-solid. LC-MS (ESI) *m/z*: 309.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.56 - 8.41 (m, 3H), 8.30 - 8.24 (m, 1H), 7.99 - 7.93 (m, 1H), 5.72 (q, *J* = 9.4 Hz, 2H), 3.95 (s, 3H).

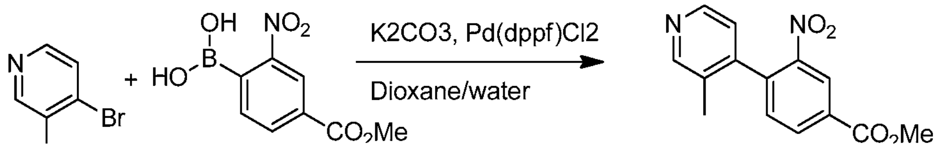


To a solution of Intermediate 32A (0.14 g, 0.45 mmol) in THF (2 mL) and water (2 mL), was added lithium hydroxide hydrate (0.076 g, 1.817 mmol). The mixture was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure to dryness. Then the crude product was washed with ether several times to afford Intermediate 32 (0.161 g, 82% yield) as a yellow solid. MS (ES): *m/z* = 295.0 $[M+H]^+$.

Intermediate 33: Sodium 4-methyl-9H-pyrido[3,4-b]indole-7-carboxylate

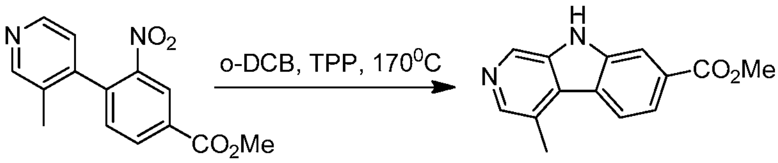


Intermediate 33A: Methyl 4-(3-methylpyridin-4-yl)-3-nitrobenzoate



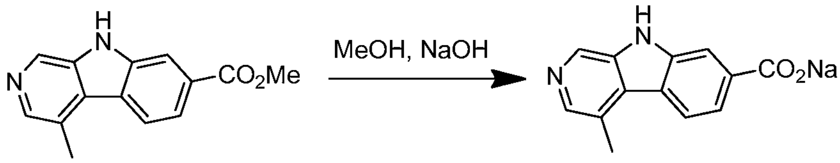
A solution of (4-(methoxycarbonyl)-2-nitrophenyl)boronic acid (0.445 g, 1.98 mmol), 4-bromo-3-methylpyridine, hydrobromide (0.50 g, 1.98 mmol) and K_2CO_3 (0.820 g, 5.93 mmol) in dioxane (20 mL) and water (4 mL) was bubbled nitrogen for 10 minutes. To this mixture was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.097 g, 0.12 mmol). The mixture was heated at 80 °C overnight. The reaction mixture was diluted with ethyl acetate. The organic phase was washed with brine solution (2x), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex.) to afford Intermediate 33A as a yellow solid (0.100 g, 18%). MS (ES): *m/z* = 273.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.61 - 8.64 (m, 1 H) 8.57 (s, 1 H) 8.48 (d, *J* = 4.96 Hz, 1 H) 8.35 (dd, *J* = 7.97, 1.69 Hz, 1 H) 7.66 (d, *J* = 7.97 Hz, 1 H) 7.23 (d, *J* = 4.96 Hz, 1 H) 3.96 (s, 3 H) 2.05 (s, 3 H).

Intermediate 33B: Methyl 4-methyl-9H-pyrido[3,4-b]indole-7-carboxylate



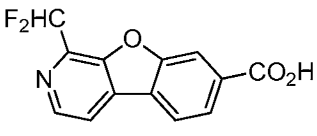
To a solution of Intermediate 33A (100 mg, 0.367 mmol) in 1,2-dichlorobenzene (3 mL), was added triphenylphosphine (241 mg, 0.918 mmol). The mixture was heated at 170 ºC for 5 h. The reaction mixture was cooled to rt, then was diluted with pet. ether. The precipitate was collected by filtration. The solid was purified twice by flash chromatography (gradient elution; 0-100% EtOAc/Hex) to afford Intermediate 33B (100 mg, 29%) as a yellow solid. MS (ES): *m/z* = 241.5 $[M+H]^+$.

Intermediate 33:

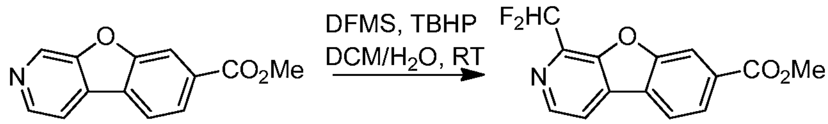


To a solution of Intermediate 33B (100 mg, 0.416 mmol) in MeOH (2 mL) and water (0.67 mL), was added NaOH (0.050 g, 1.25 mmol). The mixture was stirred at rt overnight. The solvent was evaporated, then the mixture was coevaporated with toluene to afford a 100 mg of a yellow solid that was used as without further purification. MS (ES): *m/z* = 227.5 $[M+H]^+$; ^1H NMR (300MHz, DMSO-d_6) δ 13.20 (br. s., 1H), 9.26 (s, 1H), 8.52 (d, *J* = 8.7 Hz, 1H), 8.48 (s, 1H), 8.41 (d, *J* = 0.8 Hz, 1H), 7.98 (dd, *J* = 8.3, 1.5 Hz, 1H), 2.99 (s, 3H).

Intermediate 34: 1-(Difluoromethyl)benzofuro[2,3-c]pyridine-7-carboxylic acid

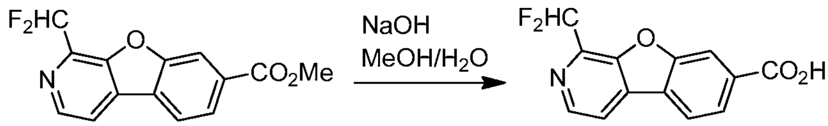


Intermediate 34A: methyl 1-(difluoromethyl)benzofuro[2,3-c]pyridine-7-carboxylate



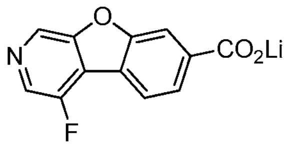
To s suspension of methyl benzofuro[2,3-c]pyridine-7-carboxylate (90 mg, 0.40 mmol) and zinc difluoromethanesulfinate (389 mg, 1.19 mmol) in DCM (5 mL) and water (2 mL) at 0 °C, was added *tert*-butyl hydroperoxide(0.192 mL, 1.98 mmol). The reaction mixture was stirred at rt overnight, then was diluted with DCM. The phases were separated, then the aqueous phase was extracted with DCM. The combined DCM phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (gradient elution; 0-80% EtOAc/Hex.) to afford Intermediate 34A (70 mg, 44%) as an off-white solid. MS (ES): m/z = 278.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.74 (d, J = 5.02 Hz, 1 H) 8.49 - 8.55 (m, 2 H) 8.40 (dd, J = 1.29, 0.60 Hz, 1 H) 8.15 (dd, J = 8.16, 1.38 Hz, 1 H) 7.23 - 7.53 (t, J = 56, 1 H) 3.95 (s, 3 H).

Intermediate 34:

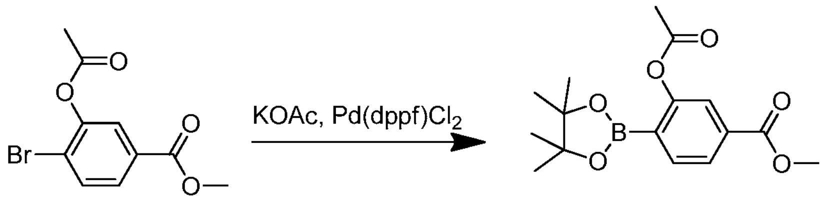


To s solution of Intermediate 34A (70 mg, 0.25 mmol) in methanol (3 mL) and water (1 mL), was added NaOH (30.3 mg, 0.758 mmol). The mixture was stirred at rt for 4 h. The solvent was evaporated, then the residue was dissolved water (15 mL) and washed with ethyl acetate (x2). The aqueous was acidified with 1.5 N HCl to pH 2 then was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford Intermediate 34 (50 mg, 59% yield) as a yellow solid. MS (ES): m/z = 278.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.74 (d, J = 5.02 Hz, 1 H) 8.52 (d, J = 5.08 Hz, 1 H) 8.48 (dd, J = 8.13, 0.53 Hz, 1 H) 8.36 (d, J = 0.69 Hz, 1 H) 8.13 (dd, J = 8.09, 1.32 Hz, 1 H) 7.25 - 7.53 (t, J = 56.8 Hz, 1 H).

Intermediate 35: Lithium 4-fluorobenzofuro[2,3-c]pyridine-7-carboxylate

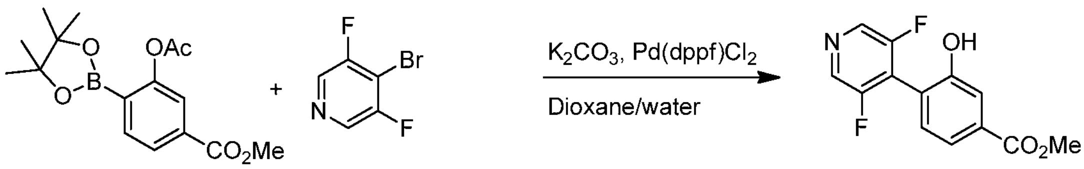


Intermediate 35A: Methyl 3-acetoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate



To a solution of methyl 3-acetoxy-4-bromobenzoate (540 mg, 1.98 mmol) in dioxane (20 mL), was added potassium acetate (485 mg, 4.94 mmol). The mixture was bubbled with nitrogen for 10 minutes, then bis(pinacolato)diboron (753 mg, 2.97 mmol) and $PdCl_2$(dppf) (87 mg, 0.12 mmol) were added. The mixture was bubbled with nitrogen for 5 minutes, then was heated at 100 °C overnight. The reaction mixture was cooled to rt, filtered through a CELITE® bed, rinsing with ethyl acetate. The filtrate was concentrated. The residue was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex.) to afford Intermediate 35A (450 mg, 71% yield) as a yellow gummy solid. MS (ES): $m/z = 239$ $[M+H]^+$.

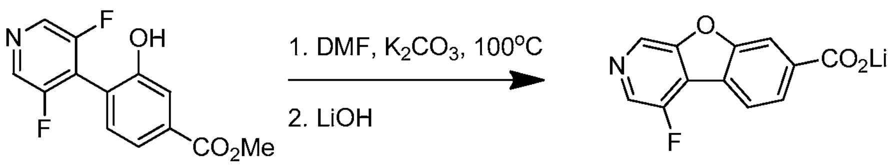
Intermediate 35B: Methyl 4-(3,5-difluoropyridin-4-yl)-3-hydroxybenzoate



A solution of Intermediate 35A (248 mg, 0.773 mmol), 4-bromo-3,5-difluoropyridine (100 mg, 0.516 mmol) and K_2CO_3 (214 mg, 1.55 mmol) in dioxane (10 mL) and water (2 mL) was bubbled with nitrogen for 10 minutes then, $PdCl_2$(dppf)-CH_2Cl_2 Adduct (25.3 mg, 0.031 mmol) were added. The mixture was heated at 80 °C for 4 h. The mixture was diluted with ethyl acetate (30 mL), washed with brine (2x), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex.) to afford Intermediate 35B (37 mg, 0.092 mmol, 17.93% yield) as a yellow solid. MS (ES): $m/z = 266.0$ $[M+H]^+$; ^1H

NMR (400MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.62 (s, 2H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.48 - 7.40 (m, 1H), 3.87 (s, 3H).

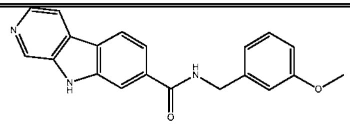
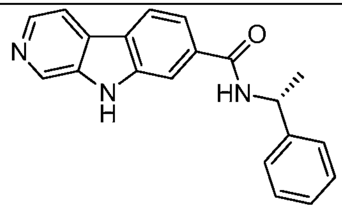
Intermediate 35:

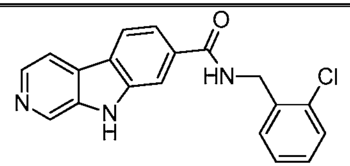
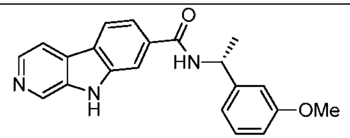
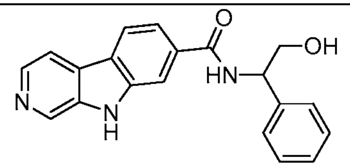


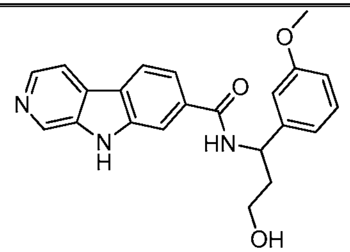
To the solution of Intermediate 35B (37 mg, 0.14 mmol) in DMF (1 mL), was added potassium carbonate (57.8 mg, 0.419 mmol). The mixture was heated at 120 °C for 4 h. The reaction mixture was cooled to rt and the solvent was evaporated to give an off-white solid. The solid was dissolved in THF (2.5 mL) and water (1 mL), then was treated with LiOH (9.77 mg, 0.408 mmol). The mixture was stirred at rt for 3 h. The mixture was concentrated, then was coevaporated with toluene (2x) to afford Intermediate 35 (45 mg) as an off-white solid, which was used as is without further purification. MS (ESI): *m/z* = 232.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.98 - 9.00 (m, 1 H) 8.59 (m, 1 H) 8.15 (s, 1 H) 8.03 - 8.07 (m, 1 H) 7.98 - 8.02 (m, 1 H).

