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

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2678255 C 2014/06/03

(11)(21) 2 678 255

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

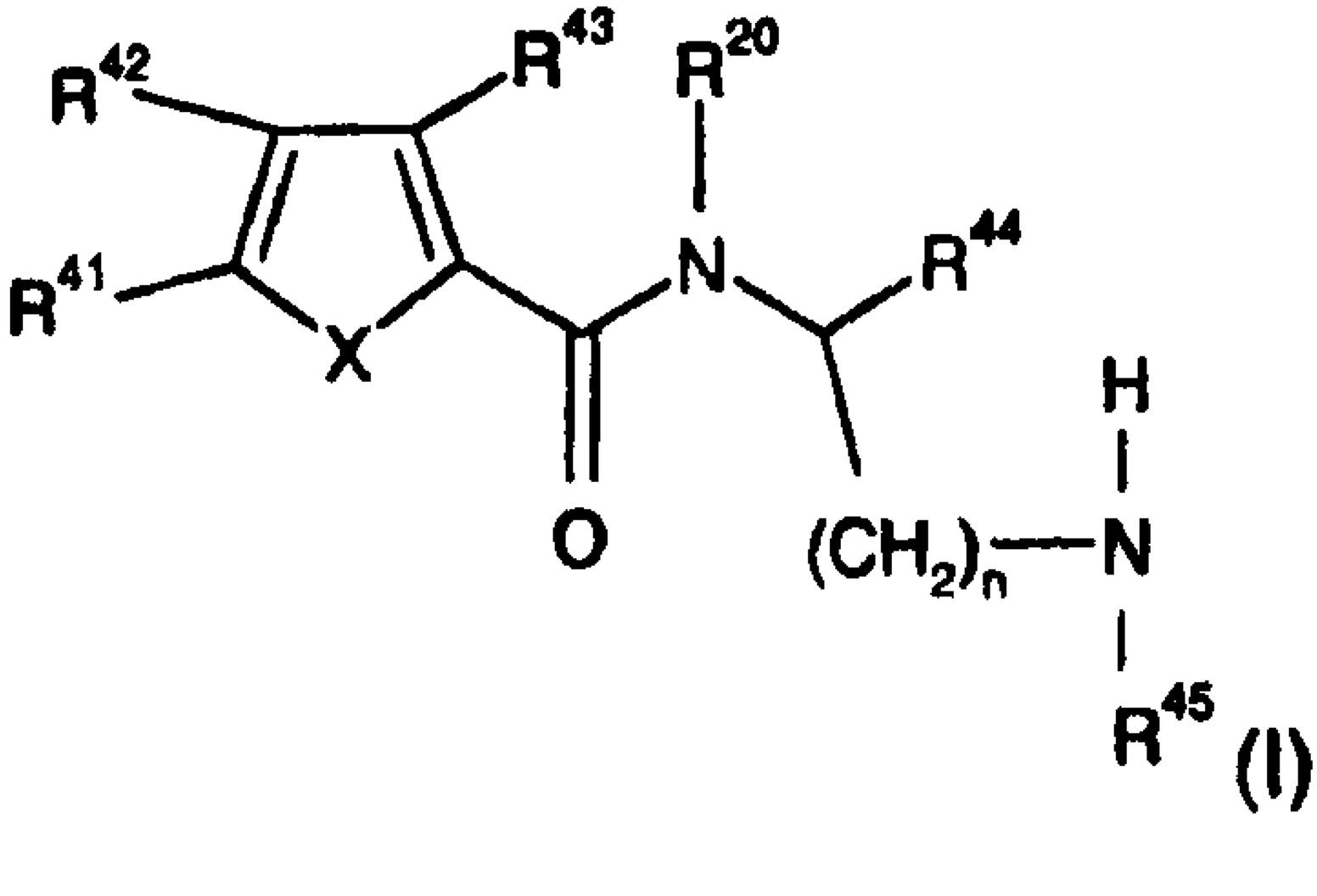
(86) Date de dépôt PCT/PCT Filing Date: 2008/02/07
(87) Date publication PCT/PCT Publication Date: 2008/08/14
(45) Date de délivrance/Issue Date: 2014/06/03
(85) Entrée phase nationale/National Entry: 2009/08/07
(86) N° demande PCT/PCT Application No.: US 2008/053269
(87) N° publication PCT/PCT Publication No.: 2008/098104
(30) Priorité/Priority: 2007/02/07 (US60/888,586)

(51) Cl.Int./Int.Cl. *C07D 409/04* (2006.01), *A61K 31/381* (2006.01), *A61K 31/4155* (2006.01), *A61P 35/00* (2006.01), *C07D 333/38* (2006.01), *C07D 405/04* (2006.01), *C07D 409/12* (2006.01), *C07D 409/14* (2006.01)

(72) Inventeurs/Inventors:
SEEFELD, MARK ANDREW, US;
ROUSE, MEAGAN B., US;
HEERDING, DIRK A., US;
PEACE, SIMON, GB;
YAMASHITA, DENNIS S., US;
MCNULTY, KENNETH C., US

(73) Propriétaire/Owner:

(54) Titre : INHIBITEURS DE L'ACTIVITE DE Akt
(54) Title: INHIBITORS OF Akt ACTIVITY



(I)

(57) Abrégé/Abstract:
Invented are novel heterocyclic carboxamide compounds, the use of such compounds as inhibitors of protein kinase B activity and in the treatment of cancer and arthritis.

CA 2678255 C 2014/06/03

(11)(21) 2 678 255

(13) C

(73) Propriétaires(suite)/Owners(continued):GLAXOSMITHKLINE LLC, US

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

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

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2008 (14.08.2008)

PCT

(10) International Publication Number
WO 2008/098104 A8

(51) International Patent Classification:
A61K 31/12 (2006.01)

(21) International Application Number:
PCT/US2008/053269

(22) International Filing Date: 7 February 2008 (07.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/888,586 7 February 2007 (07.02.2007) US

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SEEFELD, Mark, Andrew** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **ROUSE, Meagan, B.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **HEERDING, Dirk, A.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **PEACE, Simon** [GB/GB]; Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **YAMASHITA, Dennis, S.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **MCNULTY, Kenneth, C.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(74) Agents: **DUSTMAN, Wayne, J.** et al.; Glaxosmithkline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.o. Box 1539, King Of Prussia, PA 19406-0939 (US).

(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, BR, BW, BY, BZ, CA, CH, 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, IS, JP, KE, KG, KM, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, 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*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(48) Date of publication of this corrected version:
30 July 2009

(15) Information about Correction:
see Notice of 30 July 2009

(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: Invented are novel heterocyclic carboxamide compounds, the use of such compounds as inhibitors of protein kinase B activity and in the treatment of cancer and arthritis.

WO 2008/098104 A8

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	457

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	457

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

INHIBITORS OF Akt ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel heterocyclic carboxamide compounds, the use of such compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt) activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to heterocyclic carboxamide containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as protein kinase B), suitably the compounds of the invention are inhibitors of the activity of all three isoforms of the serine/threonine kinase, Akt. The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis (Liu et al. Current Opin. Pharmacology 3:317-22 (2003)).

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science,* 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science,* 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a

pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999). It was demonstrated that Akt-2 was over-expressed in 12% of ovarian carcinomas and that amplification of Akt was especially frequent in 50% of undifferentiated tumors, suggestion that Akt may also be associated with tumor aggressiveness (Bellacosa, e*t al., Int. J. Cancer*, 64, pp. 280-285, 1995). Increased Akt1 kinase activity has been reported in breast, ovarian and prostate cancers (Sun *et al. Am. J. Pathol. 159:* 431-7 (2001)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K

phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{3O8} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3 '-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)- P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. The compound UCN-01 is a reported inhibitor of PDK1. *Biochem. J.* 375(2):255 (2003). Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

Small molecule inhibitors of Akt are useful in the treatment of tumors, especially those with activated Akt (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of Akt and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. *et al. Annual Review of Biochemistry*, *70*: 247 (2001)), Cowden disease (Parsons, R.;

Simpson, L. *Methods in Molecular Biology (Totowa, NJ, United States)*, *222 (Tumor Suppressor Genes, Volume 1)*: 147 (2003)), and Lhermitte-Duclos disease (Backman, S. *et al. Current Opinion in Neurobiology*, *12(5)*: 516 (2002)). Akt3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and Akt2 is over-expressed in pancreatic and ovarian carcinomas. Akt1 is amplified in gastric cancers (Staal, *Proc. Natl. Acad. Sci.* USA *84*: 5034-7 (1987) and upregulated in breast cancers (Stal *et al. Breast Cancer Res. 5*: R37-R44 (2003)). Therefore a small molecule Akt inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. Akt inhibitors are also useful in combination with further chemotherapeutic and anticancer agents.

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

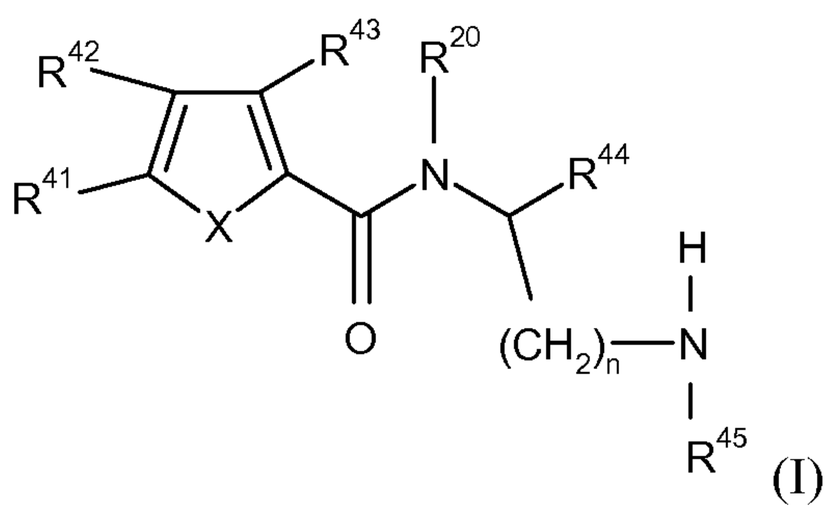
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

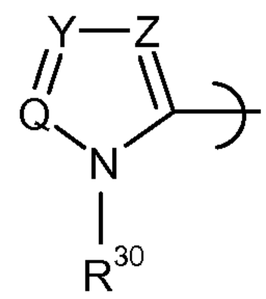
SUMMARY OF THE INVENTION

This invention relates to novel compounds of Formula (I):



(I)

wherein:



R^{41} and R^{42} are independently selected from: hydrogen, , halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan, substituted fruan, thiophene and substituted thiophene,

where Q and Y are independently selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at least one and at most 2 of Q, Y and Z are nitrogen, and R^{30} is selected from: C_{1-4}alkyl and C_{1-4}alkyl substituted with form one to three fluorine atoms,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cylcoalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan and thiophene;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAR$ wherein the AR is unsubstituted, $-(CR^{60}R^{61})_mAR$ wherein the AR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AR is a cyclic or polycyclic aromatic or saturated or unsaturated non-aromatic ring containing from 3 to 16 carbon atoms and optionally containing from one to three heteroatoms, provided that when the ring is aromatic and the number of carbon atoms is 3 the ring contains at least two

heteroatoms and when the ring is aromatic and the number of carbon atoms is 4 the ring contains at least one heteroatom, and

R^{60} and R^{61} are independently selected from: hydrogen and C_{1-4}alkyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are C_{1-4}alkyl,

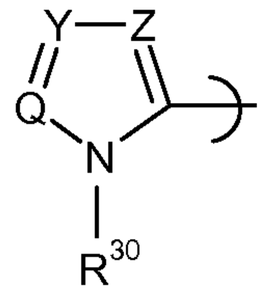
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, C_{1-4}alkyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and C_{1-4}alkyl; and

n is 0 to 2 and this moiety is optionally, if applicable, substituted by hydroxyC_{1-4}alkyl;

provided that one and only one of R^{41} and R^{42} is 

;

and/or pharmaceutically acceptable salts thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

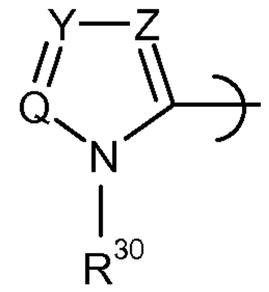
Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed herein inhibit each of the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those in which:

R^{41} and R^{42} are independently selected from: hydrogen,  , halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan, substituted fruan, thiophene and substituted thiophene,

where Q is nitrogen, Y is selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and

–C(R^{48})-, provided that at most one of Y and Z are nitrogen, and

R^{30} is selected from: C_{1-4}alkyl and C_{1-4}alkyl substituted with form one to three fluorine atoms,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cylcoalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan and thiophene;

R^{44} is absent or selected from: –($CR^{60}R^{61}$)$_m$AR wherein the AR is unsubstituted, –($CR^{60}R^{61}$)$_m$AR wherein the AR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AR is a cyclic or polycyclic aromatic or saturated or unsaturated non-aromatic ring containing from 3 to 16 carbon atoms and optionally containing from one to three heteroatoms, provided that when the ring is aromatic and the number of carbon atoms is 3 the ring contains at least two heteroatoms and when the ring is aromatic and the number of carbon atoms is 4 the ring contains at least one heteroatom, and R^{60} and R^{61} are independently selected from: hydrogen and C_{1-4}alkyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are C_{1-4}alkyl,

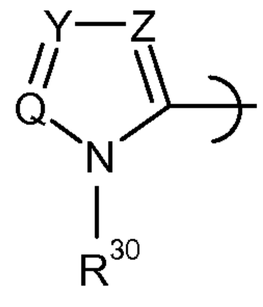
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, C_{1-4}alkyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and C_{1-4}alkyl; and

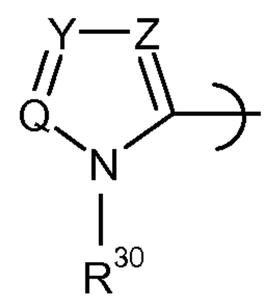
n is 0 to 2 and this moiety is optionally, if applicable, substituted by hydroxyC_{1-4}alkyl;

provided that one and only one of R^{41} and R^{42} is 

;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:

R^{41} and R^{42} are independently selected from: hydrogen, 

, halogen, C_{1-4}alkyl, trifluoromethyl, methoxy, furan and thiophene,

where Q is nitrogen, Y is selected from: nitrogen and –C(R^{70})-, and Z is selected from: nitrogen and –C(R^{48})-, provided that at most one of Y and Z are nitrogen, and