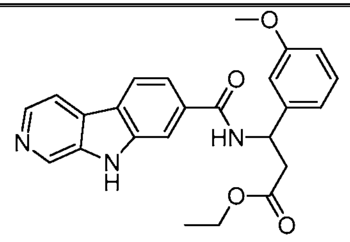
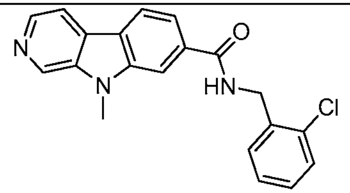
Compounds listed in Table XIV were prepared by following similar procedures to those described for Example I-1 using the appropriate intermediates described or purchased from commercial sources. Coupling reagents, such as HATU, T_3P, BOP, PyBop, and EDC/HOBt, could be used instead of the one described.

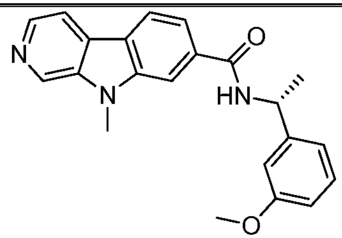
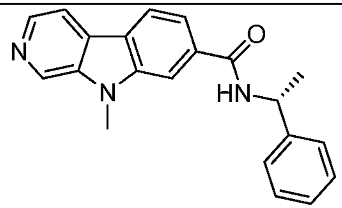
Table XIV

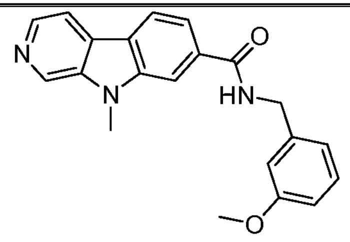
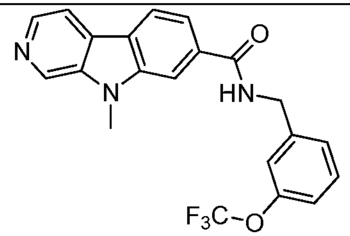
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-1		N-[(3-methoxyphenyl) methyl]-9H-pyrido [3,4-b] indole-7-carboxamide	332.2	I:5.52 J:6.21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.81 - 11.85 (m, 1 H) 9.17 (t, J = 6.27 Hz, 1 H) 8.94 - 8.98 (m, 1 H) 8.37 - 8.41 (m, 1H) 8.33 (d, J = 8.47 Hz, 1 H) 8.15 - 8.20 (m, 1H) 8.12 - 8.15 (m, 1 H) 7.79 (dd, J = 8.31, 1.47 Hz, 1 H) 7.27 (t, J = 8.13 Hz, 1 H) 6.91 - 6.98 (m, 2 H) 6.80 - 6.86 (m, 1 H) 4.52 (d, J = 6.02 Hz, 3 H) 3.75 (s, 3 H)
XIV-2		(R)-N-(1-phenylethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	316.3	I:5.61 J:6.42	^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.96 - 8.97 (s, 1 H) 8.51 (d, J = 5.40 Hz, 1 H) 8.44 - 8.47 (s, 1 H) 8.16 (d, J = 8.16 Hz, 1 H) 8.09 (d, J = 0.75 Hz, 1 H) 7.98 (d, J = 5.21 Hz, 1 H) 7.60 (dd, J = 8.19, 1.47 Hz, 1 H) 7.37 - 7.46 (m, 2 H) 7.29 - 7.34 (m, 2 H) 7.20 - 7.29 (m, 1 H) 6.44 (d, J = 7.59 Hz, 1 H) 5.41 (quin, J = 6.98 Hz, 1 H) 1.67 (d, J = 6.90 Hz, 3 H)

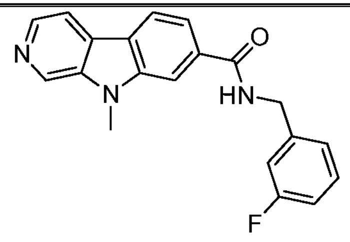
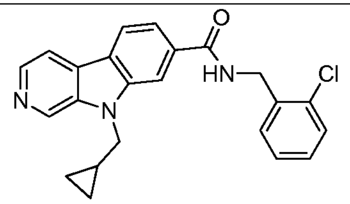
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-3		*N*-(2-chlorobenzyl)-9H-pyrido[3,4-b]indole-7-carboxamide	336.0	I:6.00 J:6.64	^{1}H NMR (400MHz,DMSO-d_6) δ = 12.70 (s, 1 H), 9.38 - 9.25 (m, 2 H), 8.78 - 8.71 (m, 1 H), 8.65 - 8.55 (m, 2 H), 8.31 (s, 1 H), 7.99 - 7.90 (m, 1 H), 7.53 - 7.40 (m, 2 H), 7.39 - 7.27 (m, 2 H), 4.64 (d, J = 5.6 Hz, 2 H)
XIV-4		(*R*)-*N*-(1-(3-methoxyphenyl)ethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	346.2	I:6.08 J:6.52	^{1}H NMR (400MHz,DMSO-d_6) δ = 12.71 (s, 1 H), 9.32 (s, 1 H), 9.08 (s, 1 H), 8.78 (s, 1 H), 8.64 - 8.54 (m, 2 H), 8.26 (s, 1 H), 7.92 (dd, J = 1.5, 8.5 Hz, 1 H), 7.30 - 7.22 (m, 1 H), 7.05 - 6.97 (m, 2 H), 6.86 - 6.77 (m, 1 H), 5.22 (t, J = 7.5 Hz, 1 H), 3.76 (s, 3 H), 1.53 (d, J = 7.0 Hz, 3 H)
XIV-5		*N*-(2-hydroxy-1-phenylethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	332.2	K:8.92 L:11.64	^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.95 (s, 1 H) 8.64 (br. s., 1 H) 8.50 (d, *J* = 5.00 Hz, 1 H) 8.07 - 8.18 (m, 2 H) 7.96 (d, *J* = 4.50 Hz, 1 H) 7.65 (d, *J* = 7.75 Hz, 1 H) 7.30 - 7.46 (m, 54 H) 7.09 (br. s., 1 H) 5.38 (br. s., 1 H) 4.09 (d, *J* = 3.50 Hz, 1 H)

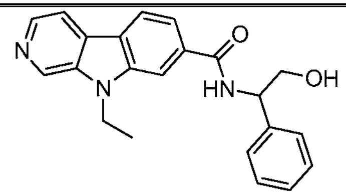
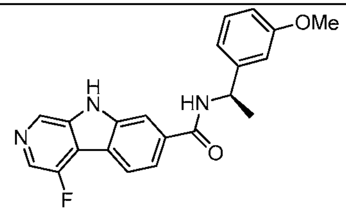
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-6		*N*-(3-hydroxy-1-(3-methoxyphenyl)propyl)-9H-pyrido[3,4-b]indole-7-carboxamide	376.2	M:1.32 N:1.66	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.82 (s, 1 H) 8.97 (s, 1 H) 8.91 (d, *J* = 8.22 Hz, 1 H) 8.39 (d, *J* = 5.27 Hz, 1 H) 8.33 (d, *J* = 8.22 Hz, 1 H) 8.18 (d, *J* = 5.27 Hz, 1 H) 8.09 (d, *J* = 0.75 Hz, 1 H) 7.76 (dd, *J* = 8.25, 1.47 Hz, 1 H) 7.25 (d, *J* = 8.16 Hz, 1 H) 7.02 (d, *J* = 1.63 Hz, 2 H) 6.83 (d, *J* = 1.76 Hz, 1 H) 5.15 - 5.25 (m, 1 H) 4.59 (d, *J* = 9.79 Hz, 1 H) 3.76 (s, 3 H) 3.41 - 3.55 (m, 2 H) 2.03 - 2.14 (m, 1 H) 1.89 - 1.99 (m, 1 H)

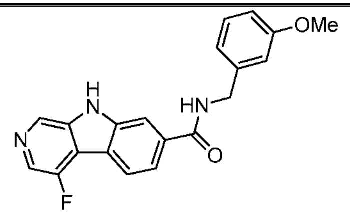
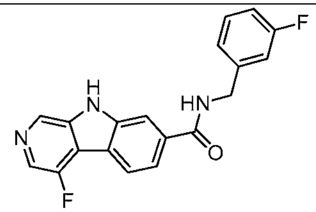
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-7		ethyl 3-(3-methoxyphenyl)-3-(9H-pyrido[3,4-b]indole-7-carboxamido)propanoate	418.2	I:6.20 J:7.03	^1H NMR (400 MHz, chloroform-d) δ ppm 9.03 (s, 1 H) 8.51 (d, J = 5.32 Hz, 1 H) 8.17 - 8.22 (m, 2 H) 8.02 (d, J = 5.57 Hz, 1 H) 7.76 (d, J = 8.57 Hz, 1 H) 7.72 (m, J = 1.50 Hz, 1 H) 7.28 - 7.31 (m, 1 H) 6.99 - 7.03 (m, 1 H) 6.97 (t, J = 2.00 Hz, 1 H) 6.80 - 6.85 (m, 1 H) 5.65 - 5.72 (m, 1 H) 4.11 - 4.12 (m, 1 H) 4.14 (q, J = 7.07 Hz, 2 H) 2.95 - 3.11 (m, 2 H) 1.21 (t, J = 6.8 Hz, 3 H)
XIV-8		N-(2-chlorobenzyl)-9-methyl-9H-pyrido[3,4-b]indole-7-carboxamide	350.2	I:6.16 J:6.97	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (m, 1 H) 9.12 (d, J = 0.88 Hz, 1 H) 8.44 (d, J = 5.21 Hz, 1 H) 8.38 (d, J = 8.16 Hz, 1 H) 8.29 (d, J = 0.69 Hz, 1 H) 8.20 (dd, J = 5.24, 1.04 Hz, 1 H) 7.86 (dd, J = 8.19, 1.41 Hz, 1 H) 7.47 - 7.50 (m, 1 H) 7.43 - 7.46 (m, 1 H) 7.34 (td, J = 7.51, 1.85 Hz, 2 H) 4.64 (d, J = 5.71 Hz, 2 H) 4.05 (s, 3 H)

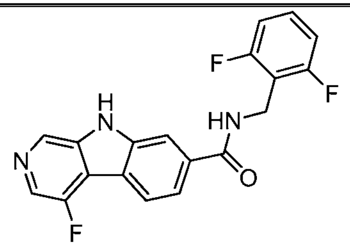
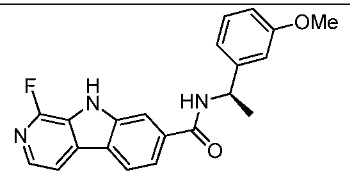
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-9		(R)-N-(1-(3-methoxyphenyl)ethyl)-9-methyl-9H-pyrido [3,4-b] indole-7-carboxamide	360.2	I:6.04 J:6.79	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.11 (d, *J* = 0.94 Hz, 1 H) 8.91 (d, *J* = 7.78 Hz, 1 H) 8.43 (d, *J* = 5.21 Hz, 1 H) 8.36 (dd, *J* = 8.22, 0.50 Hz, 1 H) 8.24 (d, *J* = 0.75 Hz, 1 H) 8.19 (dd, *J* = 5.21, 1.07 Hz, 1 H) 7.82 (dd, *J* = 8.22, 1.44 Hz, 1 H) 7.24 - 7.29 (m, 1 H) 7.00 - 7.04 (m, 2 H) 6.80 - 6.84 (m, 1 H) 5.22 (m, *J* = 7.47, 7.47 Hz, 1 H) 4.05 (s, 3 H) 3.76 (s, 3 H) 1.54 (d, *J*=7.09 Hz, 3 H)
XIV-10		(R)-9-methyl-N-(1-phenylethyl)-9H-pyrido [3,4-b]indole-7-carboxamide	330.2	I:5.99 J:6.73	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.11 (d, *J* = 0.82 Hz, 1 H) 8.94 (d, *J* = 7.97 Hz, 1H) 8.43 (d, *J* = 5.21 Hz, 1 H) 8.35 (d, *J* = 8.22 Hz, 1 H) 8.25 (d, *J* = 0.75 Hz, 1 H) 8.19 (dd, *J* = 5.21, 1.00 Hz, 1 H) 7.83 (dd, *J* = 8.22, 1.38 Hz, 1H) 7.43 - 7.48 (m, 2H) 7.21 - 7.38 (m, 3 H) 5.22 - 5.31 (m, 1 H) 4.05 (s, 3 H) 1.55 (d, *J* = 7.03 Hz, 3 H)