R^{30} is C_{1-4}alkyl,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, trifluoromethyl, aryl, heteroaryl, cylcoalkyl, heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl and methoxy;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAAR$ wherein the AAR is unsubstituted, $-(CR^{60}R^{61})_mAAR$ wherein the AAR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AAR is selected from phenyl, indole, naphthalene, pyridine and cyclohexyl, and

R^{60} and R^{61} are independently selected from: hydrogen and methyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are methyl,

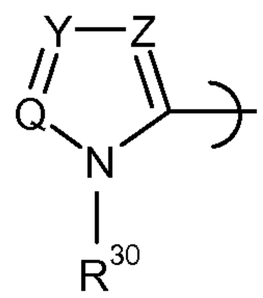
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, methyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and methyl; and

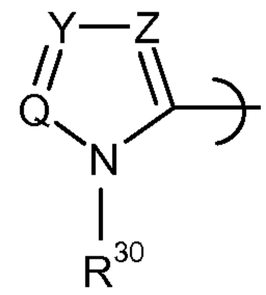
n is 1 to 2 and this moiety is optionally substituted by hydroxylmethyl;

provided that one and only one of R^{41} and R^{42} is 

;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:



R^{41} and R^{42} are independently selected from: hydrogen, halogen, C_{1-4}alkyl, trifluoromethyl, methoxy and furan,

where Q is nitrogen, Y is selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at most one of Y and Z are nitrogen, and

R^{30} is C_{1-4}alkyl,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, trifluoromethyl, phenyl, cylcopropyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl and methoxy;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAAR$ wherein the AAR is unsubstituted, $-(CR^{60}R^{61})_mAAR$ wherein the AAR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AAR is selected from phenyl, indole, naphthalene, pyridine and cyclohexyl, and

R^{60} and R^{61} are independently selected from: hydrogen and methyl,

provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are methyl,

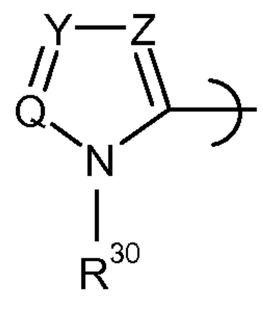
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, methyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and methyl; and

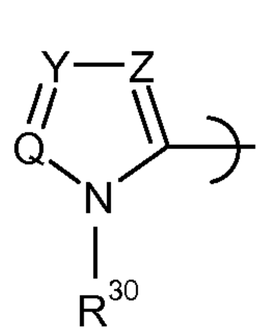
n is 1 to 2 and this moiety is optionally substituted by hydroxylmethyl;

provided that one and only one of R^{41} and R^{42} is  ;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:

R^{41} is selected from: chlorine, ethyl, methyl and methoxy;

R^{42} is  ,

where Q is nitrogen, Y is –CH- and Z is –C(R^{48})-, and

R^{30} is selected from methyl and ethyl,

where R^{48} is selected from: hydrogen, methyl, chlorine and bromine;

R^{43} is hydrogen;

R^{44} is $–CH_2$-phenyl wherein the phenyl is substituted by one or two substituents selected from fluorine and trifluoromethyl;

R^{45} is hydrogen;

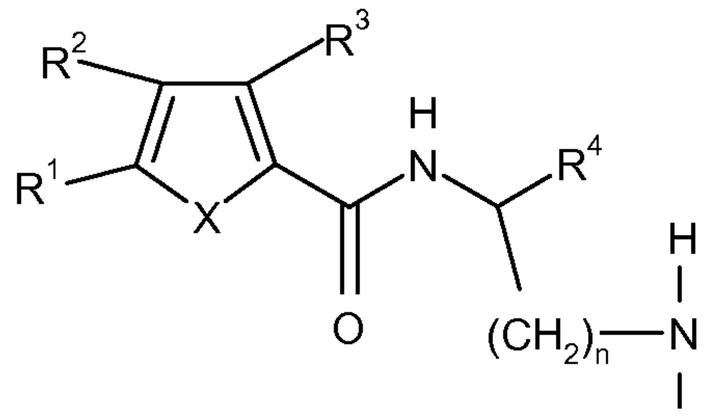
R^{20} is hydrogen;

X is selected from O and S; and

n is 1;

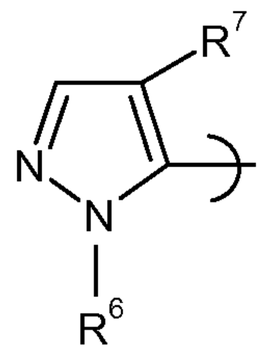
and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (AA):



(AA)

wherein:

R^1 and R^2 are independently selected from: hydrogen,  ,

halogen, C_{1-4}alkyl, furan and thiophene,

where R^6 is C_{1-4}alkyl and R^7 is selected from hydrogen, C_{1-4}alkyl and halogen;

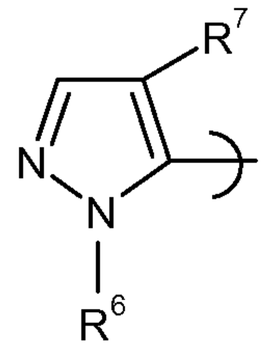
R^3 is selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^4 is selected from $-(CH_2)_m$aryl and $-(CH_2)_m$aryl wherein the aryl is substituted,
where m is 0 to 2;

R^5 is selected from hydrogen and C_{1-4}alkyl;

X is selected from O and S; and

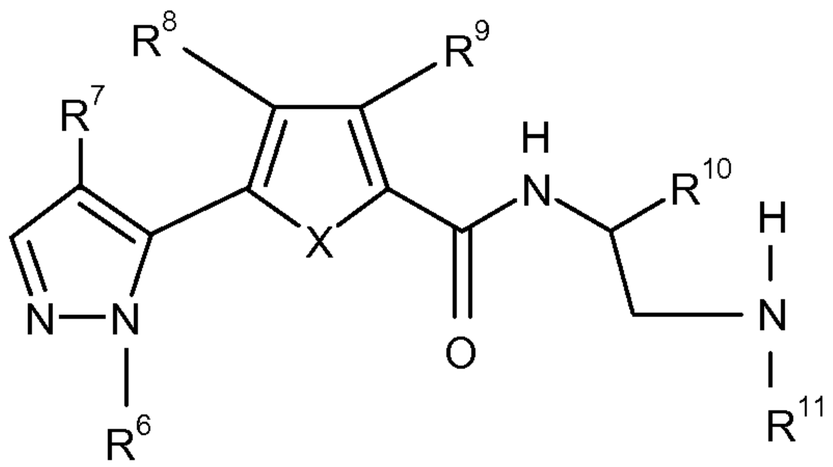
n is 0 to 2;

provided that one and only one of R^1 and R^2 is  and further

provided that at least one of R^1, R^2 and R^3 is hydrogen;

and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (BB):



(BB)

wherein:

R^8 and R^9 are independently selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^6 is C_{1-4}alkyl;

R^7 is selected from hydrogen, C_{1-4}alkyl and halogen;

R^{10} is selected from: $-(CH_2)_mC_5$-C_{12}aryl and $-(CH_2)_mC_5$-C_{12}aryl wherein the aryl is substituted,
where m is 0 to 2;

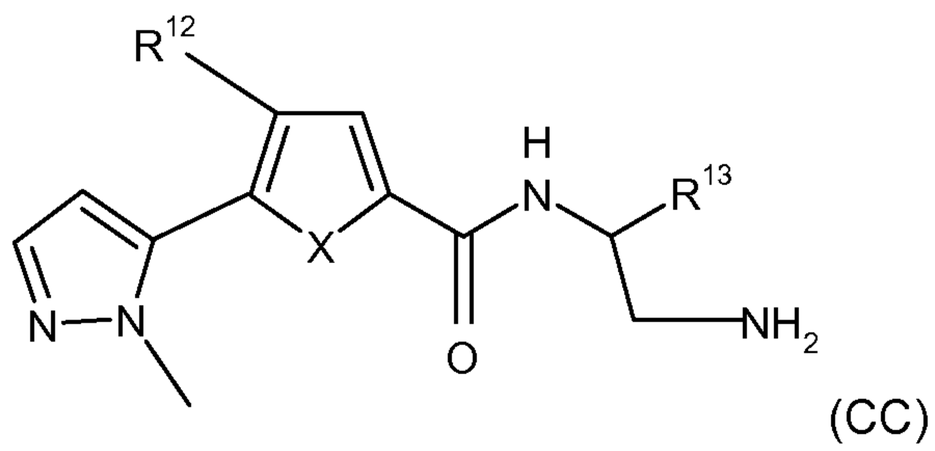
R^{11} is selected from hydrogen and C_{1-4}alkyl;

X is selected from O and S; and

provided that at least one of R^8 and R^9 is hydrogen;

and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (CC):



(CC)

wherein:

R^{12} is selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^{13} is selected from: $-(CH_2)_m$phenyl and $-(CH_2)_m$phenyl wherein the phenyl is substituted,

where m is 0 to 2;

X is selected from O and S; and

and/or pharmaceutically acceptable salts thereof.

Included among the compounds useful in the present invention are:

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(3-furanyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-N-[2-(methylamino)-1-phenylethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-(methylamino)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(1*H*-indol-3-ylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(3-amino-1-phenylpropyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(3-pyridinylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*R*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-aminoethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-methylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[3-(trifluoromethyl)phenyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1*S*)-1-(aminomethyl)-3-methylbutyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

(*N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-1,2,3-triazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*,2*S*)-2-amino-3-hydroxy-1-phenylpropyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide; and

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

and/or pharmaceutically acceptable salts thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also, it is understood that all tautomers and mixtures of tautomers are included within the scope of the compounds of Formula (I).

Certain compounds described herein may form a solvate which is understood to be a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula I a salt thereof) and a solvent. Such solvents for

the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

By the term "aryl", and derivatives thereof, used alone or as part of a larger moiety as in "–$(CH_2)_m$aryl" as used herein, unless otherwise defined, is meant monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring system is aromatic and wherein each ring in the system contains 3 to 7 members, such as phenyl, naphthalene, tetrahydronaphthalene and biphenyl.

Suitably, by the term "aryl" is meant a monocyclic aromatic ring system having a total of five to 7 ring members.

By the term "heteroaryl", and derivatives thereof, used alone or as part of a larger moiety as in "–$(CH_2)_m$heteroaryl" as used herein, unless otherwise defined, is meant a cyclic aromatic ring containing from 3 to 7 carbon atoms and containing from one to 3 heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms. Exemplary "heteroaryl" groups include pyridine and indole.

By the term " cycloalkyl", and derivatives thereof, used alone or as part of a larger moiety as in "–$(CH_2)_m$cycloalkyl" as used herein, unless otherwise defined, is meant a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms. Exemplary "cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

By the term "heterocycloalkyl", and derivatives thereof, used alone or as part of a larger moiety as in "–$(CH_2)_m$heterocycloalkyl" as used herein, unless otherwise defined, is meant a non-aromatic cyclic hydrocarbon ring having from three to six carbon atoms and containing 1 or 2 heteroatoms. Exemplary "cycloalkyl" groups include piperazine and pyrrolidine.

By the term "C_5-C_{12}aryl", used alone or as part of a larger moiety as in "–$(CH_2)_m$$C_5$-$C_{12}$aryl", as used herein, is meant an aromatic group selected from: phenyl, naphthalene, tehrahydronaphthanlene and biphenyl.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has from one to five substituents, suitably from one to three substituents, selected from the group consisting of: -CO_2R^{20}, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkyloxy, amino, C_1-C_4alkylamino, aminoC_1-C_4alkyl,

diC_1-C_4alkylamino, hydroxy, nitro, tetrazole, cyano, oxo, halogen and trifluoromethyl, where R^{20} is selected form hydrogen, C_1-C_4alkyl, and trifluoromethyl.

Suitably, the term “substituted” as used herein is meant that the subject chemical moiety has from one to three substituents, selected from the group consisting of: C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkyloxy, amino, C_1-C_4alkylamino, aminoC_1-C_4alkyl, hydroxy, tetrazole, halogen and trifluoromethyl.

Suitably, the term “substituted” as used herein is meant that the subject chemical moiety has from one to three substituents, selected from the group consisting of: halogen and trifluoromethyl.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein, including alkyl chains defined by the term “-$(CH_2)_n$”, “-$(CH_2)_m$” and the like, is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl as used herein include: -CH_3, -CH_2-CH_3, -CH_2-CH_2-CH_3, -$CH(CH_3)_2$, -CH_2-CH_2-$C(CH_3)_3$, -C≡C-$C(CH_3)_3$, -$C(CH_3)_3$, -$(CH_2)_3$-CH_3, -CH_2-$CH(CH_3)_2$, -$CH(CH_3)$-CH_2-CH_3, -CH=CH_2, and -C≡C-CH_3.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.

As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term “therapeutically effective amount” and derivatives thereof means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

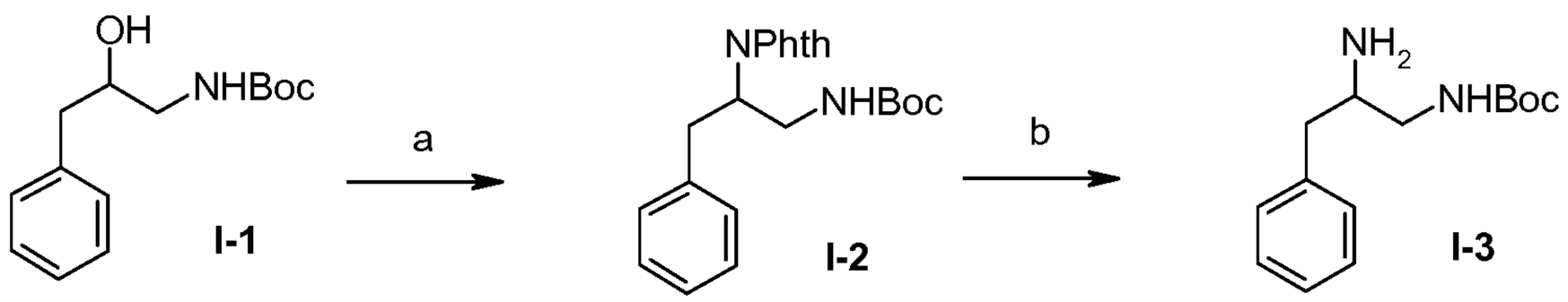
Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The pharmaceutically acceptable salts of the compounds of the invention are readily prepared by those of skill in the art.

The novel compounds of Formulas (I), (AA), (BB) and (CC) are generally prepared as shown in Schemes 1 to 3 below, or by analogous methods, provided the X and 'R' substituents in Formulas (I), (AA), (BB) and (CC) respectively do not include any such substituents that render inoperative the processes of any of Schemes 1 to 3. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

General Schemes

Scheme 1



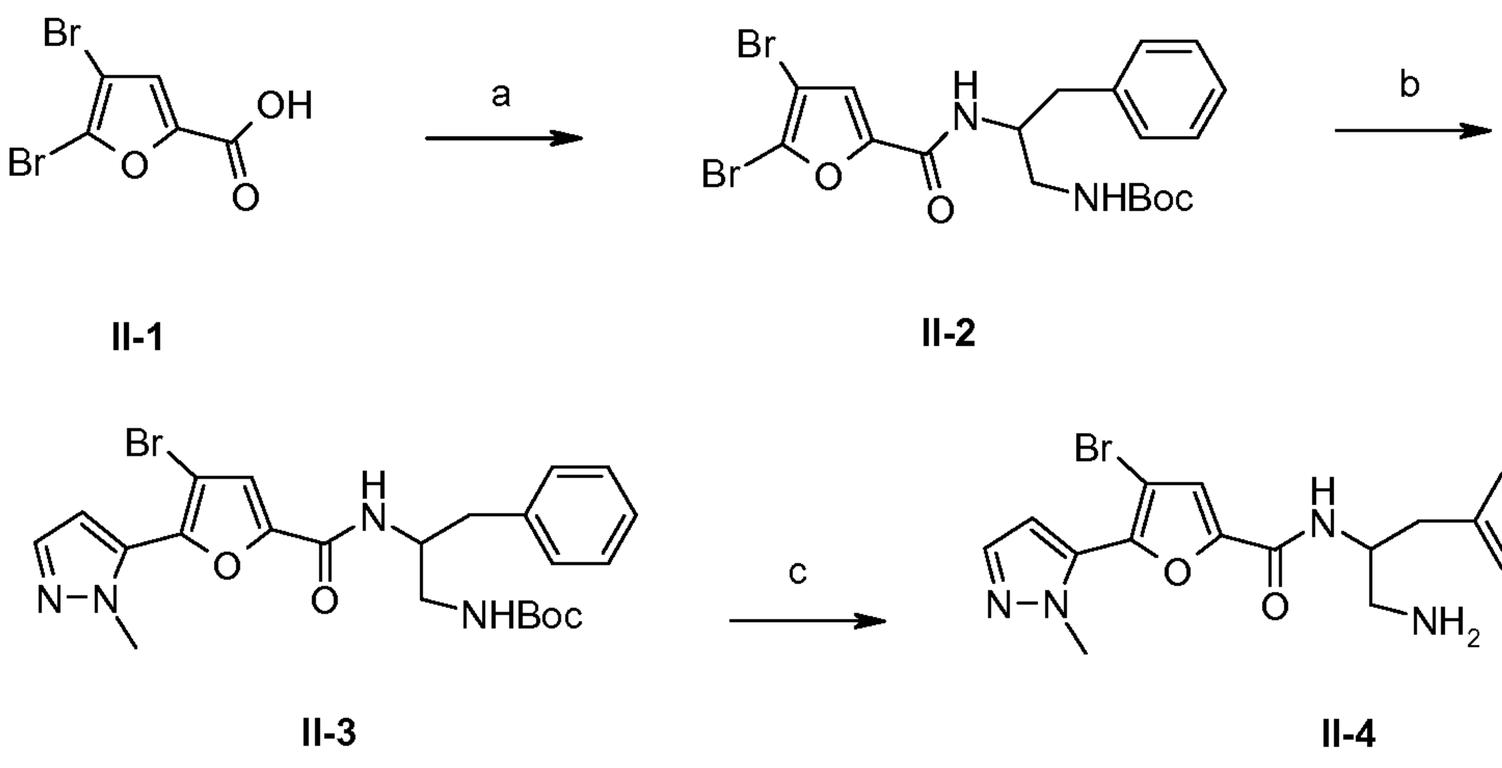
I-1 I-2 I-3

Reagents: (a) Phthalimide, PPh_3, DEAD, THF, RT; (b) NH_2NH_2, MeOH, 50 °C.

Amino alcohol (**I-1**) was reacted under Mitsunobu conditions to provide the differentially protected diamine (**I-2**). Mitsunobu reactions are well know to those skilled in the art of organic synthesis. Methods and reaction conditions for such transformations are discussed in *Synthesis* **1981**, 1-28. Selective deprotection of the phthalimide group of (**I-2**) using a nucleophilic amine such as hydrazine or methyl amine in a polar solvent such as methanol, afforded amine (**I-3**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods for

the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

Scheme 2

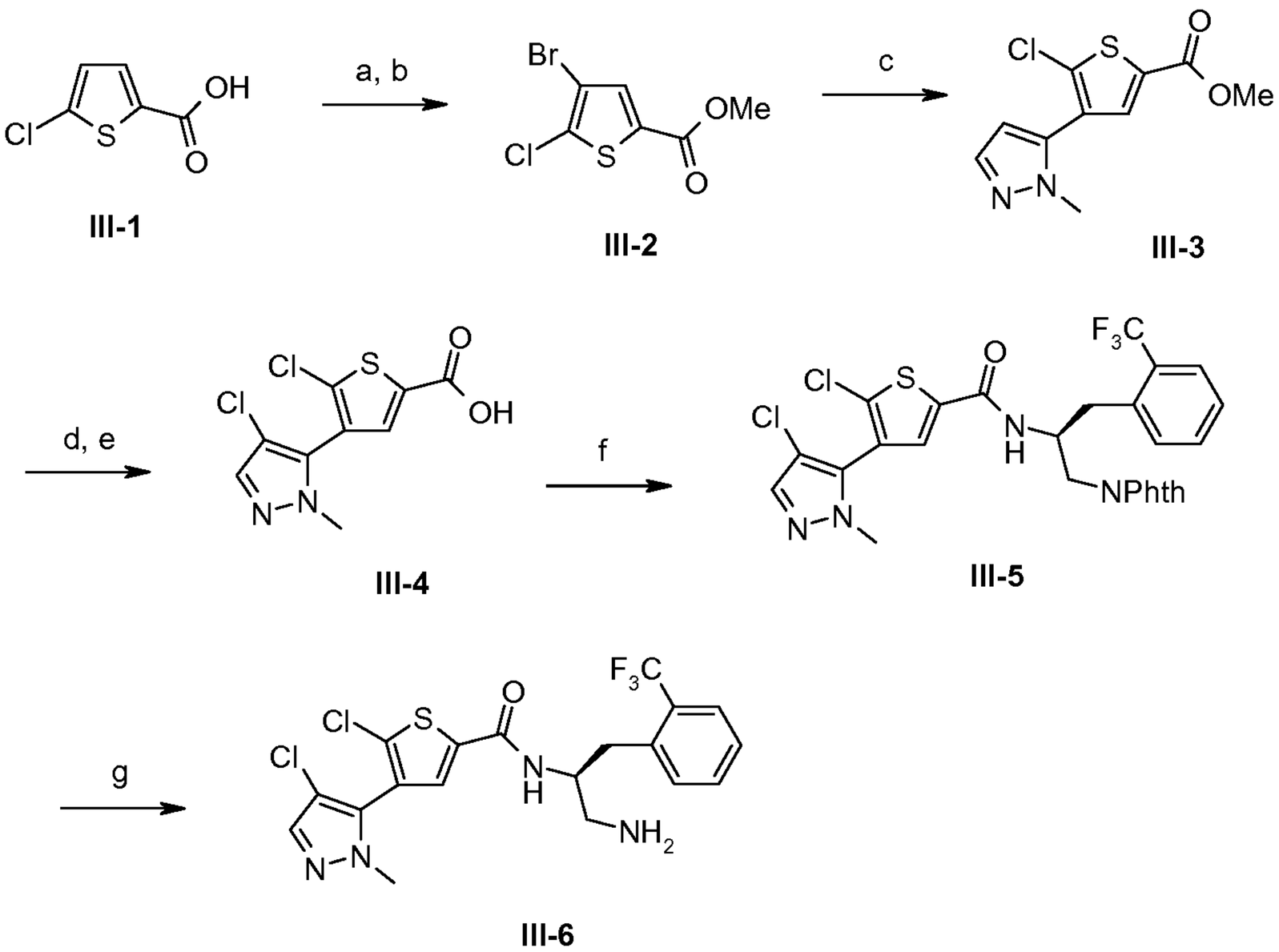


Reagents: (a) PyBrop, $(i\text{-}Pr)_2NEt$, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate, DCM, RT; (b) 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O; (c) TFA / DCM, RT.

Carboxylic acid (**II-1**) was reacted with 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate to form amide (**II-2**). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et_3N or $(i\text{-}Pr)_2NEt$. Dibromide (**II-2**) was regioselectively coupled with 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate using a Suzuki coupling procedure. Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF. Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Acidic treatment of **II-3** with HCl or TFA to remove the Boc protecting group produced amine (**II-4**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods

for the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

Scheme 3



Reagents: (a) MeOH, H_2SO_4, 60°C; (b) $AlCl_3$, Br_2, $CHCl_3$; (c) 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole, K_2CO_3, $Pd_2(t\text{-}Bu)_3$, dioxane/H_2O, 70°C; (d) NCS, THF, 70°C; (e) 6M NaOH, THF/MeOH, 50°C; (f) PyBrop, $(i\text{-}Pr)_2NEt$, 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione, DCM, RT; (g) NH_2NH_2, THF/MeOH, RT.

Carboxylic acid (**III-1**) was esterified under standard Fisher esterification conditions and then selectively halogenated with the aid of a Lewis acid to give (**III-2**). The dihalogenated ester was selectively coupled with 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole using Suzuki coupling chemistry to give (**III-3**). Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF.

Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Ester (**III-3**) was chlorinated using NCS and *in situ* saponified using aqueous NaOH. The resulting carboxylic acid (**III-4**) was coupled with 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione to form amide (**III-5**). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et_3N or $(i\text{-}Pr)_2NEt$. Amide (**III-5**) was deprotected using hydrazine to give amine (**III-6**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods for the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines,

alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented AKT inhibiting compounds are chemotherapeutic agents.

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5β,20-epoxy-1,2α,4,7β,10β,13α-hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem, Soc., 93:2325. 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl, Acad, Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol, Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I. Kingston *et al*., Studies in Organic Chemistry vol. 26, entitled “New trends in Natural Products Chemistry 1986”, Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and

Medicine, 64:583, 1991; McGuire et al., Ann. Intem, Med., 111:273,1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable

solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia, nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is

indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal

injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in

children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia,

thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

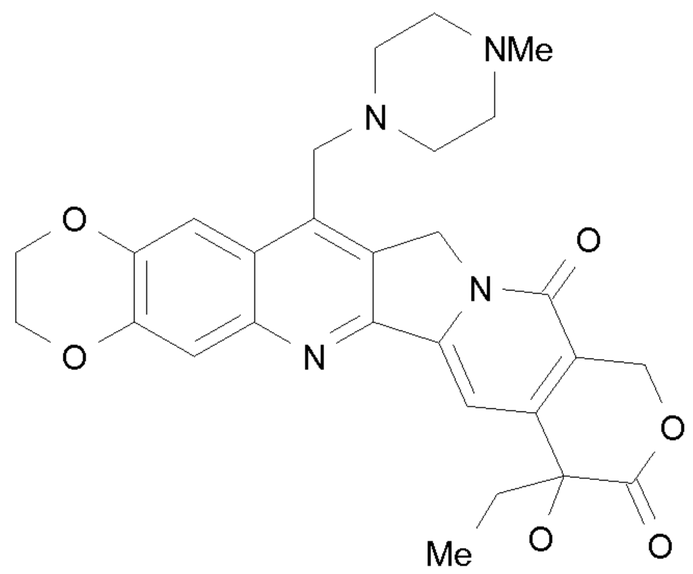
Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I: DNA: irintecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of

the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

Also of interest, is the camptothecin derivative of formula A following, currently under development, including the racemic mixture (R,S) form as well as the R and S enantiomers:



A

known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer). Such compound as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the

treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor –I (IGFI) receptor, macrophage

colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases for use in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku may also be useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

Also of interest in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases, Breast Cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also be useful in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Accordingly, non-receptor tyrosine

kinase inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($alpha_v$ $beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed compounds. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). There are a number of immunologic strategies to generate an immune response. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al. (2000), J. Clin. Oncol. 18: 1812-1823; and Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

Because the pharmaceutically active compounds of the present invention are active as AKT inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, breast, pancreatic and prostate.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

His-tagged AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine

residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y = ((Vmax * x) / (K + x)) where Vmax is the upper asymptote and K is the IC50.

Cloning of full-length human (FL) AKT1:

Full-length human AKT1 gene was amplified by PCR from a plasmid containing myristylated-AKT1-ER (gift from Robert T. Abraham, Duke University under MTA, described in Klippel et al. in Molecular and Cellular Biology 1998 Volume 18 p.5699) using the 5' primer: SEQ.ID NO: 2, 5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: SEQ.ID NO: 3, AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site and the 3'primer included an XhoI site for cloning purposes. The resultant PCR product was subcloned in pcDNA3 as a BamHI / XhoI fragment. A mutation in the sequence (TGC) coding for a Cysteine^{25} was converted to the wild-type AKT1 sequence (CGC) coding for an Arginine^{25} by site-directed mutagenesis using the QuikChange® Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic primer: SEQ.ID NO: 4, 5' ACCTGGCGGCCACGCTACTTCCTCC and selection primer: SEQ.ID NO: 5, 5' CTCGAGCATGCAACTAGAGGGCC (designed to destroy

an XbaI site in the multiple cloning site of pcDNA3) were used according to manufacturer's suggestions. For expression/purification purposes, AKT1 was isolated as a BamHI / XhoI fragment and cloned into the BamHI / XhoI sites of pFastbacHTb (Invitrogen).

Expression of FL human AKT1:

Expression was done using the BAC-to-BAC Baculovirus Expression System from Invitrogen (catalog # 10359-016). Briefly 1) the cDNA was transferred from the FastBac vector into bacmid DNA, 2) the bacmid DNA was isolated and used to transfect Sf9 insect cells, 3) the virus was produced in Sf9 cells, 4) T. ni cells were infected with this virus and sent for purification.

Purification of FL human AKT1:

For the purification of full-length AKT1, 130 g sf9 cells (batch # 41646W02) were resuspended in lysis buffer (buffer A, 1L, pH 7.5) containing 25 mM HEPES, 100 mM NaCl, and 20 mM imidazole. The cell lysis was carried out by Avestin (2 passes at 15K-20K psi). Cell debris was removed by centrifuging at 16K rpm for 1 hour and the supernatant was batch bound to 10 ml Nickel Sepharose HP beads at 4 C for over night. The beads were then transferred to column and the bound material was eluted with buffer B (25 mM HEPES, 100 mM NaCl, 300 mM imidazole, pH 7.5). AKT eluting fractions were pooled and diluted 3 fold using buffer C (25 mM HEPES, 5 mM DTT; pH 7.5). The sample was filtered and chromatographed over a 10 mL Q-HP column pre-equilibrated with buffer C at 2 mL/min.