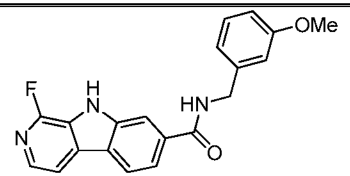
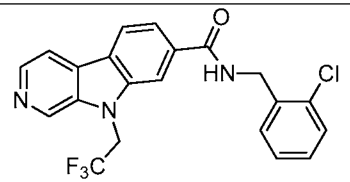
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-11		N-(3-methoxybenzyl)-9-methyl-9H-pyrido [3,4-b] indole-7-carboxamide	346.2	I:5.82 J:6.46	^{1}H NMR (400MHz, DMSO-d_6) δ 9.16 (t, *J* = 5.8 Hz, 1H), 9.10 (s, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.21 - 8.15 (m, 1H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.98 - 6.91 (m, 2H), 6.86 - 6.79 (m, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.03 (s, 3H), 3.74 (s, 3H)
XIV-12		9-methyl-N-(3-(trifluoromethoxy)benzyl)-9H-pyrido [3,4-b]indole-7-carboxamide	400.2	I:6.89 J:7.66	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (1 H, s) 9.12 (1 H, s) 8.44 (1 H, d, *J* = 5.52 Hz) 8.38 (1 H, d, *J* = 8.03 Hz) 8.27 (1 H, s) 8.20 (1 H, dd, *J* = 5.02, 1.00 Hz) 7.84 (1 H, dd, *J* = 8.53, 1.51 Hz) 7.50 (1 H, d, *J* = 8.03 Hz) 7.44 (1 H, s) 7.36 (1 H, s) 7.25 - 7.30 (1 H, m) 4.62 (2 H, d, *J* = 6.02 Hz) 4.05 (3 H, s)

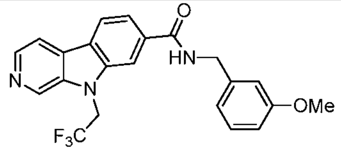
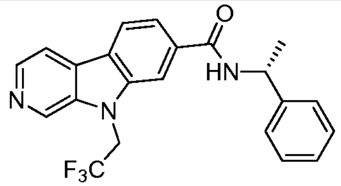
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-13		N-(3-fluorobenzyl)-9-methyl-9H-pyrido[3,4-b] indole-7-carboxamide	334.2	I:6.00 J:6.55	^1H NMR (400MHz, DMSO-d_6) δ 9.24 (t, *J* = 6.3 Hz, 1H), 9.10 (s, 1H), 8.43 (d, *J* = 5.5 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.22 - 8.15 (m, 1H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 (td, *J* = 8.0, 6.0 Hz, 1H), 7.25 - 7.15 (m, 2H), 7.13 - 7.03 (m, 1H), 4.58 (d, *J* = 5.5 Hz, 2H), 4.04 (s, 3H)
XIV-14		N-(2-chlorobenzyl)-9-(cyclopropylmethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	390.0	E:1.26 F:1.76	^1H NMR (400MHz, DMSO-d_6) δ 9.20 (t, *J* = 5.8 Hz, 1H), 9.16 (s, 1H), 8.43 (d, *J* = 5.3 Hz, 1H), 8.39 (d, *J* = 8.3 Hz, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 5.3 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.48 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.44 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.33 (qd, *J* = 7.5, 5.6 Hz, 2H), 4.64 (d, *J* = 5.5 Hz, 2H), 4.48 (d, *J* = 6.8 Hz, 2H), 1.39 (dt, *J* = 13.2, 6.5 Hz, 1H), 0.50 (d, *J* = 6.5 Hz, 4H)

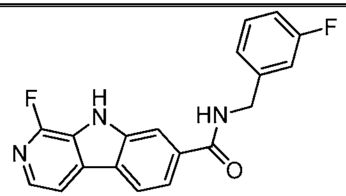
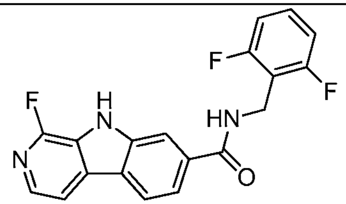
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-15		9-ethyl-N-(2-hydroxy-1-phenylethyl)-9H-pyrido [3,4-b]indole-7-carboxamide	360.3	K:8.09 L:10.63	^1H NMR (400 MHz, chloroform-d) δ ppm 8.93 - 8.97 (m, 1 H) 8.51 (d, *J* = 5.25 Hz, 1 H) 8.18 (d, *J* = 8.25 Hz, 1 H) 8.09 (d, *J* = 0.50 Hz, 1 H) 8.00 (dd, *J* = 5.25, 1.00 Hz, 1 H) 7.62 (dd, *J* = 8.25, 1.50 Hz, 1 H) 7.44 -7.35 (m, 1 H) 6.99 - 7.03 (m, 1 H) 5.35 - 5.40 (m, 1 H) 4.50 (q, *J* = 7.25 Hz, 2 H) 4.09 - 4.12 (m, 2 H) 1.50-1.58 (t, *J* = 14.51 Hz, 3 H)
XIV-16		(R)-4-fluoro-N-(1-(3-methoxyphenyl)ethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	364.0	M:1.65 N:2.11	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.19 (s, 1 H) 9.00 (d, *J* = 8.09 Hz, 1 H) 8.86 (d, *J* = 2.57 Hz, 1 H) 8.35 (d, *J* = 1.32 Hz, 1 H) 8.22 (d, *J* = 8.22 Hz, 1 H) 8.15 - 8.18 (m, 1 H) 7.85 (dd, *J* = 8.28, 1.44 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.00 - 7.04 (m, 2 H) 6.82 (ddd, *J* = 8.20, 2.46, 1.00 Hz, 1 H) 5.21 (quin, *J* = 7.20 Hz, 1 H) 3.76 (s, 3 H) 1.52 (d, *J* = 7.09 Hz, 3 H)

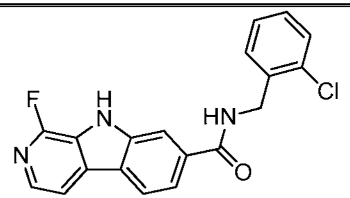
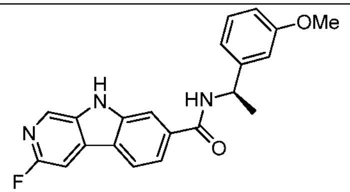
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-17		4-fluoro-N-(3-methoxybenzyl)-9H-pyrido[3,4-b]indole-7-carboxamide	350.0	M:1.59 N:2.03	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.21 (s, 1 H) 9.23 (t, J = 6.02 Hz, 1 H) 8.86 (d, J = 2.64 Hz, 1 H) 8.35 (d, J = 1.26 Hz, 1 H) 8.18 - 8.25 (m, 2 H) 7.86 (dd, J = 8.28, 1.44 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.81 - 6.86 (m, 1 H) 4.52 (d, J = 5.90 Hz, 2 H) 3.75 (s, 3 H).
XIV-18		4-fluoro-N-(3-fluorobenzyl)-9H-pyrido [3,4-b]indole-7-carboxamide	338.1	E:1.13 F:1.49	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.22 (s, 1 H) 9.29 (t, J = 5.93 Hz, 1 H) 8.86 (d, J = 2.64 Hz, 1 H) 8.35 (d, J = 1.25 Hz, 1 H) 8.19 - 8.25 (m, 2 H) 7.86 (dd, J = 8.28, 1.51 Hz, 1 H) 7.40 (td, J = 7.91, 6.15 Hz, 1 H) 7.15 - 7.24 (m, 2 H) 7.09 (td, J = 8.60, 1.88 Hz, 1 H) 4.57 (d, J = 5.90 Hz, 2 H)

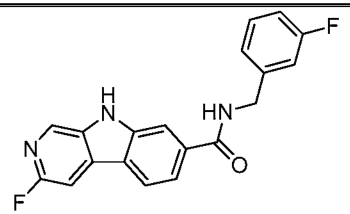
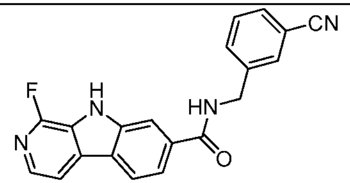
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-19		N-(2,6-difluorobenzyl)-4-fluoro-9H-pyrido[3,4-b] indole-7-carboxamide	356.2	I:6.41 J:7.13	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.18 (s, 1 H) 9.09 (t, J = 5.11 Hz, 1 H) 8.84 (d, J = 2.64 Hz, 1 H) 8.34 (d, J = 1.25 Hz, 1 H) 8.19 (d, J = 8.28 Hz, 1 H) 8.14 (d, J = 0.63 Hz, 1 H) 7.81 (dd, J = 8.28, 1.38 Hz, 1 H) 7.42 (tt, J = 8.37, 6.66 Hz, 1 H) 7.07 - 7.16 (m, 2 H) 4.59 (d, J = 5.08 Hz, 2 H)
XIV-20		(R)-1-fluoro-N-(1-(3-methoxyphenyl)ethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	364.2	I:9.77 J:9.20	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.32 (s, 1 H) 8.99 (d, J = 8.09 Hz, 1 H) 8.35 (dd, J = 8.31, 0.47 Hz, 1 H) 8.10 - 8.17 (m, 2 H) 7.94 (dd, J = 5.36, 1.79 Hz, 1 H) 7.83 (dd, J = 8.35, 1.44 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.98 - 7.05 (m, 2 H) 6.82 (ddd, J = 8.19, 2.42, 1.07 Hz, 1 H) 5.21 (quin, J = 7.36 Hz, 1 H) 3.76 (s, 3 H) 1.53 (s, 3 H)

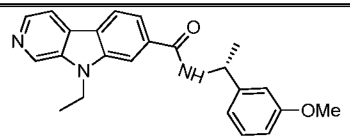
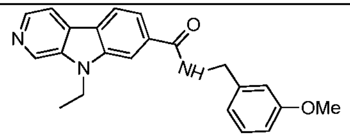
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-21		1-fluoro-N-(3-methoxybenzyl)-9H-pyrido[3,4-b]indole-7-carboxamide	350.2	I:9.11 J:8.86	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.35 (s, 1 H) 9.22 (t, J = 6.02 Hz, 1 H) 8.36 (d, J = 8.35 Hz, 1 H) 8.12 - 8.17 (m, 2 H) 7.94 (dd, J = 5.33, 1.76 Hz, 1 H) 7.84 (dd, J = 8.34, 1.44 Hz, 1 H) 7.23 - 7.30 (m, 1 H) 6.93 - 6.97 (m, 2 H) 6.81 - 6.86 (m, 1 H) 4.52 (d, J = 5.90 Hz, 2 H) 3.75 (s, 3 H).
XIV-22		N-(2-chlorobenzyl)-9-(2,2,2-trifluoroethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	418.0	M:1.81 N:2.35	^1H NMR (400MHz,DMSO-d_6) δ = 9.22 (s, 1 H), 9.17 (t, J = 5.8 Hz, 1 H), 8.54- 8.50 (m, 1 H), 8.46 - 8.40 (m, 2 H), 8.28 - 8.22 (m, 1 H), 7.95 (dd, J = 1.3, 8.3 Hz, 1 H), 7.52 - 7.42 (m, 2 H), 7.39 - 7.29 (m, 2 H), 5.68 - 5.57 (m, 2 H), 4.65 (d, J = 5.5 Hz, 2 H)

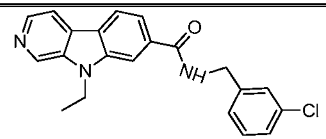
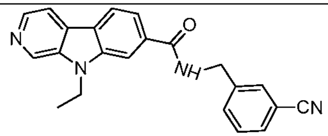
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-23		N-(3-methoxybenzyl)-9-(2,2,2-trifluoroethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	414.0	M:1.68 N:2.19	^1H NMR (400MHz,DMSO-d_6) δ = 9.21 (s, 1 H), 9.14 (t, J = 6.0 Hz, 1 H), 8.52- 8.50 (m, 1 H), 8.44 - 8.38 (m, 2 H), 8.24 (dd, J = 1.0, 5.5 Hz, 1 H), 7.91 (dd, J = 1.3, 8.3 Hz, 1 H), 7.30 - 7.23 (m, 1 H), 6.98 - 6.93 (m, 2 H), 6.87 - 6.80 (m, 1 H), 5.62 (q, J = 9.5 Hz, 2 H), 4.55 (d, J = 6.0 Hz, 2 H), 3.75 (s, 3 H)
XIV-24		(R)-N-(1-phenylethyl)-9-(2,2,2-trifluoroethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	398.0	M:1.77 N:2.29	^1H NMR (400MHz,DMSO-d_6) δ = 8.25 (s, 1 H), 7.67 (d, J = 5.5 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.46 (s, 1 H), 7.42 (d, J = 5.5 Hz, 1 H), 7.09 (dd, J = 1.3, 8.3 Hz, 1 H), 6.69 - 6.64 (m, 2 H), 6.59 - 6.53 (m, 2 H), 6.49 - 6.43 (m, 1 H), 4.63 - 4.49 (m, 3 H), 0.84 (d, J = 7.0 Hz, 3 H)