The Q-HP column was washed with 3 column volume (CV) of buffer C, then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl, 5 mM DTT; pH 7.5. 5 mL fractions collected. AKT containing fractions were pooled and concentrated to 5 ml. The protein was next loaded to a 120 ml Superdex 75 sizing column that was pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 5 mM DTT; pH 7.5. 2.5 mL fractions were collected.

AKT 1 eluting fractions were pooled, aliquoted (1 ml) and stored at –80C. Mass spec and SDS-PAGE analysis were used to confirm purity and identity of the purified full-length AKT1.

Full length AKT2 and full length AKT3 were cloned, expressed and purified in a similar fashion.

AKT Enzyme Assay

Compounds of the present invention are tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation is detected by the following procedure:

Assays are performed in 384well U-bottom white plates. 10 nM activated AKT enzyme is incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction is stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate is sealed, the beads are allowed to settle overnight, and then the plate is counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses are plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y = ((Vmax * x) / (K + x)) where Vmax is the upper asymptote and K is the IC50.

Compounds of the invention are tested for activity against AKT1, AKT2, and AKT3 in one or more of the above assays.

The majority of the compounds of the Examples were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: ≥ 5.9 against full length AKT1; ≥ 5.0 against full length AKT2; and ≥ 5.0 against full length AKT3.

The compounds of Examples 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 and 259 were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: ≥ 8.6 against full length AKT1; and ≥ 7.5 against full length AKT2. The majority of the compounds of Examples 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 and 259 were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value; ≥ 7.6 against full length AKT3.

The compound of Example 96 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 9.0 against full length AKT1; equal to 8.0 against full length AKT2; and equal to 8.8 against full length AKT3.

The compound of Example 137 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 9.0 against full length AKT1; equal to 7.8 against full length AKT2; and equal to 8.4 against full length AKT3.

The compound of Example 224 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 8.7 against full length AKT1; and equal to 7.8 against full length AKT2.

The compound of Example 161 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 8.8 against full length AKT1; equal to 7.5 against full length AKT2; and equal to 7.6 against full length AKT3.

The compound of Example 222 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 8.8 against full length AKT1; and equal to 7.9 against full length AKT2; and equal to 8.5 against full length AKT3.

In the above data, pIC50 is defined as -log(IC50) where the IC50 value is expressed in molar units.

The pharmaceutically active compounds within the scope of this invention are useful as AKT inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT inhibition, which comprises administering an effective compound of Formula (I) and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages, is preferred.

Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

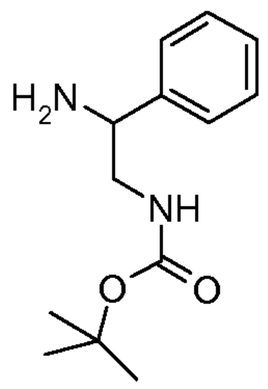
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

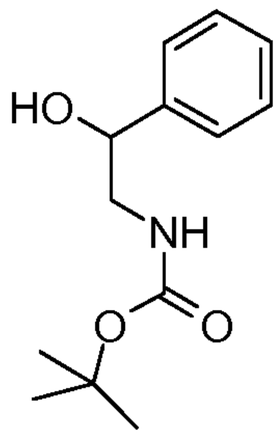
The compounds of Examples 1 to 328 are readily made according to Schemes 1 to 3 or by analogous methods.

Preparation 1

Preparation of 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate

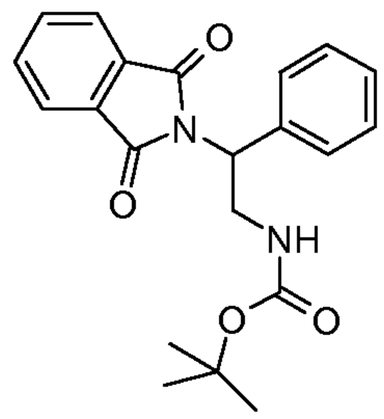


a) 1,1-dimethylethyl (2-hydroxy-2-phenylethyl)carbamate



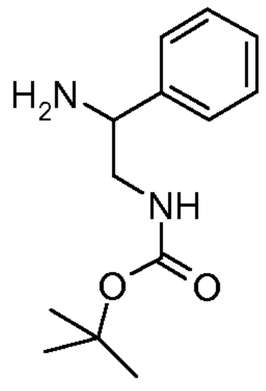
To a solution of 2-amino-1-phenylethanol (5 g, 36.4 mmol) in THF (182 mL) at 25 °C was added Boc_2O (8.7 g, 40.1 mmol) in one portion. After 0.5h, the solution was concentrated and the residue used directly without further purification: LC-MS (ES) m/z = 238 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-phenylethyl]carbamate



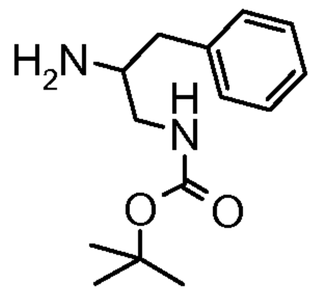
To a solution of 1,1-dimethylethyl (2-hydroxy-2-phenylethyl)carbamate (2 g, 8.44 mmol), phthalimide (1 g, 7.03 mmol) and triphenylphosphine (2.76 g, 10.5 mmol) in THF (35 mL) at 25 °C was added DEAD (1.7 mL, 10.5 mmol) dropwise. After 0.5h, the solution was concentrated and purified via column chromatography (silica, 15 % EtOAc in hexanes) affording the title compound (2 g, 80%) as a white foam: LC-MS (ES) m/z = 367 $(M+H)^+$.

c) 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate



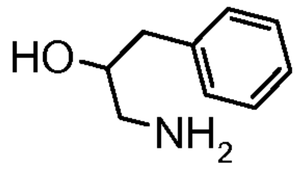
A solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-phenylethyl]carbamate (2 g, 5.46 mmol) and either $MeNH_2$ (40wt% in H_2O, 10eq.) or NH_2NH_2 (10eq.) in MeOH (0.5M, 10 mL) was heated to 60 °C in a sealed tube. After 12h, the solution was concentrated and purified via column chromatography (silica-dry load, 2% MeOH in DCM (1% NH_4OH)) affording the title compound (1.1 g, 85%) as a white solid: LC-MS (ES) m/z = 237 $(M+H)^+$.

Preparation 2



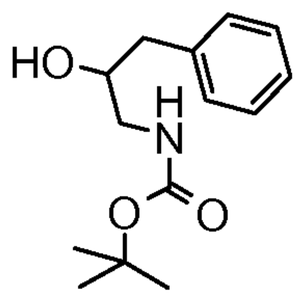
Preparation of 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate

a) 1-amino-3-phenyl-2-propanol



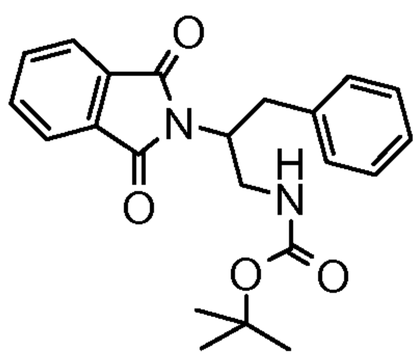
A solution of 2-(phenylmethyl)oxirane (7.5 g, 56.3 mmol) in NH_4OH (100 mL) was stirred at 25 °C in a sealed tube. After 12h, the solution was concentrated and used directly: LCMS (ES) m/e 152 $(M+H)^+$.

b) 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)carbamate



To a solution of 1-amino-3-phenyl-2-propanol (7.6 g, 50 mmole) in THF (50 mL) at RT was added $(Boc)_2O$ (12.0 g, 55 mmole). After stirring at RT for 2 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (5% MeOH in DCM (0.5% NH_4OH)) affording the title compound (13.1 g, 91%) as a clear yellow oil: LCMS (ES) m/z 252 $(M+H)^+$.

c) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]carbamate

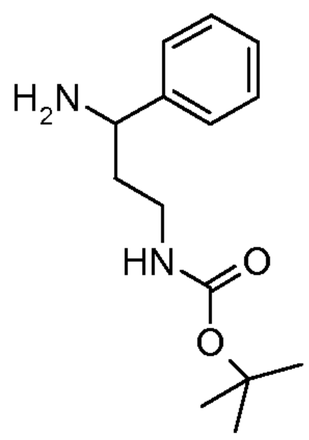


To a solution of 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)carbamate (10.0 g, 39.8 mmol), PPh_3 (12.5 g, 47.8 mmol) and phthalimide (6.44 g, 43.8 mmol) in THF (125 mL) at RT was added DEAD (9.4 mL, 59.7 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 2:1) to give the title compound as a white solid (12.6 g, 83%): LCMS (ES) m/z 381 $(M+H)^+$.

d) 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate

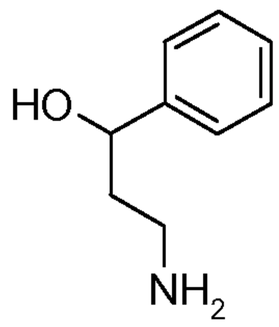
NH_2NH_2 (12.5 mL, 394 mmol) was added to a THF/MeOH (50mL / 50mL) solution of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (7.5 g, 19.7 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (3.75 g, 76%) as a white solid: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparation 3



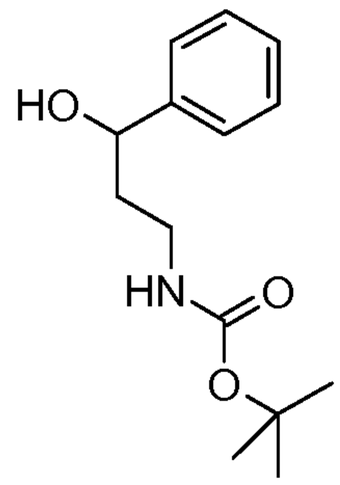
Preparation of 1,1-dimethylethyl (3-amino-3-phenylpropyl)carbamate

a) 3-amino-1-phenyl-1-propanol



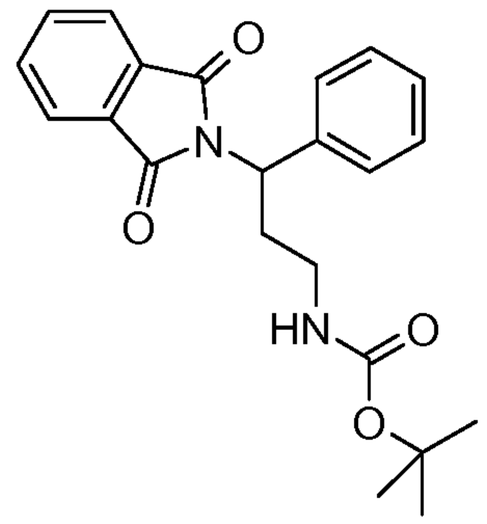
Benzoylacetonitrile (2 g, 13.8 mmol) in THF (35 mL) was added dropwise via addition funnel to a 0 °C solution of LAH (1.6 g, 41.3 mmol) in THF (35 mL). The resulting solution warmed to 25 °C and then was heated to 60 °C for an additional 2h. After cooling to 0 °C, a saturated solution of sodium potassium tartrate was added dropwise and the solution was extracted several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 5-8% MeOH in DCM (1% NH_4OH)) affording the amino alcohol (1.4 g, 67%) as a clear oil: LCMS (ES) m/z 152 $(M+H)^+$.

b) 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)carbamate



3-amino-1-phenyl-1-propanol (1.4 g, 9.27 mmol) was dissolved in THF (50 mL) and Boc_2O (2.4 g, 11.1 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through via silica (0.5-1% MeOH in DCM (1% NH_4OH)) affording the title compound (1.6 g, 69%) as a pale white solid: LCMS (ES) m/z 152 $(M+H)^+$.

c) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-phenylpropyl]carbamate



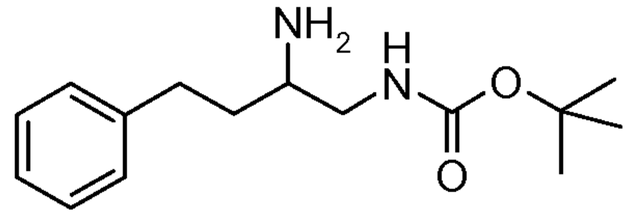
To a solution of 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)carbamate (3 g, 11.95 mmol), PPh_3 (4 g, 15.5 mmol) and phthalimide (1.8 g, 11.95 mmol) in THF (60 mL) at RT was added DEAD (2.4 mL, 15.5 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 4:1) to give the title compound as a white solid (2.2 g, 48%): LCMS (ES) m/z 381 $(M+H)^+$.

c) 1,1-dimethylethyl (3-amino-3-phenylpropyl)carbamate

NH_2NH_2 (1.8 mL, 57.7 mmol) was added to a THF/MeOH (1:1, 30 mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-phenylpropyl]carbamate (2.2 g, 5.79 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was

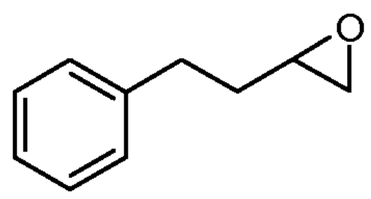
concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 1% NH_4OH to give the title compound (1.1 g, 76%) as a white solid: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparation 4



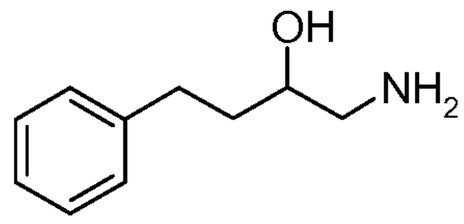
Preparation of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate

a) 2-(2-phenylethyl)oxirane



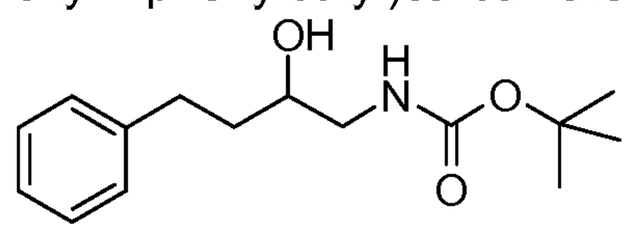
3-chlorobenzenecarboperoxoic acid (12.1 g, 54.0 mmol) is added in one portion to a solution of 3-buten-1-ylbenzene (7.15 g, 54.1 mmol) in CH_2Cl_2 at 0 °C followed by warming to 25 °C overnight. Saturated $NaHCO_3$ was added and the mixture separated and the resulting clear oil (8.0 g, quant.) was carried forward without further purification: LC-MS (ES) m/z = 149 $(M+H)^+$.

b) 1-amino-4-phenyl-2-butanol



2-(2-phenylethyl)oxirane (8.0 g, 54 mmol) was placed in a sealed tube with 7N NH_3-MeOH (130 mL) and stirred 2 hours at 70 °C followed by concentration to a clear oil (and was used without further purification in the following step.

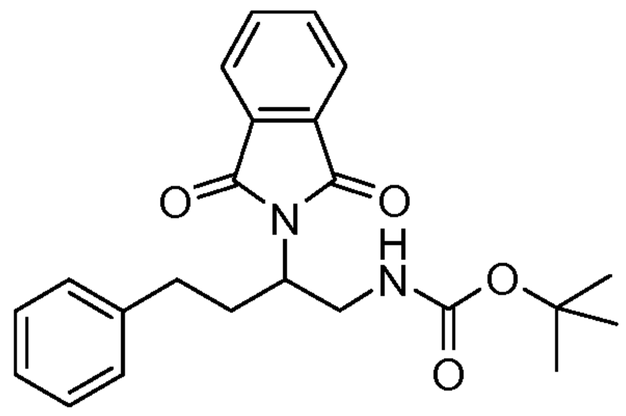
c) 1,1-dimethylethyl (2-hydroxy-4-phenylbutyl)carbamate



1-amino-4-phenyl-2-butanol (7.4 g, 50.0 mmol) was dissolved in THF (50 mL) and Boc_2O (13 g, 59.6 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through a silica plug (5% MeOH

in DCM (0.5% NH_4OH)) affording the title compound (13.1 g, 91%) as a clear yellow oil: LCMS (ES) m/z 266 $(M+H)^+$.

d) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-phenylbutyl]carbamate

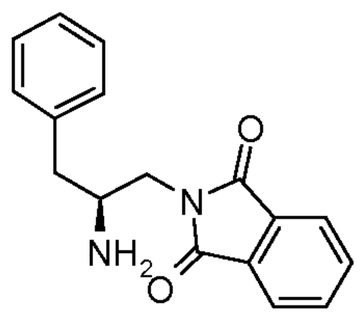


To a solution of 1,1-dimethylethyl (2-hydroxy-4-phenylbutyl)carbamate (3.0 g, 11.4 mmol), PPh_3 (3.6 g, 13.7 mmol) and phthalimide (1.84 g, 12.5 mmol) in THF (60 mL) at RT was added DEAD (1.8 mL, 11.4 mmol) over 5 min. After 0.5 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAC, 2:1) to give the title compound as a white solid (3.1 g, 69%): LCMS (ES) m/z 395 $(M+H)^+$.

e) 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate

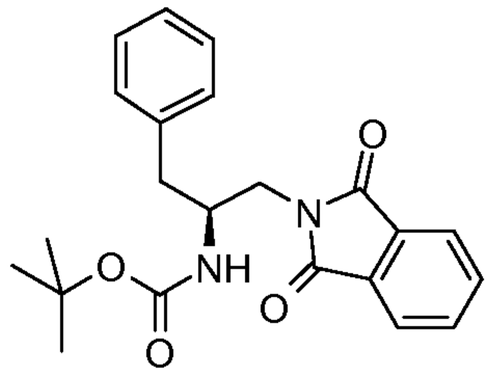
NH_2NH_2 (2.5 mL, 79.6 mmol) was added to a THF/MeOH (40mL/40mL) solution of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (3.1 g, 7.83 mmol) and stirred overnight. After 12 hours, the solution was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (1.4 g, 66%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 5



Preparation of 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione

a) 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]carbamate

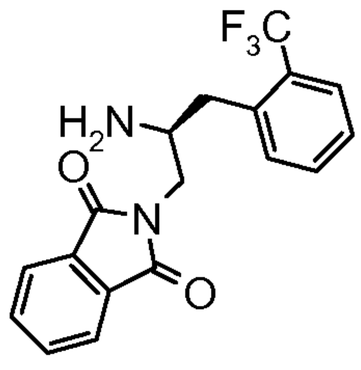


To a solution of (S)-(-)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol (3.0 g, 11.9 mmole), PPh_3 (3.74 g, 14.4 mmole) and phthalimide (1.93 g, 13.1 mmole) in THF (75 mL) at RT was added DEAD (2.8 mL, 17.8 mmole) over 5 min. After 1.5 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAC, 2:1) to give the title compound as a white solid (4.3 g, 95%): LCMS (ES) m/z 381 $(M+H)^+$.

b) 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione

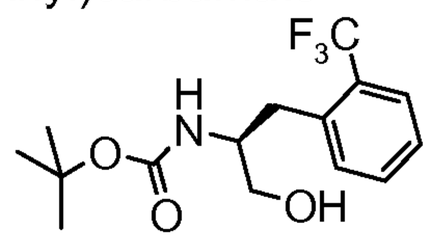
To a solution of 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]carbamate (4.3 g, 11.3 mmole) in MeOH (100 mL) at RT was added 4M HCl in dioxane (50 mL). After stirring for 3h at RT, the reaction solution was concentrated to a white solid (quant.) : LCMS (ES) m/z 281 $(M+H)^+$.

Preparation 6



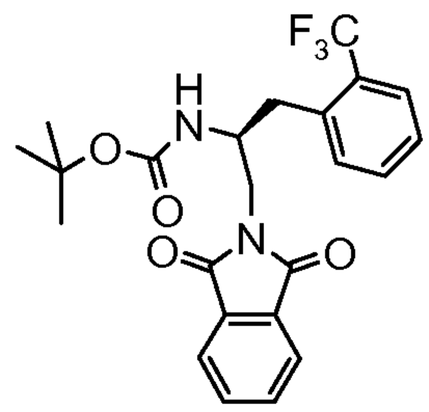
Preparation of 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione

a) 1,1-dimethylethyl ((1S)-2-hydroxy-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate



To a solution of N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine (5 g, 15 mmol) in THF (75 mL) at 0 °C stirred was added BH_3-THF (45 mL, 45 mmol-1M in THF). After 12h, the reaction was quenched with AcOH:MeOH (1:5, 24 mL) and partitioned between saturated aqueous $NaHCO_3$ and DCM. The aqueous phase was then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4 and used directly (4.2 g, 88%): LCMS (ES) m/e 320 $(M+H)^+$.

b) 1,1-dimethylethyl ((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate

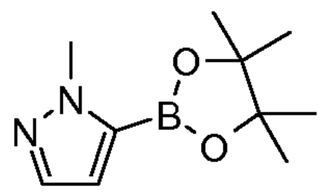


To a solution of 1,1-dimethylethyl ((1S)-2-hydroxy-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate (4.2 g, 13.2 mmol), triphenylphosphine (4.5 g, 17.1 mmol) and phthalimide (1.9 g, 13.2 mmol) in THF (66 mL) at 25 °C was added diethyl azodicarboxylate (2.7 mL, 17.1 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (1 % MeOH in DCM) affording the title compound (3.2 g, 54 %) as a white solid: LCMS (ES) m/z 449 $(M+H)^+$.

c) 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione

To a solution of 1,1-dimethylethyl ((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate (3.2 g, 7.1 mmol) in MeOH (35 mL) at RT was added 4M HCl in dioxane (18 mL). After 12h, the solution was concentrated affording the title compound (2.7 g, quant.) as the HCl salt: LCMS (ES) m/z 349 $(M+H)^+$.

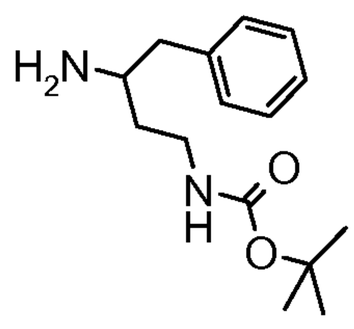
Preparation 7



Preparation of 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole

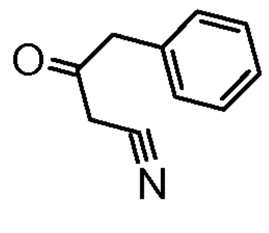
To a solution of 1-methyl pyrazole (4.1 g, 50 mmole) in THF (100 mL) at 0°C was added n-BuLi (2.2M in THF, 55 mmole). The reaction solution was stirred for 1 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem*. 41, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.3 mL, 60 mmole). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organic fractions were washed with H_2O (2 x 100 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a tan solid (8.0 g, 77%) which was used without further purification. LCMS (ES) m/z 127 $(M+H)^+$ for $[RB(OH)_2]$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1H), 6.75 (s, 1H), 4.16 (s, 3H), and 1.41 (s, 12H).

Preparation 8



Preparation of 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

a) 3-oxo-4-phenylbutanenitrile



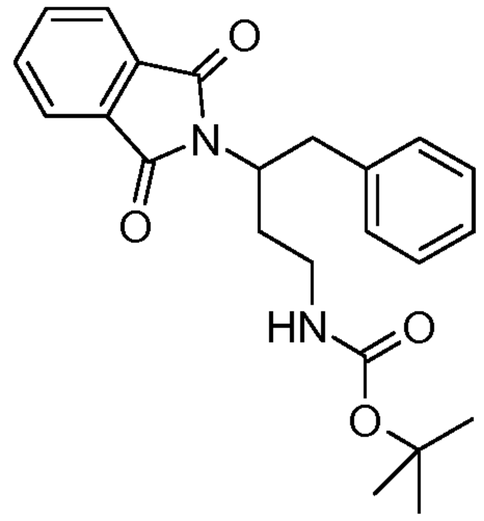
To a solution of cyanoacetic acid (2 g, 23.5 mmol) in THF (100 mL) at -78 °C was added nBuLi (10 mL, 25.9 mmol, 2.5M in hexanes). After 30min, phenylacetyl chloride (1.6 mL, 11.8 mmol) was added dropwise. Following an additional 30min, the solution was partitioned between 1N HCl-Et_2O and the aqueous phase was washed several times with Et_2O. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column

chromatography (silica, 30% EtOAc in hexanes) yielding the title compound (770 mg, 40%) as a tan oil: LCMS (ES) m/z 160 $(M+H)^+$.

b) 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

A solution of 3-oxo-4-phenylbutanenitrile (1.1 g, 6.92 mmol) in THF (10 mL) was added to a 0 °C solution of lithium aluminum hydride (787 mg, 20.8 mmol) in THF (25 mL). After 12h, the solution was quenched with H_2O (943 uL), 6N NaOH (716 uL) and H_2O (3.5 mL). The resulting precipitate was filtered and the pad was washed several times with DCM. The filtrate was concentrated then redissolved in THF (30 mL) and Boc_2O (1.5 g, 6.92 mmol) was added in one portion. After 30 min, the solution was concentrated and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound (1g, 55%-2steps) as an orange solid: LCMS (ES) m/z 265 $(M+H)^+$.

c) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-4-phenylbutyl]carbamate



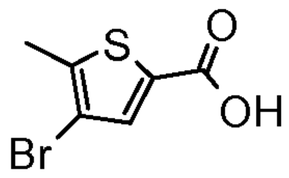
To a solution of 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate (1 g, 3.77 mmol), PPh_3 (1.3 g, 4.91 mmol) and phthalimide (555 mg, 3.77 mmol) in THF (18 mL) at RT was added DEAD (772 uL, 4.91 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 5:1) to give the title compound as a white solid (725 mg, 49%): LCMS (ES) m/z 395 $(M+H)^+$.

d) 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

NH_2NH_2 (577 uL, 18.4 mmol) was added to a THF/MeOH (1:1, 10 mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-4-

phenylbutyl]carbamate (725 mg, 1.84 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 1% NH_4OH to give the title compound (483 mg, quant.) as a white solid: LC-MS (ES) m/z = 264 $(M+H)^+$.

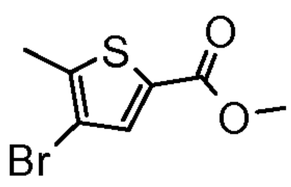
Preparation 9



Preparation of 4-bromo-5-methyl-2-thiophenecarboxylic acid

A solution of bromine (725 uL, 14.1 mmol) in AcOH (2.8 mL) was added dropwise to 5-methyl-2-thiophenecarboxylic acid (2 g, 14.1 mmol) and $FeCl_3$ (456 mg, 2.81 mmol) in AcOH (28 mL) at 25 °C. After 5h, the solution was poured onto ice and the precipitate was filtered and washed with water affording the title compound (3 g, quant.) as a yellow powder: LCMS (ES) m/z 222 $(M+H)^+$.

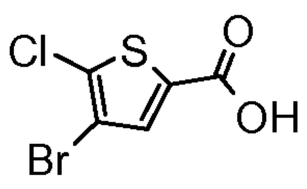
Preparation 10



Preparation of methyl 4-bromo-5-methyl-2-thiophenecarboxylate

A solution of 4-bromo-5-methyl-2-thiophenecarboxylic acid (3 g, 13.6 mmol) in MeOH (67 mL) and H_2SO_4 (3 mL) was stirred at 50 °C. After 12h, the solution was added to ice-H_2O and the pH was adjusted to ~11. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound (3 g, 94%) as an orange solid: LCMS (ES) m/z 236 (M+H)+.

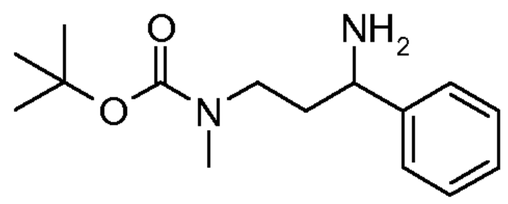
Preparation 11



Preparation of 4-bromo-5-chloro-2-thiophenecarboxylic acid

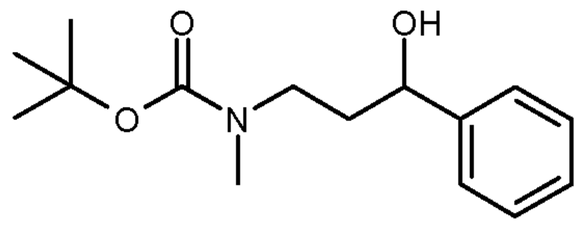
A solution of bromine (634 uL, 12.3 mmol) in AcOH (2.5 mL) was added dropwise to 5-chloro-2-thiophenecarboxylic acid (2 g, 12.3 mmol) and $FeCl_3$ (399 mg, 2.50 mmol) in AcOH (25 mL) at 25 °C. The reaction mixture was warmed to reflux where additional bromine (634 uL, 12.3 mmol) and $FeCl_3$ (399 mg, 2.50 mmol) were added. After 7d, the solution was poured onto ice and the precipitate was filtered and washed with water affording the title compound (3 g, quant.) as a yellow powder: LCMS (ES) m/z 242 $(M+H)^+$.