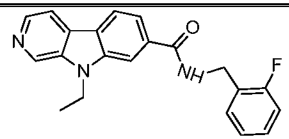
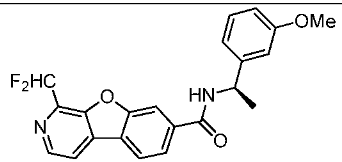
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-25		1-fluoro-N-(3-fluorobenzyl)-9H-pyrido [3,4-b]indole-7-carboxamide	338.2	I:9.36 J:9.02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.35 (s, 1 H) 9.29 (t, *J* = 5.96 Hz, 1 H) 8.37 (dd, *J* = 8.31, 0.60 Hz, 1 H) 8.13 - 8.18 (m, 2 H) 7.94 (dd, *J* = 5.36, 1.79 Hz, 1 H) 7.84 (dd, *J* = 8.31, 1.47 Hz, 1 H) 7.40 (td, *J* = 7.94, 6.15 Hz, 1 H) 7.15 - 7.24 (m, 2 H) 7.06 - 7.12 (m, 1 H) 4.56 (d, *J* = 5.96 Hz, 2 H).
XIV-26		N-(2,6-difluorobenzyl)-1-fluoro-9H-pyrido[3,4-b] indole-7-carboxamide	356.2	I:9.30 J:8.95	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.32 (s, 1 H) 9.09 (t, *J* = 5.15 Hz, 1 H) 8.33 (d, *J* = 8.35 Hz, 1 H) 8.08 - 8.15 (m, 2 H) 7.93 (dd, *J* = 5.33, 1.82 Hz, 1 H) 7.78 (dd, *J* = 8.31, 1.47 Hz, 1 H) 7.42 (tt, *J* = 8.39, 6.64 Hz, 1 H) 7.06 - 7.16 (m, 2 H) 4.59 (d, *J* = 5.15 Hz, 2 H)

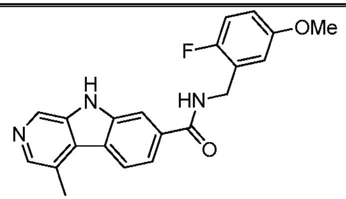
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-27		N-(2-chlorobenzyl)-1-fluoro-9H-pyrido[3,4-b]indole-7-carboxamide	354.0	I:9.90 J:9.44	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.37 (s, 1 H) 9.25 (t, *J* = 5.77 Hz, 1 H) 8.38 (d, *J* = 8.28 Hz, 1 H) 8.13 - 8.20 (m, 2 H) 7.95 (dd, *J* = 5.33, 1.76 Hz, 1 H) 7.87 (dd, *J* = 8.35, 1.44 Hz, 1 H) 7.47 - 7.51 (m, 1 H) 7.40 - 7.45 (m, 1 H) 7.29 - 7.38 (m, 2 H) 4.62 (d, *J* = 5.77 Hz, 2 H)
XIV-28		(R)-3-fluoro-N-(1-(3-methoxyphenyl)ethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	364.2	E:1.53 F:1.51	^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.80 (s, 1 H) 8.95 (d, *J* = 8.09 Hz, 1 H) 8.54 (dd, *J* = 1.41, 0.91 Hz, 1 H) 8.35 (d, *J* = 8.28 Hz, 1 H) 8.09 (d, *J* = 0.69 Hz, 1 H) 7.94 (d, *J* = 2.07 Hz, 1 H) 7.76 (dd, *J* = 8.31, 1.47 Hz, 1 H) 7.23 - 7.30 (m, 1 H) 6.99 - 7.04 (m, 2 H) 6.82 (ddd, *J* = 8.20, 2.49, 0.97 Hz, 1 H) 5.21 (quin, *J* = 7.37 Hz, 1 H) 3.76 (s, 3 H) 1.52 (d, *J* = 7.03 Hz, 3 H).

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-29		3-fluoro-N-(3-fluorobenzyl)-9H-pyrido [3,4-b]indole-7-carboxamide	338.1	E:1.47 F:1.43	^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.83 (s, 1 H) 9.24 (t, J = 5.90 Hz, 1 H) 8.53 (s, 1 H) 8.35 (d, J = 8.28 Hz, 1 H) 8.11 (d, J = 0.75 Hz, 1 H) 7.93 (d, J = 2.01 Hz, 1 H) 7.77 (dd, J = 8.28, 1.25 Hz, 1 H) 7.39 (td, J = 7.91, 6.02 Hz, 1 H) 7.14 - 7.24 (m, 2 H) 7.08 (td, J = 8.60, 1.88 Hz, 1 H) 4.55 (d, J = 5.77 Hz, 2 H)
XIV-30		N-(3-cyanobenzyl)-1-fluoro-9H-pyrido[3,4-b] indole-7-carboxamide	345.1	E:1.33 F:1.30	^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.37 (s, 1 H) 9.32 (t, J = 5.90 Hz, 1 H) 8.37 (d, J = 8.28 Hz, 1 H) 8.13 - 8.18 (m, 2 H) 7.94 (dd, J = 5.33, 1.82 Hz, 1 H) 7.80 - 7.86 (m, 2 H) 7.70 - 7.77 (m, 2 H) 7.56 - 7.61 (m, 1 H) 4.59 (d, J = 5.90 Hz, 2 H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-31		(R)-9-ethyl-N-(1-(3-methoxyphenyl)ethyl)-9H-pyrido[3,4-b]indole-7-carboxamide	374.2	E:1.21 F:1.66	^{1}H NMR (400 MHz, methanol-d_4) δ ppm 9.00 (s, 1 H) 8.29 - 8.46 (m, 2 H) 8.11 - 8.24 (m, 2 H) 7.82 (dd, *J* = 8.22, 1.44 Hz, 1 H) 7.24 - 7.41 (m, 1 H) 7.01 - 7.13 (m, 2 H) 6.84 (ddd, *J* = 8.22, 2.45, 1.00 Hz, 1 H) 5.32 (q, *J* = 7.03 Hz, 1 H) 4.53 - 4.69 (m, 2 H) 3.73 - 4.02 (m, 3 H) 1.64 (d, *J* = 7.09 Hz, 3 H) 1.51 (t, *J* = 7.22 Hz, 3 H)
XIV-32		9-ethyl-N-(3-methoxybenzyl)-9H-pyrido[3,4-b]indole-7-carboxamide	360.2	E:1.11 F:1.50	^{1}H NMR (400 MHz, methanol-d_4) δ ppm 9.01 (s, 1 H) 8.31 - 8.46 (m, 2 H) 8.16 - 8.27 (m, 2 H) 7.84 (dd, *J* = 8.25, 1.47 Hz, 1 H) 7.20 - 7.36 (m, 1 H) 6.96 - 7.10 (m, 2 H) 6.77 - 6.93 (m, 1 H) 4.47 - 4.73 (m, 6 H) 3.82 (s, 3 H) 1.51 (t, *J* = 7.22 Hz, 3 H)

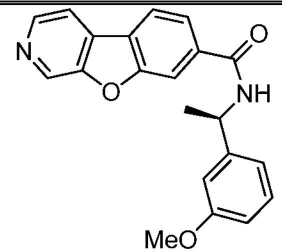
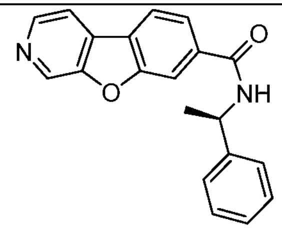
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-33		N-(3-chlorobenzyl)-9-ethyl-9H-pyrido[3,4-b] indole-7-carboxamide	364.2	E:1.22 F:1.64	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 - 9.34 (m, 2 H) 8.36 - 8.50 (m, 2 H) 8.30 (d, J = 0.69 Hz, 1 H) 8.21 (dd, J = 5.21, 1.07 Hz, 1 H) 7.87 (dd, J = 8.22, 1.44 Hz, 1 H) 7.42 - 7.54 (m, 2 H) 7.23 - 7.40 (m, 2 H) 4.41 - 4.73 (m, 4 H) 1.42 (t, J = 7.15 Hz, 3 H)
XIV-34		N-(3-cyanobenzyl)-9-ethyl-9H-pyrido[3,4-b] indole-7-carboxamide	355.2	E:1.04 F:1.42	^{1}H NMR (400MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.37 (t, J = 5.8 Hz, 1H), 8.67 (br. s., 1H), 8.63 - 8.55 (m, 2H), 8.39 (s, 1H), 7.95 (dd, J = 8.3, 1.3 Hz, 1H), 7.83 (s, 1H), 7.78 - 7.70 (m, 2H), 7.62 - 7.55 (m, 1H), 4.70 (q, J = 7.5 Hz, 2H), 4.62 (d, J = 6.0 Hz, 2H), 1.44 (t, J = 7.3 Hz, 3H)

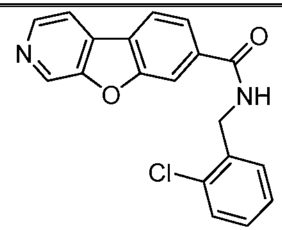
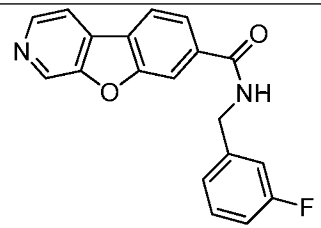
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XIV-35		9-ethyl-N-(2-fluorobenzyl)-9H-pyrido [3,4-b]indole-7-carboxamide	338.2	E:1.15 F:1.53	^1H NMR (400MHz, methanol-d_4) δ 8.98 (s, 1H), 8.38 (d, J = 5.5 Hz, 1H), 8.36 - 8.30 (m, 1H), 8.22 - 8.15 (m, 2H), 7.81 (dd, J = 8.0, 1.5 Hz, 1H), 7.47 (td, J = 7.7, 1.8 Hz, 1H), 7.36 - 7.27 (m, 1H), 7.21 - 7.08 (m, 2H), 4.61 (q, J = 7.0 Hz, 2H), 4.56 (s, 2H), 1.49 (t, J = 7.3 Hz, 3H)
XIV-36		(R)-N-(1-(3-methoxyphenyl)ethyl)-4-methyl-9H-pyrido[3,4-b] indole-7-carboxamide	360.2	M:1.66 N:2.11	^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.83 (s, 1 H) 8.96 (d, J = 8.16 Hz, 1 H) 8.81 (s, 1 H) 8.27 (d, J = 8.35 Hz, 1 H) 8.19 (d, J = 0.63 Hz, 1 H) 8.12 (d, J = 0.94 Hz, 1 H) 7.79 (dd, J = 8.31, 1.54 Hz, 1 H) 7.23 - 7.28 (m, 1 H) 6.99 - 7.04 (m, 2 H) 6.81 (ddd, J = 8.20, 2.37, 1.10 Hz, 1 H) 5.21 (quin, J = 7.34 Hz, 1 H) 3.75 (s, 3 H) 2.81 (s, 3 H) 1.52 (d, J = 7.09 Hz, 3 H)

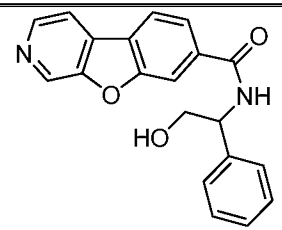
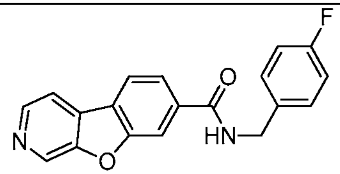
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XIV-37		N-(2-fluoro-5-methoxybenzyl)-4-methyl-9H-pyrido[3,4-b]indole-7-carboxamide	364.2	M:1.62 N:2.06	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.86 (s, 1 H) 9.17 (t, J = 5.87 Hz, 1 H) 8.82 (s, 1 H) 8.29 (d, J = 8.35 Hz, 1 H) 8.12 - 8.21 (m, 2 H) 7.81 (dd, J = 8.35, 1.51 Hz, 1 H) 7.10 - 7.17 (m, 1 H) 6.95 (dd, J = 6.12, 3.17 Hz, 1 H) 6.86 (dt, J = 8.85, 3.67 Hz, 1 H) 4.54 (d, J = 5.71 Hz, 2 H) 3.71 (s, 3 H) 2.82 (s, 3 H).

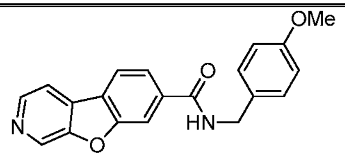
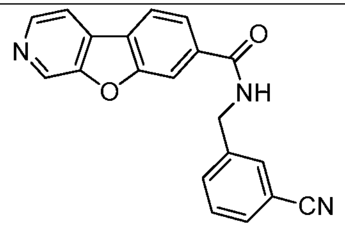
Compounds listed in Table XV were prepared by following similar procedures to those described for Example I-1 using the appropriate intermediates described or purchased from commercial sources. Coupling reagents, such as HATU, T_3P, BOP, PyBop, and EDC/HOBt, could be used instead of the one described.

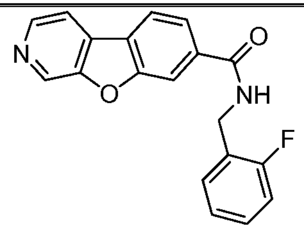
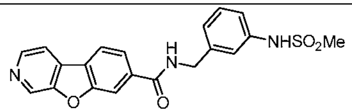
Table XV

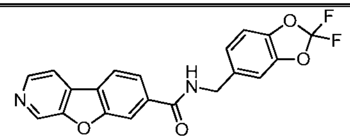
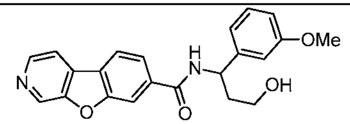
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-1		(R)-N-(1-(3-methoxyphenyl)ethyl) benzofuro[2,3-c] pyridine-7-carboxamide	347.2	I:6.30 J:6.45	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (d, *J* = 0.69 Hz, 1 H), 9.02 (d, *J* = 7.97 Hz, 1 H), 8.65 (d, *J* = 5.02 Hz, 1 H), 8.36 - 8.42 (m, 1 H), 8.32 (d, *J* = 0.82 Hz, 1 H), 8.26 (dd, *J* = 5.08, 1.00 Hz, 1 H), 8.04 (dd, *J* = 8.16, 1.38 Hz, 1 H), 7.22 - 7.31 (m, 1 H), 7.01 (d, *J* = 2.45 Hz, 2 H), 6.82 (ddd, *J* = 8.20, 2.49, 0.91 Hz, 1 H), 5.20 (quin, *J* = 7.23 Hz, 1 H), 3.76 (s, 3 H), 1.52 (d, *J* = 7.09 Hz, 3 H)
XV-2		(R)-N-(1-phenylethyl) benzofuro[2,3-c] pyridine-7-carboxamide	317.1	I:6.23 J:6.35	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (d, *J* = 0.69 Hz, 1 H), 9.05 (d, *J* = 7.97 Hz, 1 H), 8.65 (d, *J* = 5.08 Hz, 1 H), 8.39 (dd, *J* = 8.13, 0.41 Hz, 1 H), 8.33 (d, *J* = 0.82 Hz, 1 H), 8.26 (dd, *J* = 5.08, 1.00 Hz, 1 H), 8.04 (dd, *J* = 8.16, 1.44 Hz, 1 H), 7.42 - 7.47 (m, 2 H), 7.32 - 7.38 (m, 2 H), 7.21 - 7.28 (m, 1 H), 5.23 (quin, *J* = 7.23 Hz, 1 H), 1.54 (d, *J* = 7.03 Hz, 3 H)

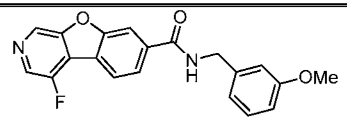
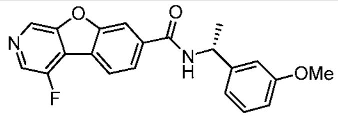
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XV-3		N-(2-chlorobenzyl) benzofuro[2,3-c] pyridine-7-carboxamide	337.0	I:6.72 J:6.92	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, J = 5.7 Hz, 1 H), 9.18 (s, 1 H), 8.66 (d, J = 5.0 Hz, 1 H), 8.42 (d, J = 8.2 Hz, 1 H), 8.36 (s, 1 H), 8.28 (dd, J = 1.0, 5.1 Hz, 1 H), 8.08 (dd, J = 1.4, 8.2 Hz, 1 H), 7.52 - 7.47 (m, 1 H), 7.46 - 7.41 (m, 1 H), 7.40 - 7.25 (m, 2 H), 4.63 (d, J = 5.8 Hz, 2 H)
XV-4		N-(3-fluorobenzyl) benzofuro[2,3-c] pyridine-7-carboxamide	321.1	I:6.25 J:6.47	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.34 (t, *J* = 5.87 Hz, 1 H), 9.17 (d, *J* = 0.56 Hz, 1 H), 8.66 (d, *J* = 5.08 Hz, 1 H), 8.41 (d, *J* = 8.16 Hz, 1 H), 8.33 (d, *J* = 0.75 Hz, 1 H), 8.27 (dd, *J* = 5.08, 1.00 Hz, 1 H), 8.06 (dd, *J* = 8.16, 1.38 Hz, 1 H), 7.40 (td, *J* = 7.87, 6.21 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 7.10 (td, *J* = 8.56, 2.26 Hz, 1 H), 4.57 (d, *J* = 5.96 Hz, 2 H)

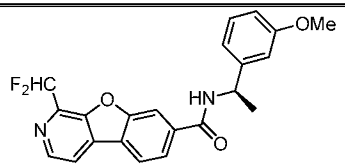
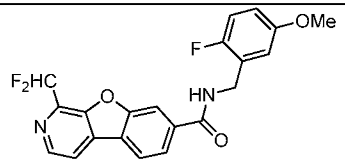
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^{1}H NMR (δ, ppm)
XV-5		N-(2-hydroxy-1-phenylethyl)benzofuro[2,3-c]pyridine-7-carboxamide, TFA	333.2	K:9.14 L:10.29	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 (s, 1 H), 8.97 (d, J = 8.28 Hz, 1 H), 8.66 (d, J = 4.96 Hz, 1 H), 8.40 (d, J = 8.16 Hz, 1 H), 8.36 (d, J = 0.75 Hz, 1 H), 8.27 (dd, J = 5.08, 1.00 Hz, 1 H), 8.06 (dd, J = 8.16, 1.44 Hz, 1 H), 7.44 (d, J = 7.34 Hz, 2 H), 7.32 - 7.39 (m, 2 H), 7.23 - 7.29 (m, 1 H), 5.10 - 5.18 (m, 1 H), 5.01 (t, J = 5.84 Hz, 1 H), 3.74 - 3.82 (m, 1 H), 3.65 - 3.73 (m, 1 H)
XV-6		N-(4-fluorobenzyl) benzofuro[2,3-c] pyridine-7-carboxamide, TFA	321.2	K:11.64 L:12.77	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.34 (t, J = 5.80 Hz,1 H), 9.29 (br. s., 1 H), 8.73 (d, J = 5.02 Hz, 1 H), 8.46 (d, J = 8.16 Hz, 1 H), 8.41 (d, J = 5.21 Hz, 1 H), 8.35 (s, 1 H), 8.08 (dd, J = 8.16, 1.19 Hz, 1 H), 7.38 - 7.45 (m, 2 H), 7.14 - 7.22 (m, 2 H), 4.54 (d, J = 5.90 Hz, 2 H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-7		N-(4-methoxybenzyl) benzofuro[2,3-c] pyridine-7- carboxamide	333.2	K:11.18 L:12.31	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J* = 6.02 Hz, 1 H), 9.16 (d, *J* = 0.75 Hz, 1 H), 8.66 (s, 1 H), 8.39 (d, *J* = 8.09 Hz, 1 H), 8.31 (s, 1 H), 8.24 - 8.29 (m, 1 H), 8.04 (dd, *J* = 8.16, 1.38 Hz, 1 H), 7.27 - 7.33 (m, 2 H), 6.89 - 6.94 (m, 2 H), 4.48 (d, *J* = 5.90 Hz, 2 H), 3.74 (s, 3 H)
XV-8		N-(3-cyanobenzyl) benzofuro[2,3-c] pyridine-7- carboxamide	328.2	I:5.88 J:6.07	^1H NMR (300MHz, DMSO-d_6) δ ppm 9.37 (t, J = 6.0 Hz, 1 H), 9.17 (s, 1 H), 8.65 (t, J = 5.1 Hz, 1 H), 8.40 (d, J = 8.2 Hz, 1 H), 8.33 (s, 1 H), 8.27 (dd, J = 0.9, 5.1 Hz, 1 H), 8.05 (dd, J = 1.3, 8.2 Hz, 1 H), 7.82 (s, 1 H), 7.74 (t, J = 8.0 Hz, 2 H), 7.62 - 7.51 (m, 1 H), 4.59 (d, J = 5.9 Hz, 2 H)

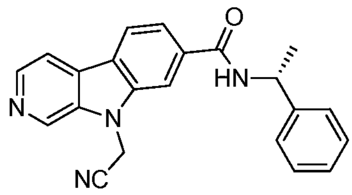
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-9		N-(2-fluorobenzyl) benzofuro[2,3-c] pyridine-7-carboxamide	321.2	I:5.98 J:6.74	^1H NMR (400MHz, DMSO-d_6) δ ppm 9.30 (t, J = 5.8 Hz, 1 H), 9.17 (s, 1 H), 8.66 (d, J = 5.0 Hz, 1 H), 8.41 (dd, J = 0.5, 8.2 Hz, 1 H), 8.36 - 8.31 (m, 1 H), 8.27 (dd, J = 1.0, 5.1 Hz, 1 H), 8.06 (dd, J = 1.4, 8.2 Hz, 1 H), 7.46 - 7.40 (m, 1 H), 7.39 - 7.30 (m, 1 H), 7.26 - 7.10 (m, 2 H), 4.60 (d, J = 5.7 Hz, 2 H)
XV-10		N-(3-(methylsulfonamido) benzyl)benzofuro[2,3-c]pyridine-7-carboxamide	396.0	M:1.21 N:1.66	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.74 (s, 1 H), 9.31 (t, *J* = 5.93 Hz, 1 H), 9.15 (d, *J* = 0.80 Hz, 1 H), 8.65 (d, *J* = 5.20 Hz, 1 H), 8.40 (d, *J* = 8.00Hz, 1 H), 8.31 (d, *J* = 0.80 Hz, 1 H), 8.27 (dd, *J* = 5.08, 1.07 Hz, 1 H), 8.05 (dd, *J* = 8.16, 1.44 Hz, 1 H), 7.27 - 7.35 (m, 1 H), 7.21 - 7.26 (m, 1 H), 7.01 - 7.15 (m, 2 H), 4.53 (d, *J* = 5.84 Hz, 2 H), 2.99 (s, 3 H)

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-11		N-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)methyl)benzofuro[2,3-c]pyridine-7-carboxamide	383.0	M:1.79 N:2.33	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.32 (t, J = 5.90 Hz, 1 H), 9.17 (d, J = 0.69 Hz, 1 H), 8.66 (s, 1 H), 8.40 (d, J = 8.16 Hz, 1 H), 8.32 (s, 1 H), 8.27 (dd, J = 5.08, 1.00 Hz, 1 H), 8.04 (dd, J = 8.13, 1.41 Hz, 1 H), 7.43 (d, J = 1.51 Hz, 1 H), 7.38 (d, J = 8.28 Hz, 1 H), 7.23 (dd, J = 8.31, 1.66 Hz, 1 H), 4.55 (d, J = 5.90 Hz, 2 H)
XV-12		N-(3-hydroxy-1-(3-methoxyphenyl)propyl)benzofuro[2,3-c]pyridine-7-carboxamide	377.2	M:1.31 N:1.79	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (d, J = 0.80 Hz, 1 H), 9.00 (d, J = 8.16 Hz, 1 H), 8.66 (d, J = 4.80 Hz, 1 H), 8.39 (dd, J = 8.13, 0.53 Hz, 1 H), 8.22 - 8.33 (m, 1 H), 8.02 (dd, J = 8.16, 1.44 Hz, 1 H), 7.20 - 7.32 (m, 1 H), 6.95 - 7.04 (m, 2 H), 6.81 (ddd, J = 8.22, 2.48, 0.97 Hz, 1 H), 5.20 (td, J = 8.41, 6.21 Hz, 1 H), 3.75 (s, 3 H), 3.37 - 3.56 (m, 2 H), 2.02 - 2.15 (m, 1 H), 1.90 - 2.00 (m, 1 H), 1.87 (s, 2 H)

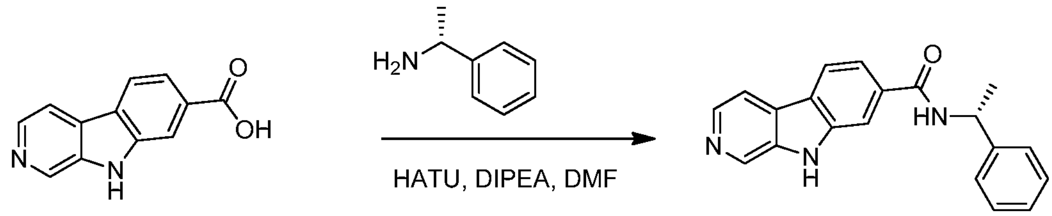
Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-13		4-fluoro-N-(3-methoxybenzyl) benzofuro[2,3-c] pyridine-7-carboxamide	351.0	M:2.21 N:2.27	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.33 (t, J = 5.87 Hz, 1 H) 9.10 (dd, J = 1.98, 0.53 Hz, 1 H) 8.68 (s, 1 H) 8.38 (dd, J = 1.38, 0.56 Hz, 1 H) 8.28 (dd, J = 8.16, 0.56 Hz, 1 H) 8.10 (dd, J = 8.13, 1.41 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.81 - 6.86 (m, 1 H) 4.53 (d, J = 5.90 Hz, 2 H) 3.75 (s, 3 H).
XV-14		(R)-4-fluoro-N-(1-(3-methoxyphenyl)ethyl) benzofuro[2,3-c] pyridine-7-carboxamide	365.2	E:1.59 F:166	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 - 9.12 (m, 2 H) 8.69 (s, 1 H) 8.39 (d, J = 0.75 Hz, 1 H) 8.27 (dd, J = 8.13, 0.53 Hz, 1 H) 8.10 (dd, J = 8.16, 1.44 Hz, 1 H) 7.23 - 7.30 (m, 1 H) 6.98 - 7.03 (m, 2 H) 6.82 (ddd, J = 8.22, 2.51, 0.94 Hz, 1 H) 5.16 - 5.25 (m, 1 H) 3.76 (s, 3 H) 1.53 (d, J = 7.09 Hz, 3 H).