Preparation 12



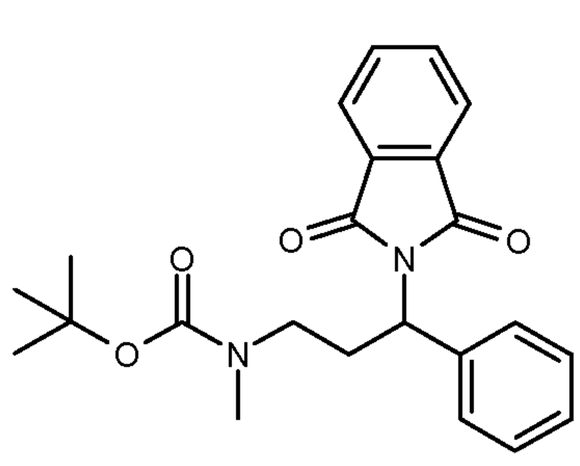
Preparation of 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate

a) 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)methylcarbamate



3-(methylamino)-1-phenyl-1-propanol (4.12 g, 24.9 mmol) was dissolved in THF (30 mL) and Boc_2O (1M/THF, 30 mL, 30 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through a silica plug (5% MeOH in DCM (0.5% NH_4OH)) affording the title compound (6.4 g, 97%) as a clear yellow oil: LCMS (ES) m/z 265 $(M+H)^+$.

b) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate

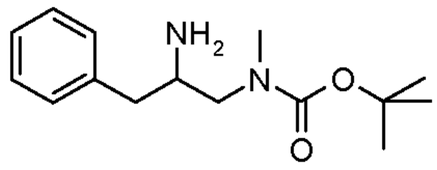


To a solution of 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)methylcarbamate (2.8 g, 10.4 mmol), PPh_3 (3.3 g, 12.7 mmol) and phthalimide (1.86 g, 12.6 mmol) in THF (50 mL) at RT was added DEAD (1.98 mL, 12.6 mmol) over 5 min. After 0.5 h at RT, MeOH (10 mL) was added and the reaction solution was absorbed onto silica and purified via chromatography (hexanes/EtOAC, 2:1) to give the title compound as a white solid (2.7 g, 65%): LCMS (ES) m/z 395 $(M+H)^+$.

c) 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate

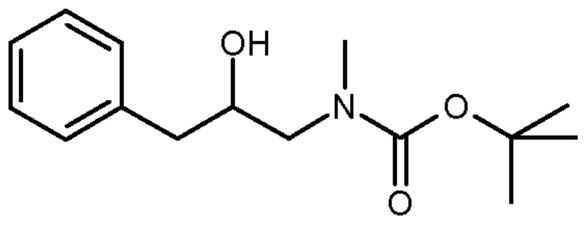
NH_2NH_2 (1.7 mL, 54.2 mmol) was added to a THF/MeOH (50mL/10mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate (2.7 g, 6.8 mmol) and stirred overnight. After 12 hours, the solution was absorbed onto silica and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (1.4 mg, 77%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 13



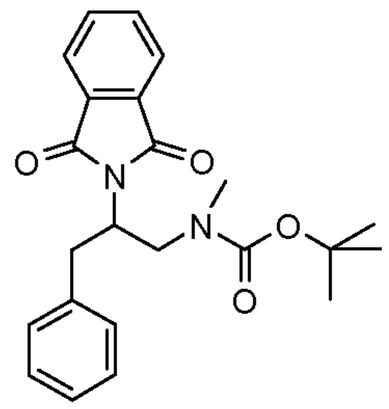
Preparation of 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate

a) 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)methylcarbamate



To a solution of 1-(methylamino)-3-phenyl-2-propanol (13 g, 78 mmol) [prepared according to Galons, H. et al *Eur. J. Med. Chem. Chim. Ther.* **1979** 14, 165-170.] in THF (390 mL) at RT was added $(Boc)_2O$ (21.6 g, 99 mmol). After stirring at RT for 2 h, the reaction solution was absorbed onto silica and purified via chromatography (35% EtOAc/Hex) affording the title compound (11.6 g, 56%) as a clear yellow oil: LCMS (ES) m/z 266 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate

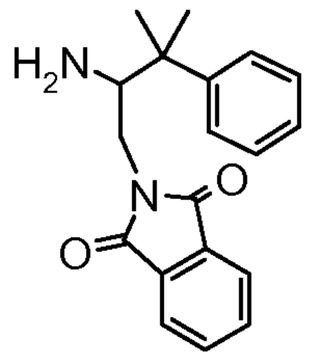


To a solution of 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)methylcarbamate (11.6 g, 43.72 mmol), PPh_3 (14.3 g, 54.5 mmol) and phthalimide (8.7 g, 59.1mmol) in THF (220 mL) at RT was added DEAD (8.5 mL, 54 mmol) over 15 min. After 0.5 h at RT, MeOH (10 mL) was added and the reaction solution was absorbed onto silica and purified via chromatography (hexanes/EtOAC, 2:1) to give the title compound as a white solid (9.97 g, 57%): LCMS (ES) m/z 395 $(M+H)^+$.

c) 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate

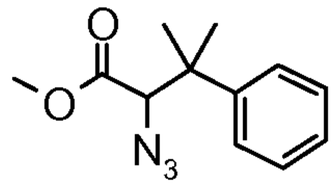
NH_2NH_2 (7 mL, 0.2 mol) was added to a THF/MeOH (100mL/25mL) solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate (2.7 g, 6.8 mmol) and stirred overnight. After 12 hours, the solution was absorbed onto silica and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (5.8 mg, 88%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 14



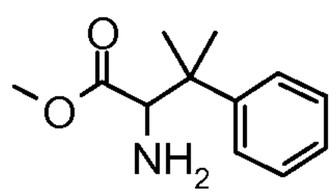
Preparation of 2-(2-amino-3-methyl-3-phenylbutyl)-1H-isoindole-1,3(2H)-dione

a) methyl 2-azido-3-methyl-3-phenylbutanoate



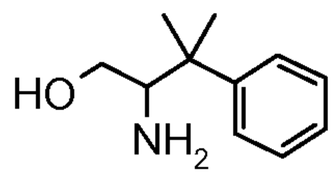
To a solution of KHMDS (36 mL, 17.9 mmol) in THF (70 mL) at -78 °C was added methyl 3-methyl-3-phenylbutanoate (3 g, 15.6 mmol) in THF (15 mL) dropwise. After 1h, trisylazide (5 g, 18.7 mmol) in THF (15 mL) was added dropwise over 10 min. After an additional 5 min, acetic acid (4.1 mL) was added and the reaction mixture warmed to 25 °C over 1h. The solution was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) yielding the title compound (2.6 g, 71%) contaminated with 33% methyl 3-methyl-3-phenylbutanoate to be purified out in the following steps: LCMS (ES) m/e 234 $(M+H)^+$.

b) methyl beta,beta-dimethylphenylalaninate



A solution of methyl 2-azido-3-methyl-3-phenylbutanoate (2.6 g, 11.2 mmol) and PPh_3 (4.4 g, 16.7 mmol) in H_2O (400 uL) and THF (100 mL) was stirred at 25 °C over 2d then at 50 °C for 12h. The solution was concentrated and purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) yielding the title compound (1.4 g, quant.): LCMS (ES) m/e 208 $(M+H)^+$.

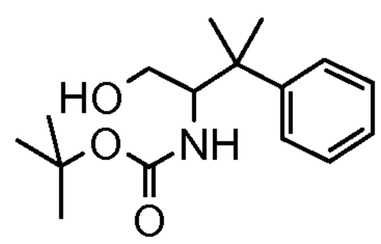
c) 2-amino-3-methyl-3-phenyl-1-butanol



To a solution of methyl beta,beta-dimethylphenylalaninate (1.4 g, 6.76 mmol) in THF (20 mL) at 0 °C was added dropwise a solution of lithium aluminum hydride (384 mg, 10.1 mmol) in THF (10 mL). After warming to 25 °C over 12h, the solution was quenched by sequential addition of H_2O (659 uL), 6N NaOH (500 uL) and H_2O (2.4 mL). The resulting precipitate was filtered and the pad washed thoroughly with DCM. The filtrate was concentrated and purified via column

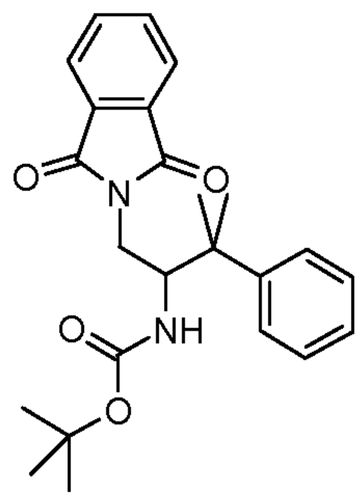
chromatography (silica, 2-5% MeOH in DCM (1% NH_4OH)) yielding the title compound (770 mg, 64%): LCMS (ES) m/e 179 $(M+H)^+$.

d) 1,1-dimethylethyl [1-(hydroxymethyl)-2-methyl-2-phenylpropyl]carbamate



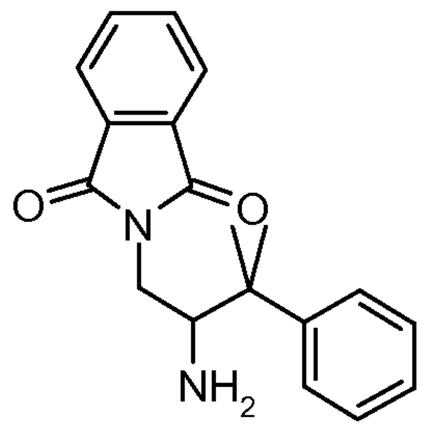
Boc_2O (1 g, 4.76 mmol) was added in one portion to 2-amino-3-methyl-3-phenyl-1-butanol (770 mg, 4.33 mmol) in THF (20 mL) at 25 °C. After 30 min, the solution was concentrated yielding the title compound (1.2 g, quant.) as a white solid which was used without further purification: LCMS (ES) m/e 279 (M+H)+.

e) 1,1-dimethylethyl {1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2-methyl-2-phenylpropyl}carbamate



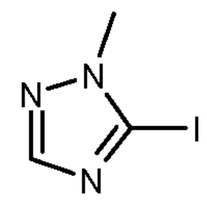
To a solution of 1,1-dimethylethyl [1-(hydroxymethyl)-2-methyl-2-phenylpropyl]carbamate (775 mg, 2.8 mmol), triphenylphosphine (915 mg, 3.5 mmol) and phthalimide (499 mg, 3.4 mmol) in THF (15 mL) at 25 °C was added diethyl azodicarboxylate (0.54 mL, 3.4 mmol). After stirring at RT for 1 h, MeOH was added (5 mL) and the solution was adsorbed onto silica and purified via column chromatography (1 % MeOH in DCM) affording the title compound (723 mg, 64 %) as a white solid: LCMS (ES) m/z 409 $(M+H)^+$.

f) 2-(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione



To a solution of 1,1-dimethylethyl {1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2-methyl-2-phenylpropyl}carbamate (723 mg, 1.77 mmol) in $CHCl_3$:MeOH (10:1, 55 mL) at RT was added 4M HCl in dioxane (10 mL). After stirring for 3h at RT, the reaction solution was concentrated to a white solid (quant.): LCMS (ES) m/z 309 $(M+H)^+$.

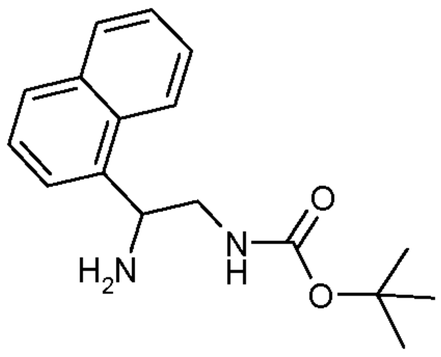
Preparation 15



Preparation of 5-iodo-1-methyl-1*H*-1,2,4-triazole

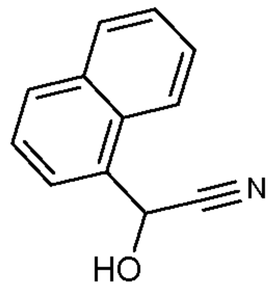
1-methyl-1*H*-1,2,4-triazole (2.05 g, 24.7 mmol) was added slowly over 15 minutes to an Et_2O solution of nBuLi at -70 °C. The mixture was stirred for 60 minutes at -70 °C and allowed to warm to -30 °C. A solution of I_2 (6.5 g, 25.6 mmol) in THF (27 mL) was added slowly over 15 minutes and the mixture was allowed to warm to room temperature and stir for 60 minutes. The mixture was partitioned with saturated $Na_2S_2O_3$, the phases were separated and the organic solvent removed. The crude iodide was used without further purification: LCMS (ES) m/z 210 $(M+H)^+$.