Ex. No.	Structure	Name	LCMS $[M+H]^+$	HPLC Method, RT (min.)	^1H NMR (δ, ppm)
XV-15		(R)-1-(difluoromethyl)-N-(1-(3-methoxyphenyl)ethyl)benzofuro[2,3-c]pyridine-7-carboxamide	397.2	M:2.59 N:2.54	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.00 (d, J = 8.03 Hz, 1 H) 8.71 (d, J = 5.02 Hz, 1 H) 8.48 (d, J = 5.02 Hz, 1 H) 8.40 - 8.46 (m, 2 H) 8.06 (dd, J = 8.16, 1.38 Hz, 1 H) 7.37 (t, J = 53.6 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 6.98 - 7.03 (m, 2 H) 6.81 (ddd, J = 8.19, 2.48, 0.94 Hz, 1 H) 5.19 (quin, J = 7.14 Hz, 1 H) 3.75 (s, 3 H) 1.51 (d, J = 7.09 Hz, 3 H).
XV-16		1-(difluoromethyl)-N-(2-fluoro-5-methoxybenzyl)benzofuro[2,3-c]pyridine-7-carboxamide	401.0	M:2.58 N:2.56	^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, J = 5.65 Hz, 1 H) 8.72 (d, J = 5.02 Hz, 1 H) 8.43 - 8.50 (m, 2 H) 8.38 (d, J =0.75 Hz, 1 H) 8.08 (dd, J =8.16, 1.38 Hz, 1 H) 7.37 (t, J =52.0, 1 H) 7.14 (t, J = 9.29 Hz, 1 H) 6.96 (dd, J = 6.12, 3.17 Hz, 1 H) 6.87 (dt, J = 8.91, 3.61 Hz, 1 H) 4.55 (d, J = 5.71 Hz, 2 H) 3.72 (s, 3 H).

Example XVI-1: (R)-9-(Cyanomethyl)-N-(1-phenylethyl)-9H-pyrido[3,4-b]indole-7-carboxamide

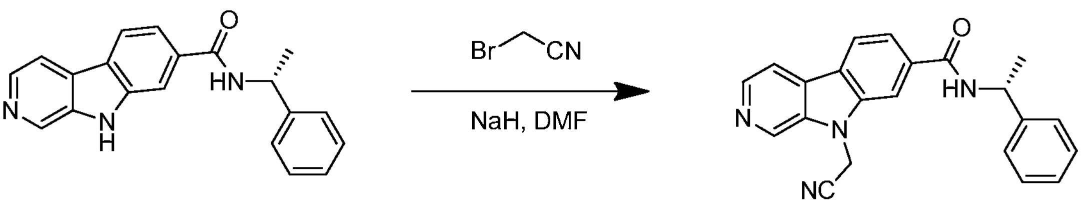


Example XVI-1A: (R)-N-(1-Phenylethyl)-9H-pyrido[3,4-b]indole-7-carboxamide



To a solution of Intermediate 22 (0.100 g, 0.471 mmol) in DMF (2 mL), HATU (0.358 g, 0.942 mmol) was added. The mixture was stirred for 20 min, then (R)-1-phenylethanamine (0.120 mL, 0.942 mmol) was added to the reaction mixture, followed by the addition of DIEA (0.247 mL, 1.41 mmol). The mixture was stirred at rt overnight. Water was added, then the reaction mixture was extracted with EtOAc (2x). The combined organic phase was dried with Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography (gradient, 0-5% MeOH/$CHCl_3$) to afford Example XVI-1A (139 mg) as a yellow semi-solid. LC-MS (ESI) *m/z*: 316.1 $[M+H]^+$.

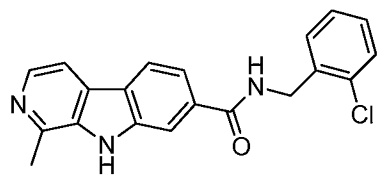
Example XVI-1:



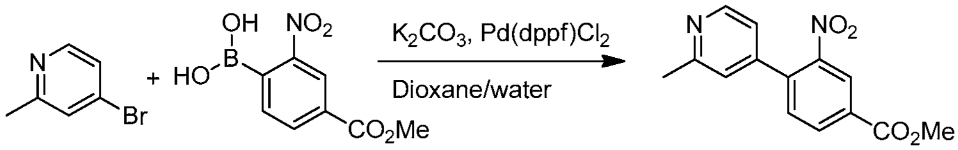
To s solution of Example XVI-1A (0.139 g, 0.295 mmol) in DMF (2 mL) at 0 °C, sodium hydride (0.014 g, 0.35 mmol) was added. The mixture was stirred at RT for 15 min, then 2-bromoacetonitrile (0.031 mL, 0.44 mmol) was added. The mixture was stirred at rt for 1 h. Water was added, then the mixture was extracted with EtOAc (2x). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC (Acetonitrile/water/NH_4OAc) to afford

Example XVI-1 (2 mg, 2% yield). MS (ESI) *m/z*: 355 [M+H]$^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.24 (s, 1 H), 8.97 (d, J = 8.0 Hz, 1 H), 8.54 (d, J = 5.0 Hz, 1 H), 8.43 (d, J = 8.5 Hz, 1 H), 8.38 (s, 1 H), 8.27 (dd, J = 1.0, 5.0 Hz, 1 H), 7.93 (dd, J = 1.5, 8.0 Hz, 1 H), 7.49 - 7.44 (m, 2 H), 7.39 - 7.33 (m, 2 H), 7.28 - 7.22 (m, 1 H), 5.95 (s, 2 H), 5.28 (quin, J = 7.2 Hz, 1 H), 1.56 (d, J = 7.0 Hz, 3 H).

Example XVI-2: N-(2-Chlorobenzyl)-1-methyl-9H-pyrido[3,4-b]indole-7-carboxamide

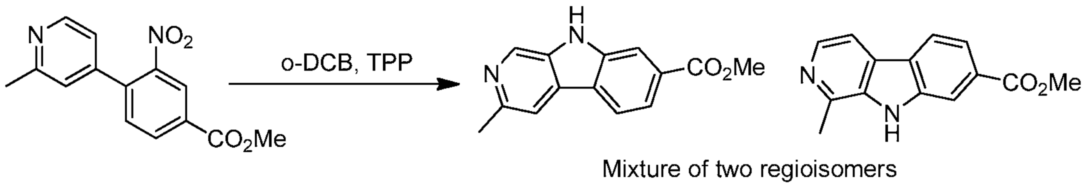


Example XVI-2A: Methyl 4-(2-methylpyridin-4-yl)-3-nitrobenzoate



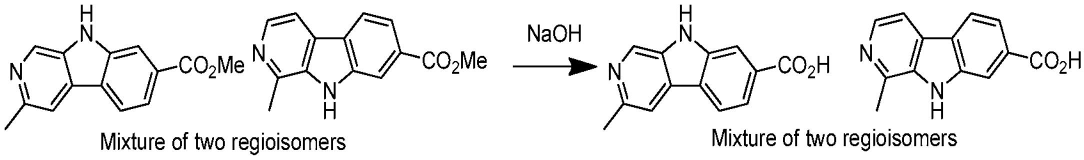
A solution of 4-bromo-2-methylpyridine (1.0 g, 5.81 mmol) and K_2CO_3 (2.41 g, 17.4 mmol) in dioxane (20 mL) and water (4 mL) was bubbled with nitrogen for 10 minutes. To this mixture were added (4-(methoxycarbonyl)-2-nitrophenyl)boronic acid (1.308 g, 5.81 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.285 g, 0.349 mmol). The mixture was heated at 80 °C overnight. The reaction mixture was cooled to rt and diluted with EtOAc. The mixture was washed with brine solution (2x), dried with Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex.) to afford Example XVI-2A (520 mg, 30% yield) as a yellow solid. LC-MS (ESI) *m/z*: 273.5 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 - 8.56 (m, 2 H) 8.32 (dd, J = 8.00, 1.73 Hz, 1 H) 7.75 (d, J = 8.03 Hz, 1 H) 7.31 - 7.34 (m, 1 H) 7.22 (ddd, J = 5.11, 1.73, 0.56 Hz, 1 H) 3.95 (s, 3 H) 2.53 (s, 3 H).

Example XVI-2B: Methyl 1-methyl-9H-pyrido[3,4-b]indole-7-carboxylate and methyl 3-methyl-9H-pyrido[3,4-b]indole-7-carboxylate (~1:1 mixture)



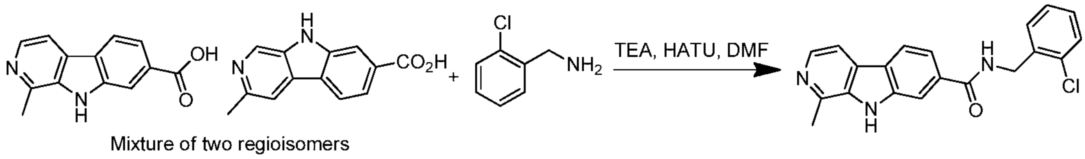
To a solution of Example XVI-2A (800 mg, 2.94 mmol) in 1,2-dichlorobenzene (8 mL), was added triphenylphosphine (1.93 g, 7.35 mmol). The mixture was heated at 170 °C for 5 h, then was cooled to rt. Pet. ether was added and the resultant precipitate was collected by filtration. The solid was purified by flash chromatography (gradient elution; 0-100% EtOAc/Hex.) to afford Example XVI-2B (690 mg) as a mixture of isomers. The mixture was contaminated with triphenylphosphine oxide and was taken onto the following step without further purification. LC-MS (ESI) *m/z*: 241.5 $[M+H]^+$.

Example XVI-2C: 3-Methyl-9H-pyrido[3,4-b]indole-7-carboxylic acid and 1-methyl-9H-pyrido[3,4-b]indole-7-carboxylic acid (~1:1 mixture)



To a solution of Example XVI-2B (0.69 g, 2.87 mmol) in MeOH (6 mL) and water (2 mL), was added NaOH (0.345 g, 8.62 mmol). The mixture was stirred at rt overnight, then was concentrated. The mixture was taken up in water (10 mL) and the solid was removed by filtration. The filtrate was washed with ethyl acetate. The aqueous phase was acidified to pH 4 with 1.5N HCl and the resultant precipitated solid was collected by filtration. The solid was washed with water and pet. ether to gave Example XVI-2C (260 mg) as a yellow solid. LC-MS (ESI) *m/z*: 227.5 $[M+H]^+$.

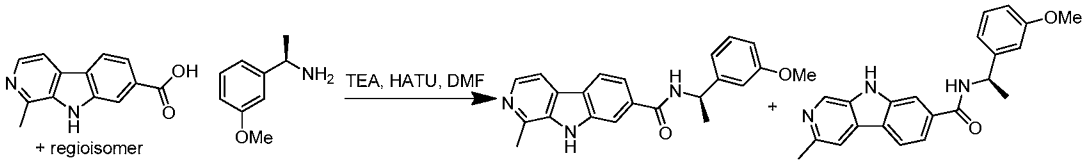
Example XVI-2:



To a solution of Example XVI-2C (60 mg, 0.27 mmol) in DMF (2 mL), was added (2-chlorophenyl)methanamine (75 mg, 0.53 mmol), TEA (0.185 mL, 1.33 mmol) and HATU (111 mg, 0.292 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with ice cold water (15 mL) and stirred for 15 minutes. The precipitate was collected by filtration, washed with water and pet. ether and dried. The material was purified by Supercritical Fluid Chromatography (SFC) to afford Example XVI-2. LC-MS (ESI) *m/z*: 350.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.79 (br. s., 1 H) 9.21 (t, *J* = 5.77 Hz, 1 H) 8.28 - 8.33 (m, 1 H) 8.25 (d, *J* = 5.33 Hz, 1 H) 8.14 (d, *J* = 0.75 Hz, 1 H) 7.99 (dd, *J* = 5.33, 0.44 Hz, 1 H) 7.80 (dd, *J* = 8.28, 1.51 Hz, 1 H) 7.46 - 7.51 (m, 1 H) 7.39 - 7.44 (m, 1 H) 7.28 - 7.38 (m, 2 H) 4.61 (d, *J* = 5.77 Hz, 2 H) 2.79 (s, 3 H).

Example XVI-3: (R)-N-(1-(3-Methoxyphenyl)ethyl)-1-methyl-9H-pyrido[3,4-b]indole-7-carboxamide, and

Example XVI-4: (R)-N-(1-(3-Methoxyphenyl)ethyl)-3-methyl-9H-pyrido[3,4-b]indole-7-carboxamide



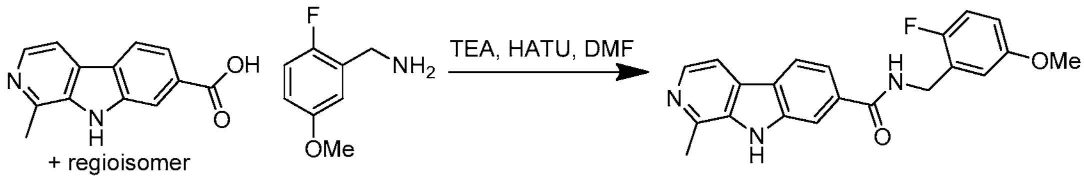
To a solution of Example XVI-2C (60 mg, 0.265 mmol) in DMF (2 mL), were added (R)-1-(3-methoxyphenyl)ethanamine (80 mg, 0.530 mmol), TEA (0.185 mL, 1.33 mmol) and HATU (111 mg, 0.292 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with ice cold water (15 mL) and stirred for 15 minutes. The precipitate was collected by filtration, washed with water and pet. ether and dried. The material was purified by Supercritical Fluid Chromatography (Co-Solvent 0.3% DEA in methanol) to afford Example XVI-3 and Example XVI-4.

Example XVI-3: 40 mg. LC-MS (ESI) *m/z*: 360.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.76 (s, 1 H) 8.94 (d, *J* = 8.22 Hz, 1 H) 8.22 - 8.31 (m, 2 H) 8.08 (d, *J* = 0.69 Hz, 1 H) 7.98 (d, *J* = 5.33 Hz, 1 H) 7.77 (dd, *J* = 8.28, 1.44 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 6.98 - 7.04 (m, 2 H) 6.78 - 6.84 (m, 1 H) 5.20 (quin, *J* = 7.29 Hz, 1 H) 3.76 (s, 3 H) 2.78 (s, 3 H) 1.51 (d, *J* = 7.09 Hz, 3 H).

Example XVI-4: 12 mg. LC-MS (ESI) *m/z*: 360.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.61 (s, 1 H) 8.92 (d, *J* = 8.16 Hz, 1 H) 8.82 (d, *J* = 1.07 Hz, 1 H) 8.26 (d, *J* = 8.22 Hz, 1 H) 8.06 (d, *J* = 0.75 Hz, 1 H) 7.99 (s, 1 H) 7.73 (dd, *J* = 8.25, 1.47 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 6.98 - 7.03 (m, 2 H) 6.81 (ddd, *J* = 8.20, 2.46, 1.00

Hz, 1 H) 5.15 - 5.24 (quin, J = 7.29 Hz, 1 H) 3.75 (s, 3 H) 2.62 (s, 3 H) 1.51 (d, J = 7.03 Hz, 3 H).

Example XVI-5: N-(2-Fluoro-5-methoxybenzyl)-1-methyl-9H-pyrido[3,4-b]indole-7-carboxamide



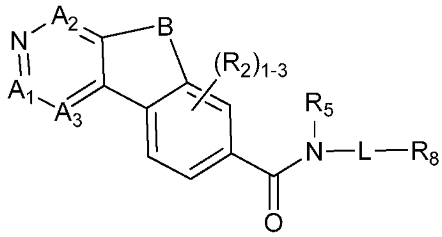
To a solution of Example XVI-2C (60 mg, 0.265 mmol) in DMF (2 mL), were added (2-fluoro-5-methoxyphenyl)methanamine (82 mg, 0.53 mmol), TEA (0.185 mL, 1.33 mmol) and HATU (111 mg, 0.292 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with ice cold water (15 mL) and stirred for 15 minutes. The precipitate was collected by filtration, washed with water and pet. ether, and dried. The material was purified by Supercritical Fluid Chromatography (Co-Solvent 0.3% DEA in methanol) to afford 37 mg (38%) of Example XVI-5. LC-MS (ESI) *m/z*: 364.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.78 (s, 1 H) 9.16 (t, J = 5.84 Hz, 1 H) 8.29 (dd, J = 8.25, 0.47 Hz, 1 H) 8.24 (d, J = 5.33 Hz, 1 H) 8.11 (d, J = 0.82 Hz, 1 H) 7.99 (d, J = 5.33 Hz, 1 H) 7.77 (dd, J = 8.28, 1.51 Hz, 1 H) 7.14 (t, J = 9.32 Hz, 1 H) 6.95 (dd, J = 6.12, 3.17 Hz, 1 H) 6.86 (dt, J = 8.82, 3.66 Hz, 1 H) 4.54 (d, J = 5.77 Hz, 2 H) 3.71 (s, 3 H) 2.79 (s, 3 H).

Example XVI-6: N-(3-Methoxybenzyl)-1-methyl-9H-pyrido[3,4-b]indole-7-carboxamide

To a solution of Example XVI-2C (60 mg, 0.265 mmol) in DMF (2 mL), were added (3-methoxyphenyl)methanamine (72.8 mg, 0.530 mmol), TEA (0.185 mL, 1.33 mmol) and HATU (111 mg, 0.292 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with ice cold water (15 mL) and stirred for 15 minutes. The precipitate was collected by filtration, washed with water and pet. ether, and dried. The material was purified by Supercritical Fluid Chromatography (Co-Solvent 0.3% DEA in methanol) to afford 34 mg (37%) of Example XVI-6. LC-MS (ESI) *m/z*: 346.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.76 (s, 1 H) 9.18 (t, *J* = 5.99 Hz, 1 H) 8.29 (dd, *J* = 8.25, 0.53 Hz, 1 H) 8.24 (d, *J* = 5.33 Hz, 1 H) 8.12 (d, *J* = 0.75 Hz, 1 H) 7.98 (dd, *J* = 5.33, 0.50 Hz, 1 H) 7.77 (dd, *J* = 8.28, 1.51 Hz, 1 H) 7.24 - 7.30 (m, 1 H) 6.92 - 6.97 (m, 2 H) 6.80 - 6.86 (m, 1 H) 4.52 (d, *J* = 5.96 Hz, 2 H) 3.75 (s, 3 H) 2.79 (s, 3 H).

WHAT IS CLAIMED IS:

1. A compound according to formula (I):



(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

A_1 and A_2 are CR_1;

A_3 is independently selected from N and CR_1;

B is independently selected from -O-, $-CR_3R_4O-$, $-OCR_3R_4-$, $-NR_a-$, -C(O)O-, -OC(O)-, $-C(O)NR_a-$, $-NR_aC(O)-$, and -S-;

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5(CR_6R_7)_q-$, $-(CR_6R_7)_sO(CR_6R_7)_q-$, and $-(CR_6R_7)_sC(O)(CR_6R_7)_q-$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, NR_aR_a, C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)NR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $(CH_2)_rCN$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from C_{3-10} carbocyclyl and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl

substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

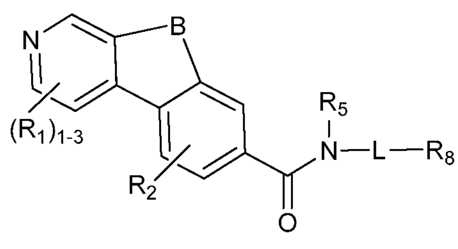
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4;

s, at each occurrence, is independently selected from 1, and 2; provided when s and q are in the same term, $s + q \leq 3$.

2. The compound of claim 1, having Formula (II):



(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

B is independently selected from -O- and $-NR_a-$;

L is $-(CR_6R_7)_q$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, and $-(CH_2)_rC(=O)OR_b$;

R_8 is selected from phenyl, C_{3-6} cycloalkyl and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, C_{1-4}alkyl substituted with 0-5 R_e, $-NR_aS(O)_pC_{1-4}$ alkyl, $-OR_b$, and -CN;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H and C_{1-6} alkyl substituted with 0-5 R_e;

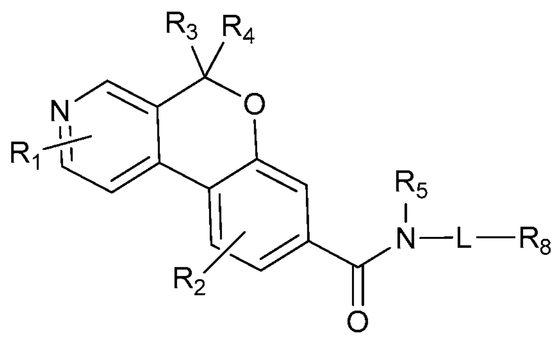
R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), F, Cl, Br, CN, NO_2, $-(CH_2)_rOC_{1-5}$ alkyl, and $-(CH_2)_rOH$;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

3. The compound of claim 1, having Formula (III):



(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is independently selected from $-(CR_6R_7)_q-$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NR_aC(=O)R_b$, and $-NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, OH, CN, and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$,

$-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

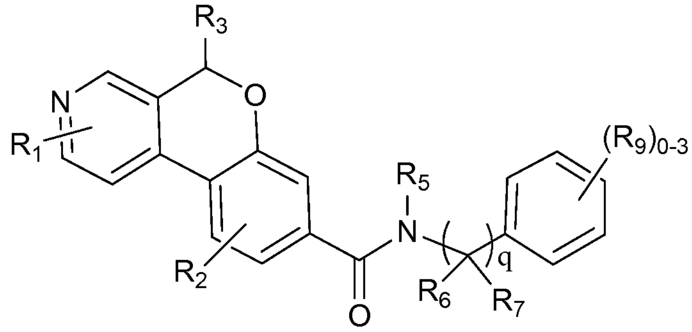
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

4. The compound of claim 3, having Formula (IV):



(IV)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NR_aC(=O)R_b$, and $-NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, and NR_aR_a;

R_3 is independently selected from H and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

5. The compound of claim 4 or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

R_1 and R_2 are H;

R_3 is independently selected from H and Me;

R_5 is H;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

6. The compound of claim 5 or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-4 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

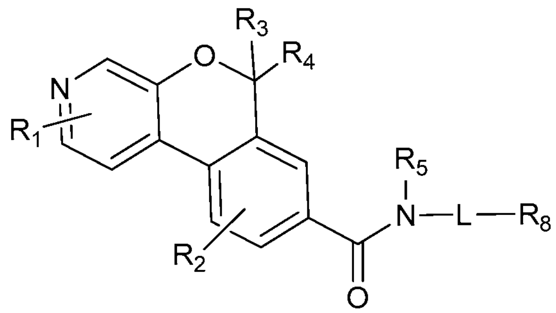
R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

7. The compound of claim 1, having Formula (V):



(V)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NR_aC(=O)R_b$, and $-NR_aC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H, F, Cl, Br, OH, CN, C_{1-4} alkyl substituted with 0-3 R_e, and C_{3-6} carbocyclyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$,

$-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

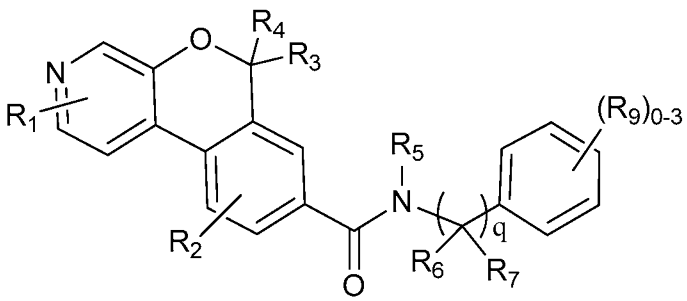
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1 and 2.