Preparation 16



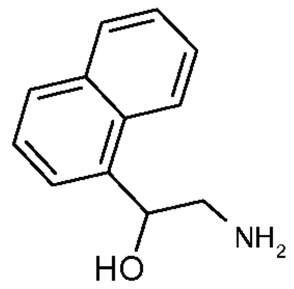
Preparation of 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate

a) hydroxy(1-naphthalenyl)acetonitrile



To a solution of potassium cyanide in ether (100 mL) at 0 °C was added dropwise a mixture of 1-naphthalenecarbaldehyde (1.56 g, 10 mmol) and acetic acid (1.41g, 23.5 mmol) in ether (10 mL). The resulting mixture was warmed to 25 °C. for 20h, where the precipitate was filtered and the filtrate was concentrated affording the title compound as a clear oil (1.67 g, 9.14 mmol, 91%): LCMS (ES) m/z 184 $(M+H)^+$.

b) 2-amino-1-(1-naphthalenyl)ethanol

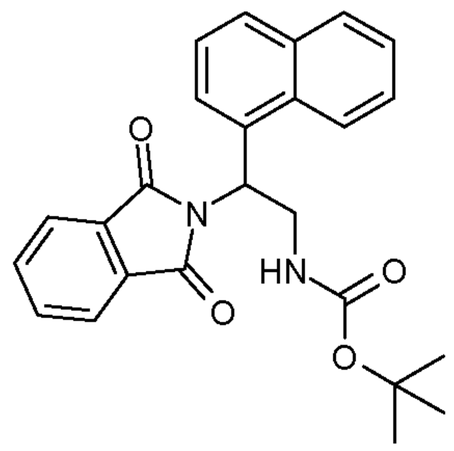


To a solution of hydroxy(1-naphthalenyl)acetonitrile (1.67 g, 9.14 mol) in THF (90 mL) at 0 °C was added dropwise a solution of LAH-THF (1M, 11 mL, 11 mmol). After 2 hrs, the solution was quenched by sequential addition of H_2O (0.42 mL), 6N NaOH (6M, 0.32 mL) and H_2O (1.6 mL). The resulting precipitate was filtered and the filtrate was concentrated and used directly yielding the title compound (0.897 g, 4.8 mmol, 53%) as a clear oil: LCMS (ES) m/z 188 $(M+H)^+$.

c). 1,1-dimethylethyl [2-hydroxy-2-(1-naphthalenyl)ethyl]carbamate

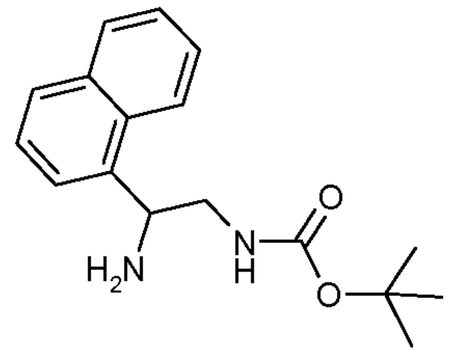
To a solution of 2-amino-1-(1-naphthalenyl)ethanol(1.38g, 4.8 mmol) in dichloromethane (50 mL) was added Boc anhydride (1.155 g, 5.3 mmole). After stirring at RT for 12 h, the reaction solution was concentrated and partitioned between $NaHCO_3$ sat./DCM. The aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound as a white solid (1.378 g, 4.8 mmol, quant): LCMS (ES) m/z 288 (M+H)+.

d) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-(1-naphthalenyl)ethyl]carbamate



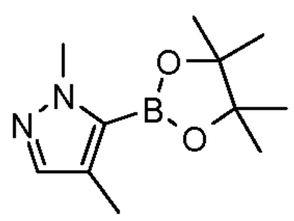
To a solution of 1,1-dimethylethyl [2-hydroxy-2-(1-naphthalenyl)ethyl]carbamate (1.38 g, 4.8 mmol), triphenylphosphine (1.52 g, 5.76 mmol) and phthalimide (0.74 g, 5.04 mmol) in THF (50 mL) at 25 °C was added diethyl azodicarboxylate (0.87 mL, 5.52 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (20% EtOAc in hexanes) affording the title compound (1.29 g, 3.1 mmol, 65 %) as a white solid: LCMS (ES) m/z 387 (M+H)+.

e) 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate



To a solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-(1-naphthalenyl)ethyl]carbamate (1.29 g, 3.1 mmol) in MeOH (30 mL) was added anhydrous hydrazine (0.5 mL, 15.5 mmol) at 25 °C. After 12h, the solution was partitioned between DCM/H_2O. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound as a white solid (491 mg, 1.72 mmole, 55%): LCMS (ES) m/z 287 $(M+H)^+$.

Preparation 17

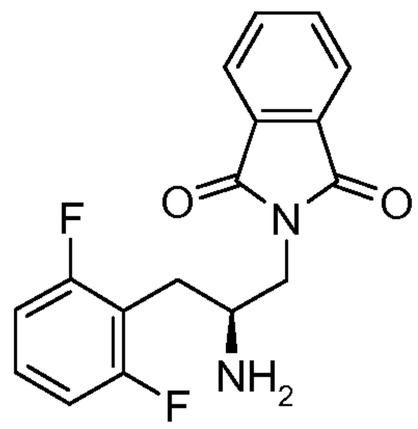


Preparation of 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

To a suspension of NaH (60% in mineral oil, 3.5 g, 146 mmol, washed with 200 mL of hexane) in THF (200 mL) was added 4-methyl-1H-pyrazole (10 g, 122 mmol) at 0 °C dropwise. After stirring at RT for 1h, to above suspension was added MeI (7.3 mL, 117 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight. The NaI by-product was removed by filtration and the filtrate solution was used directly in the next step.

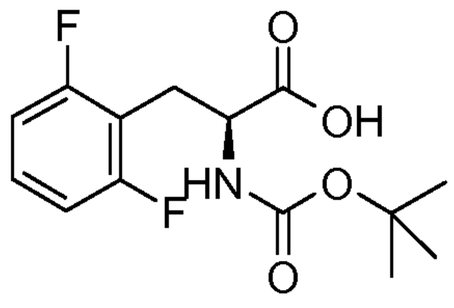
At 0°C, to above THF solution of 1,4-dimethyl pyrazole was added n-BuLi (2.5M in hexane, 58.5 mL, 146 mmole). The reaction solution was stirred for 2 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem*. **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27.2 g, 146 mmole). After 15 min at -78°C, the reaction was allowed to warm to 0°C and stir for 3h. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown solid (21 g, 78%) which was used directly without further purification: LC-MS: 141 $(M-C_6H_{12})^+$, 223 $(M+H)^+$. ^1H NMR ($CDCl_3$): δ 7.28 (s, 1H), 4.03 (s, 3H), 2.22 (s, 3H), and 1.32 (s, 12H).

Preparation 18



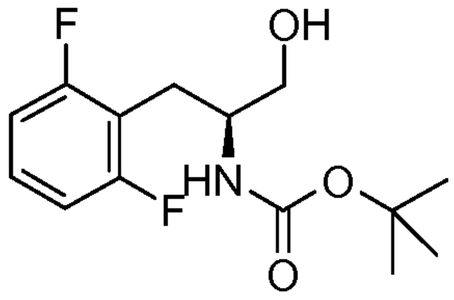
Preparation of 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

a) *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2,6-difluoro-L-phenylalanine



1,4-Dioxane (55 mL) and water (12 mL) was added to 2,6-difluoro-L-phenylalanine (3.00 g, 12.62 mmol) in a 200 mL round-bottomed flask. The mixture was cooled to 0 ºC followed by the slow addition of NaOH (12.62 mL, 31.6 mmol) and then Boc_2O (3.42 g, 15.20 mmol). The mixture was allowed to warm to room temperature and monitored for completion by LC-MS. Upon completion, the mixture was cooled to 0 ºC and made neutral by the slow addition of 2.5M HCl (12 mL). The solvents removed under reduced pressure. The resulting solid was sonicated with 20%MeOH/$CHCl_3$ (150mL), filtered and the organic solvent removed to give the product (4.3 g, 14.4 mmol, quant.) as a white solid which was used in the next step without further purification: LC-MS (ES) m/z = 302 $(M+H)^+$.

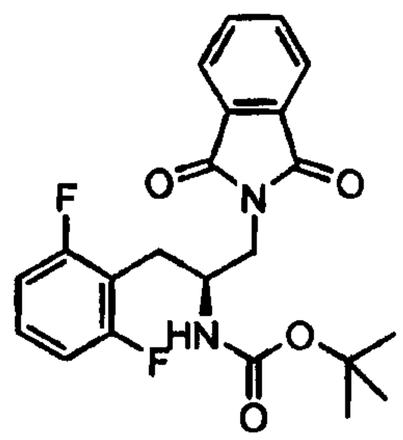
b) 1,1-dimethylethyl [(1*S*)-2-(2,6-difluorophenyl)-1-(hydroxymethyl)ethyl]carbamate



BH_3.THF (64.7 ml, 64.7 mmol) was added slowly to a tetrahydrofuran (THF) (60 mL) solution of N-{[(1,1-dimethylethyl)oxy]carbonyl}-2,6-difluoro-L-phenylalanine (4.33 g, 14.37 mmol) at 0 ºC in a 200 mL round-bottomed flask. The

mixture was stirred for 2 hours and then placed in the freezer overnight. Excess reagent was quenched by the slow addition of AcOH in MeOH at 0 °C and the mixture warmed to room temperature for 2 hours. The THF volume was reduced by 1/2 and the product partitioned between $CHCl_3$ and aqueous $NaHCO_{3\,(sat)}$. The combined organic fractions were dried over Na_2SO_4 and used directly without further purification (3.4 g, 78%): LC-MS (ES) m/z = 288 $(M+H)^+$.

c) 1,1-dimethylethyl {(1*S*)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}carbamate



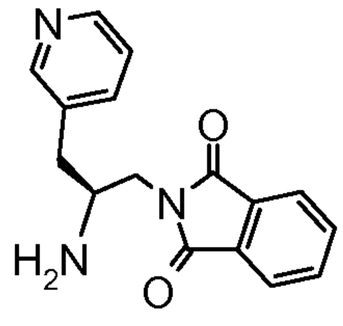
To a 200 mL round-bottomed flask was added 1,1-dimethylethyl [(1S)-2-(2,6-difluorophenyl)-1-(hydroxymethyl)ethyl]carbamate (3.38 g, 11.76 mmol), phthalimide (2.02 g, 13.73 mmol), and PS – TPP (Polymer bound TriphenylPhosphine (2.15 mmol/g, 4.92 g, 14.76 mmol) in Tetrahydrofuran (THF) (58.8 ml). DEAD (2.23 ml, 14.09 mmol) was added and the mixture stirred at ambient temperature for approximately 30 minutes at which point MeOH was added. The mixture was filtered through Celite* adsorbed onto silica and purified via column chromatography affording the title compound (2.7 g, 55%): LC-MS (ES) m/z = 317 $(M+H)^+$.

d) 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

In a 200 mL round-bottomed flask was added 1,1-dimethylethyl {(1S)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}carbamate (2.72 g, 6.40 mmol) in Chloroform (75 ml) and Methanol (10 ml). HCl / 1,4-Dioxane (40.0 ml, 160 mmol) was added and the mixture stirred overnight. The solvents were removed affording the title compound (2.4 g, quant.) as the HCl salt: LC-MS (ES) m/z = 317 $(M+H)^+$.

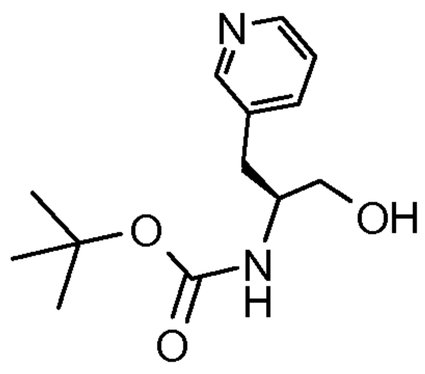
* Trade-mark

Preparation 19



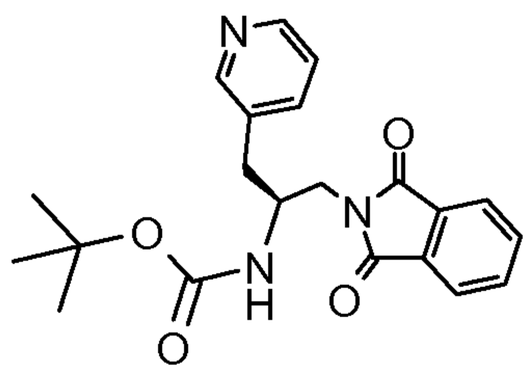
Preparation of 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

a) 1,1-dimethylethyl [(1*S*)-2-hydroxy-1-(3-pyridinylmethyl)ethyl]carbamate



To a solution of Boc-L-3-pyridylaniline (1.064 g, 4 mmol) in THF (5 mL) at 0 °C was added BH_3-THF (20 mL, 20 mmol-1M in THF) dropwise. After 2 h, the reaction was quenched with AcOH:MeOH (1:5, 14.3 mL) at 0 °C, followed by Et_3N (1.67 mL, 12 mmol) and I_2 (2.03 g, 8 mmol). The resulting mixture was warmed to ambient temperature and stirred for 20h, turning from brown to colorless. The solution was concentrated and partitioned between DCM and water. The aqueous phase was then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated to afford the desired product as a colorless oil which was used without further purification (957.6 mg, 95%): LC-MS (ES) m/z= 253 $(M+H)^+$.

b) 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(3-pyridinylmethyl)ethyl]carbamate



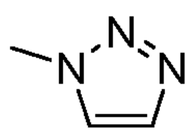
To a solution of 1,1-dimethylethyl [(1*S*)-2-hydroxy-1-(3-pyridinylmethyl)ethyl]carbamate (958 mg, 3.8 mmol), triphenylphosphine (1.21 g,

4.6 mmol) and phthalimide (617 mg, 4.2 mmol) in THF (40 mL) at 25 °C was added diethyl azodicarboxylate (0.72 mL, 4.6 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (0-50% ethyl acetate / hexane) affording the title compound (797 mg, 55 %) as a white solid: LCMS (ES) m/z 382 $(M+H)^+$.

c) 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

To a solution of 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(3-pyridinylmethyl)ethyl]carbamate (796.7 mg, 2.1 mmol) in DCM (10 mL) at RT was added 1M HCl in dioxane (10 mL). After 20h, the solution was concentrated affording the title compound (404 mg, 68%) as the HCl salt: LCMS (ES) m/z 282 $(M+H)^+$.

Preparation 20

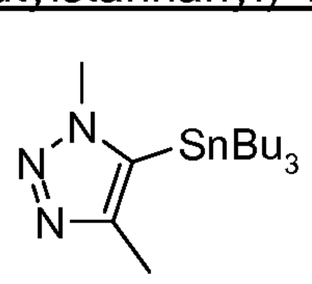


Preparation of 1-methyl-1*H*-1,2,3-triazole

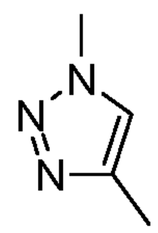
To a solution of 1,2,3-trazole (10 g, 145 mmol) in 150 ml of THF were added potassium carbonate (40 g, 290 mmol) and MeI (13.58 ml, 217 mmol). The resulting reaction mixture was stirred at rt for 3hr. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (9.2 g, 78%). 1H NMR (400 MHz, $CDCl_3$) δppm 7.71 (s, 1H), 7.55 (s, 1H), 4.14 (s, 3H).

Preparation 21

Preparation of 1,4-dimethyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole

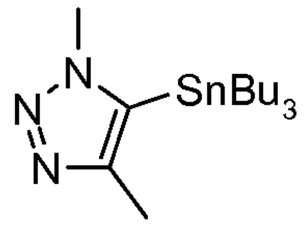


a) 1,4-dimethyl-1*H*-1,2,3-triazole



A solution of methylamine (25.4 ml, 50.8 mmol, 2M in MeOH) was added dropwise to a suspension of N'-(2,2-dichloro-1-methylethylidene)-4-methylbenzenesulfonohydrazide (ref: Sakai, K. et al, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 179-183) (3 g, 10.16 mmol) in methanol (10 ml) at 0 °C. The solid went into solution. The resulting dark brown mixture was stirred at 0 °C for 2h, evaporated, and the solid was filtered and rinsed with EtOAc. The combined filtrates were concentrated and purified on a 25M biotage column, which was eluted with 50-75% of EA/hexane to give 0.57 g of brown liquid. LC-MS (ES) m/z = 98 $(M+H)^+$, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27 (s, 1H), 4.06 (s, 3H), 2.35 (s, 3H).