8. The compound of claim 7, having Formula (VIa):



(VIa)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

R_1 is independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, $-(CH_2)_rOR_b$, $-NHC(=O)R_b$, and $-NHC(=O)OR_b$;

R_2 is independently selected from H, F, Cl, Br, OH, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, and C_{1-4} alkyl substituted with 0-3 R_e;

R_3 and R_4 are independently selected from H, C_{1-4} alkyl substituted with 0-3 R_e, and C_{3-6} cycloalkyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r$-C_{3-6} carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, $-(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl

substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

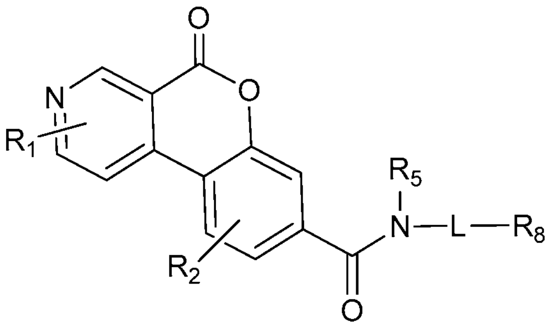
R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from 1 and 2; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

9. The compound of claim 1, having Formula (VII):



(VII)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

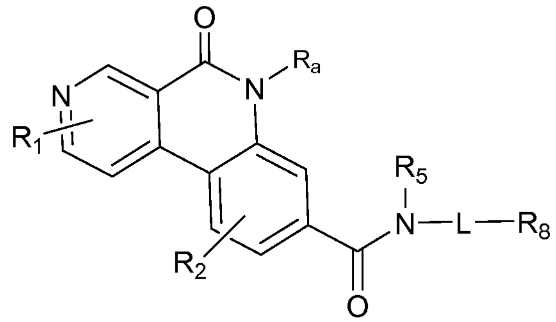
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

10. The compound of claim 1, having Formula (VIII):



(VIII)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, and $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$,

$-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

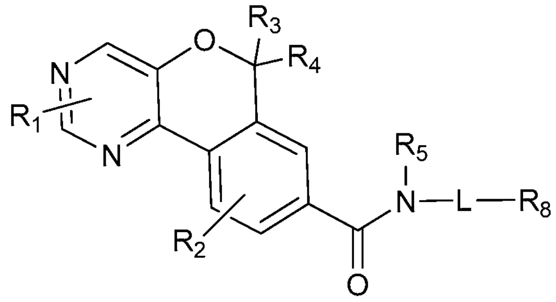
p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

11. The compound of claim 1, having Formula (IX):



(IX)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is independently selected from $-(CR_6R_7)_q$, $-(CR_6R_7)_sNR_5-$, $-(CR_6R_7)_sO-$, and $-(CR_6R_7)_sC(O)-$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_3 and R_4 are independently selected from H and C_{1-4} alkyl substituted with 0-3 R_e, C_{1-4} alkenyl substituted with 0-3 R_e, and C_{1-4} alkynyl substituted with 0-3 R_e;

R_5 is independently selected from H and C_{1-4} alkyl optionally substituted with F, Cl, Br, CN, $-OR_b$, $-S(O)_pR_c$, $-C(=O)R_b$, $-NR_aR_a$, $-C(=O)NR_aR_a$, $-C(=O)(CH_2)_rNR_aR_a$, CN, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)NR_aR_a$, $-NR_aC(=O)NR_aR_a$, $-C(=O)OR_b$, $-S(O)_pNR_aR_a$, $-NR_aS(O)_pNR_aR_a$, $-NR_aS(O)_pR_c$, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_6 and R_7 are independently selected from H, C_{1-4}alkyl substituted with 0-4 R_e, $-(CH_2)_rOR_b$, $-(CH_2)_rS(O)_pR_c$, $-(CH_2)_rC(=O)R_b$, $-(CH_2)_rNR_aR_a$, $-(CH_2)_rC(=O)(CH_2)_rNR_aR_a$, $-(CH_2)_rNR_aC(=O)R_b$, $-(CH_2)_rNR_aC(=O)OR_b$, $-(CH_2)_rOC(=O)NR_aR_a$, $-(CH_2)_rNR_aC(=O)NR_aR_a$, $-(CH_2)_rC(=O)OR_b$, $-(CH_2)_rS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pNR_aR_a$, $-(CH_2)_rNR_aS(O)_pR_c$, $(CH_2)_r-C_{3-6}$ carbocyclyl substituted with 0-3 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-3 R_e;

alternatively, R_6 and R_7 together with the carbon atom to which they are both attached form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e; alternatively, when q is 2 or 3, two adjacent R_6 groups form a cycloalkyl or heterocyclyl, each substituted with 0-5 R_e;

R_8 is selected from aryl, C_{3-6}cycloalkyl, and heterocyclyl, each substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, -$(CHR_d)_rS(O)_pR_c$, -$(CHR_d)_rS(O)_pNR_aR_a$, -$(CHR_d)_rNR_aS(O)_pR_c$, -$(CHR_d)_rOR_b$, -$(CHR_d)_rCN$, -$(CHR_d)_rNR_aR_a$, -$(CHR_d)_rNR_aC(=O)R_b$, -$(CHR_d)_rNR_aC(=O)NR_aR_a$, -$(CHR_d)_rC(=O)OR_b$, -$(CHR_d)_rC(=O)R_b$, -$(CHR_d)_r$ $OC(=O)R_b$, -$(CHR_d)_rC(=O)NR_aR_a$, -$(CHR_d)_r$-cycloalkyl, -$(CHR_d)_r$-heterocyclyl, -$(CHR_d)_r$-aryl, and -$(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

alternatively, two adjacent R_9 groups are combined to form a carbocyclic or heterocyclic ring comprising carbon atoms and 1-3 hetero atoms selected from N, O, and $S(O)_p$, wherein the carbocyclic and heterocyclic rings are substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, -$(CH_2)_r$-C_{3-10} carbocyclyl substituted with 0-5 R_e, and -$(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, -$(CH_2)_r$-C_{3-10} carbocyclyl, -$(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, -$(CH_2)_rOC_{1-5}$ alkyl, -$(CH_2)_rOH$, -$(CH_2)_rNR_fR_f$, -$(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, -$C(=O)NR_fR_f$, -$C(=O)R_f$, $S(O)_pNR_fR_f$, -$NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3;

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

s, at each occurrence, is independently selected from 1, and 2.

12. The compound of claim 11 or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is $-(CR_6R_7)_q$;

R_1 and R_2 are H;

R_3 and R_4 are independently selected from H and C_{1-4}alkyl substituted with 0-3 R_e

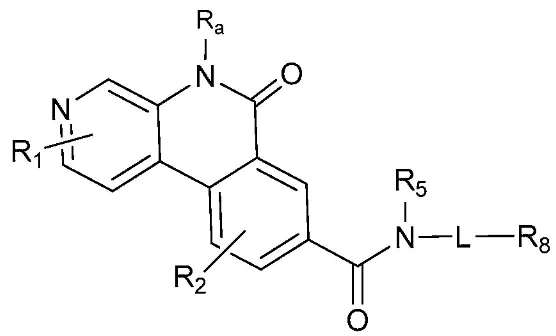
R_5 is H;

R_6 and R_7 are independently selected from H and C_{1-4}alkyl;

R_8 is selected from aryl and heterocyclyl, each substituted with 0-5 R_9; and

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl, OH, OC_{1-4} alkyl, $-C(=O)OC_{1-4}$ alkyl, $-C(=O)NH_2$, $-C(=O)NHC_{1-4}$ alkyl, $-C(=O)NHC_{3-6}$ cycloalkyl, C_{3-6}cycloalkyl, heterocyclyl, aryl, and heteroaryl.

13. The compound of claim 1, having Formula (X):



(X)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein

L is $-(CR_6R_7)_q$;

R_1 and R_2 are independently selected from H, F, Cl, Br, CN, NR_aR_a, $-OC_{1-4}$ alkyl substituted with 0-3 R_e, C_{1-4} alkyl substituted with 0-3 R_e, and $-(CH_2)_rOR_b$;

R_5 is independently selected from H and C_{1-4} alkyl;

R_6 and R_7 are independently selected from H and C_{1-4}alkyl substituted with 0-4 R_e;

R_8 is aryl substituted with 0-5 R_9;

R_9 is independently selected from F, Cl, Br, C_{1-4}alkyl substituted with 0-5 R_e, C_{2-4}alkenyl substituted with 0-5 R_e, C_{2-4}alkynyl substituted with 0-5 R_e, =O, nitro, $-(CHR_d)_rS(O)_pR_c$, $-(CHR_d)_rS(O)_pNR_aR_a$, $-(CHR_d)_rNR_aS(O)_pR_c$, $-(CHR_d)_rOR_b$, $-(CHR_d)_rCN$, $-(CHR_d)_rNR_aR_a$, $-(CHR_d)_rNR_aC(=O)R_b$, $-(CHR_d)_rNR_aC(=O)NR_aR_a$, $-(CHR_d)_rC(=O)OR_b$, $-(CHR_d)_rC(=O)R_b$, $-(CHR_d)_r OC(=O)R_b$, $-(CHR_d)_rC(=O)NR_aR_a$, $-(CHR_d)_r$-cycloalkyl, $-(CHR_d)_r$-heterocyclyl, $-(CHR_d)_r$-aryl, and $-(CHR_d)_r$-heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with 0-4 R_e;

R_a, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e; or R_a and R_a together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R_e;

R_b, at each occurrence, is independently selected from H, C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6} alkenyl substituted with 0-5 R_e, C_{2-6} alkynyl substituted with 0-5 R_e, $-(CH_2)_r-C_{3-10}$ carbocyclyl substituted with 0-5 R_e, and $-(CH_2)_r$-heterocyclyl substituted with 0-5 R_e;

R_c, at each occurrence, is independently selected from C_{1-6} alkyl substituted with 0-5 R_e, C_{2-6}alkenyl substituted with 0-5 R_e, C_{2-6}alkynyl substituted with 0-5 R_e, C_{3-6} carbocyclyl, and heterocyclyl;

R_d, at each occurrence, is independently selected from H and C_{1-4}alkyl substituted with 0-5 R_e;

R_e, at each occurrence, is independently selected from C_{1-6} alkyl (optionally substituted with F, Cl, Br, and OH), C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_r-C_{3-10}$ carbocyclyl, $-(CH_2)_r$-heterocyclyl, F, Cl, Br, CN, NO_2, =O, CO_2H, CO_2C_{1-6} alkyl, $-(CH_2)_rOC_{1-5}$ alkyl, $-(CH_2)_rOH$, $-(CH_2)_rNR_fR_f$, $-(CH_2)_rNR_fR_fC(=O)C_{1-4}$alkyl, $-C(=O)NR_fR_f$, $-C(=O)R_f$, $S(O)_pNR_fR_f$, $-NR_fR_fS(O)_pC_{1-4}$alkyl, and $S(O)_pC_{1-4}$alkyl;

R_f, at each occurrence, is independently selected from H, F, Cl, Br, C_{1-5}alkyl, and C_{3-6} cycloalkyl; or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring;

p, at each occurrence, is independently selected from zero, 1, and 2;

q, at each occurrence, is independently selected from zero, 1, 2, and 3; and

r, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

14. A pharmaceutical composition comprising one or more compounds according to any of claims 1-13 and a pharmaceutically acceptable carrier or diluent.

15. A compound according to any one of claims 1-13 for use in therapy.

16. Use of a compound according to any one of claims 1-13 for prophylaxis and/or treatment of diseases associated with the enzyme ROCK2.

17. Use of a compound according to claim 16 for prophylaxis and/or treatment of cancers, inflammation, infectious diseases, HIV, erectile dysfunction, cardiovascular diseases and disorders, hypertension, angina pectoris, cerebral ischaemia, cerebral vasospasm, myocardial ischemia, coronary vasospasm, heart failure, myocardial hypertrophy, atherosclerosis, restenosis, spinal cord injuries, neuronal degeneration, thrombotic disorders, asthma, glaucoma, and osteoporosis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/044988

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D498/04 A61K31/4353 A61K31/519 A61P9/00
A61P11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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 practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/062766 A2 (UNIV MICHIGAN [US]; GLICK GARY D [US]) 26 May 2011 (2011-05-26) claims; examples; table 1	1-17
A	WO 2012/054367 A1 (BOEHRINGER INGELHEIM INT [DE]; KIRRANE JR THOMAS MARTIN [US]; MARSHALL) 26 April 2012 (2012-04-26) page 75 - page 80; claims; examples	1-17
A	WO 2011/159857 A1 (SQUIBB BRISTOL MYERS CO [US]; LIU CHUNJIAN [US]; LIN JAMES [US]; DELUC) 22 December 2011 (2011-12-22) page 43, line 11 - page 48, line 15; claims; examples	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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 application or patent 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
5 September 2014	12/09/2014

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

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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Y	W. VAN BIESEN: "Rho/Rho-kinase and C-reactive protein relationship in hypertension and atherosclerosis", NEPHROLOGY DIALYSIS TRANSPLANTATION, vol. 21, no. 4, 19 December 2005 (2005-12-19), pages 1130-1131, XP055138489, ISSN: 0931-0509, DOI: 10.1093/ndt/gfl039 the whole document -----	1-17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/044988

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