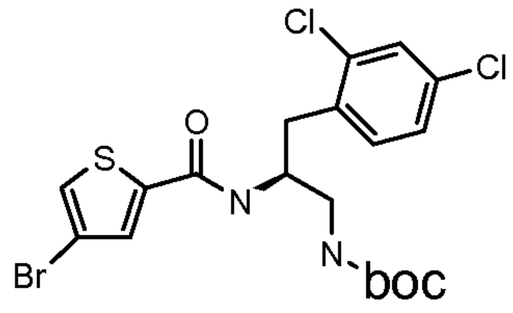
b) 1,4-dimethyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole



A solution of 1,4-dimethyl-1,2,3-triazole (0.56 g, 5.77 mmol) in THF (5 mL) was added dropwise to a solution of BuLi (2.77 ml, 6.92 mmol, 2.5 M in hexane) in 30 mL of THF at -78 °C under N_2. The resulting cloudy mixture was stirred at -70 °C for 1h.

Then tributyltinchloride (1.711 ml, 6.34 mmol) was added. The reaction mixture became clear and was stirred at this temperature for 30 min, and gradually warmed to rt. To the reaction mixture was added 10 ml of NH_4Cl and 10 ml of water. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on FCC (20% EA/Hexane) to give 1.7 g of a clear liquid (73%). LC-MS (ES) m/z = 388 $(M+H)^+$, ^1H NMR ($CDCl_3$, 400 MHz) δ 4.05 (s, 3H), 2.38 (s, 3H), 1.5-0.9 (m, 27H)

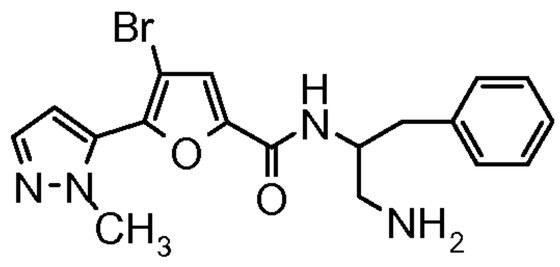
Preparation 22



Preparation of 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate

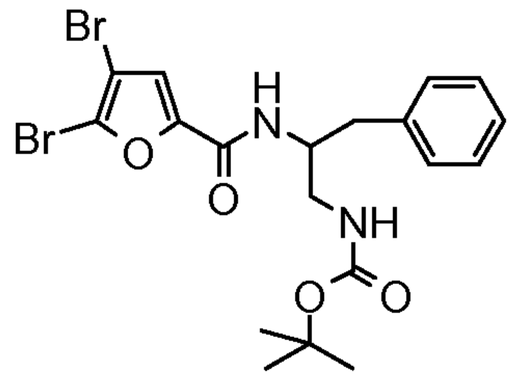
A solution of 4-bromo-2-thiophenecarboxylic acid (1.29 g, 6.22 mmol), 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (2.0 g, 5.19 mmol), PyBrop (3.62 g, 7.78 mmol) and Hunig's Base (3.62 ml, 20.74 mmol) in DCM (50 ml) was stirred at RT for 30 min. The reaction mixture was washed with H_2O, 1N HCl, $NaHCO_3$ (sat. aq.) and brine. The solvent was removed and the residue was dissolved in MeOH, hydrazine monohydrate (1.3 g, 26 mmol) was added. The reaction was stirred at rt overnight. The white solid formed, and was filtered and rinsed with DCM. To the filtrates were added $(Boc)_2O$ (1.7g, 7.78 mmol) and $NaHCO_3$ (sat. aq., 3 ml). The reaction mixture was stirred at RT for 2 hours and was washed with $NaHCO_3$ (sat. aq.) and brine. The solvent was removed and the residue was purified by biotage (50% H/E) to give the product (2.0g, 76%). LC-MS (ES) m/z = 531.0 $(M+Na)^+$.

Example 1



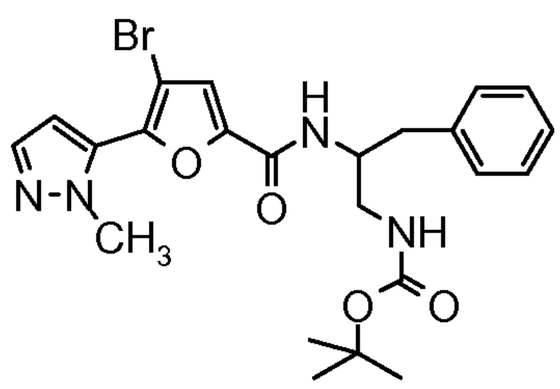
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 4,5-dibromo-2-furancarboxylic acid (2.81 g, 10.4 mmol), PyBrOP (5.6 g, 12.0 mmol) and diisopropylethyl amine (4.2 mL, 24.0 mmol) in DCM (70 mL) at 25 °C was added 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (2.0 g, 8.0 mmol). After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, hexanes/EtOAc, 2:1) affording the title compound (4.3 g, 82%) as a white solid: LC-MS (ES) m/z = 503 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate



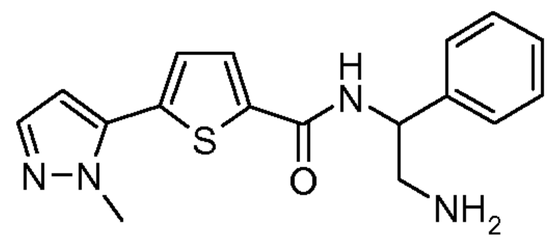
To a solution of 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate (0.30 g, 0.60 mmol) in dioxane/H_2O (5:1, 8.6 mL) was added K_2CO_3 (0.25 g, 1.8 mmol), tetrakistriphenylphosphine Pd(0) (70 mg, 0.06 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (0.12 g, 0.60 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (0.20 g, 66%) as a white solid: LC-MS (ES) m/z = 504.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

1,1-Dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.20 g, 0.40 mmol) was dissolved in DCM (10 mL) and treated with TFA (5 mL). After 2 h, the solution was

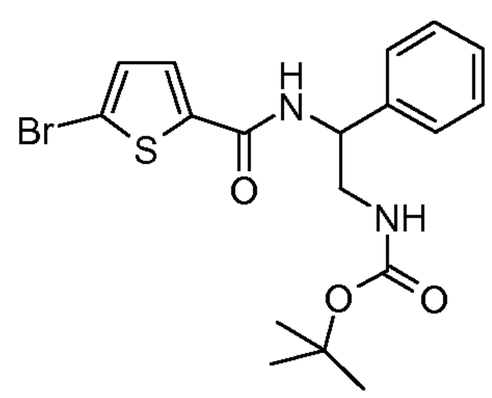
concentrated, and purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt of the title compound (0.16 g, 91%) as a white powder: LC-MS (ES) m/z = 405 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.59 (s, 1H), 7.33 (m, 3H), 7.30 (m, 2H), 6.85 (s, 1H), 4.57 (m, 1H), 4.03 (s, 3H), 3.25 (m, 1H), 3.14 (m, 1H), and 2.98 (m, 2H).

Example 2



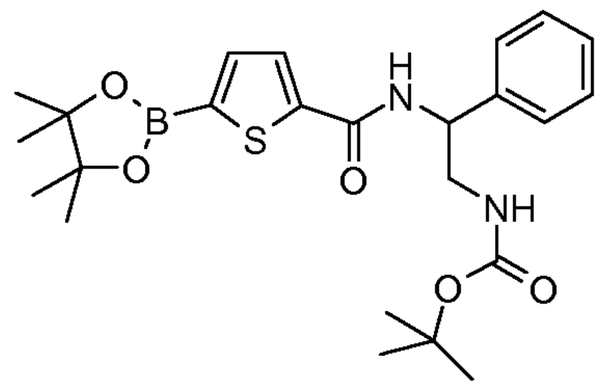
Preparation of *N*-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-2-phenylethyl)carbamate



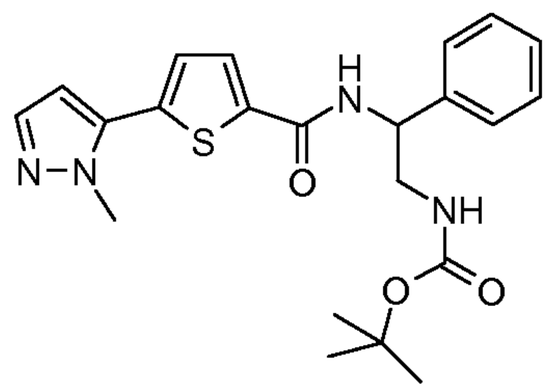
To a solution of 5-bromo-2-thiophenecarboxylic acid (3.2 g, 15.2 mmol), PyBrOP (8.5 g, 18.2 mmol) and diisopropylethyl amine (10.6 mL, 60.9 mmol) in DCM (76 mL) at 25 °C was added 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate (3.6 g, 3.14 mmol)[prepared in Preparation 1]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fraction were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 1% MeOH in DCM) affording the title compound (4 g, 62%) as a white solid: LC-MS (ES) m/z = 426 $(M+H)^+$.

b) 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-2-phenylethyl)carbamate (1 g, 2.35 mmol) in DMF (9 mL) were added KOAc (693 mg, 7.05 mmol), bis(pinocolato)diboron (1.2 g, 4.71 mmol) and Pd(dppf)Cl_2 (169 mg, 0.212 mmol). The reaction contents were heated to 80°C in a sealed tube for 18 hours and were then partitioned between 6N NaOH and DCM. The pH of the aqueous fraction was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated to a solid under vacuum and used directly in the next reaction: LC-MS (ES) m/z = 473 $(M+H)^+$ boronic ester, 391$(M+H)^+$ boronic acid.

c) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate

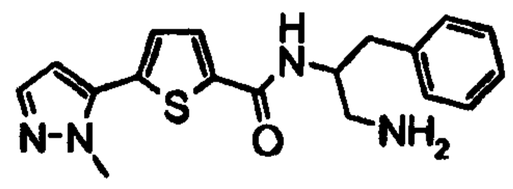


To a solution of 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate (200 mg, 0.42 mmol) in dioxane/H_2O (5:1, 8.6 mL) was added K_2CO_3 (234 mg, 1.69 mmol), tetrakistriphenylphosphine Pd(0) (24 mg, 0.02 mmol), and 5-iodo-1-methyl-1H-pyrazole (97 mg, 0.47 mmol) [prepared according to Effenberger, F.; et al *J. Org. Chem.* **1984**, 49, 24, 4687]. The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (1% MeOH in DCM) to give the title compound (56 mg, 31%) as a yellow solid: LC-MS (ES) m/z = 427.

d) *N*-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (56 mg, 0.131 mmol) was dissolved in MeOH (2 mL) and treated with excess 4M HCl in dioxane (656 μL, 2.62 mmol). After 4h, the solution was concentrated affording the title compound (46 mg, quant.) as a yellow solid: LC-MS (ES) m/z 327 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 9.46 (d, J = 8.2 Hz, 1H), 8.27 (bs, 1H), 8.20 (d, J = 4.0 Hz, 1H), 7.48-7.75 (m, 3H), 7.37-7.40 (m, 2H), 7.31-7.33 (m, 1H), 6.58 (d, J = 1.9 Hz, 1H), 5.21-5.30 (m, 1H), 3.97 (s, 3H), 3.36-3.41 (m, 1H), 3.19-3.25 (m, 1H).

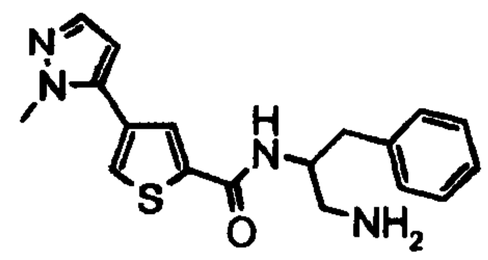
Example 3



Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an tan solid according to Example 2, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (1.65 g, 7.97 mmol)[prepared in Preparation 2] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate: LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ 8.74 (d, J = 8.5 Hz, 1H), 8.05 (bs, 1H), 7.89 (d, J = 3.9 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 3.9 Hz, 1H), 7.26-7.29 (m, 3H), 7.20-7.22 (m, 1H), 6.56 (d, J = 2.0 Hz, 1H), 4.31-4.42 (m, 1H), 2.98-3.01 (m, 2H), 2.91-2.93 (m, 2H).

Example 4

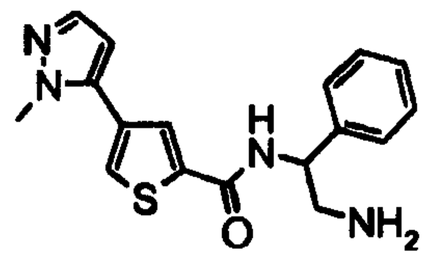


Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 2, except substituting 4-bromo-2-thiophenecarboxylic acid (1 g, 4.83 mmol) for 5-bromo-2-thiophenecarboxylic acid and 1,1-dimethylethyl (2-amino-3-

phenylpropyl)carbamate (1.2 g, 4.83 mmol)[prepared in Preparation 2] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate: LC-MS (ES) m/z 441 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.98 (bs, 1H), 8.29 (s, 1H), 8.17 (bs, 2H), 7.98 (s, 1H), 7.46 (s, 1H), 7.27-7.29 (m, 3H), 7.19 (s, 1H), 6.46 (s, 1H), 4.35-4.37 (m, 1H), 3.51 (s, 3H), 2.75-3.12 (m, 4H).

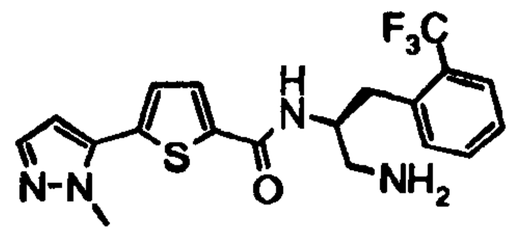
Example 5



Preparation of N-(2-amino-1-phenylethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

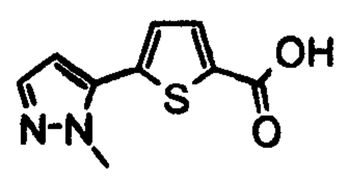
The title compound was prepared as a yellow solid according to Example 2, except substituting 4-bromo-2-thiophenecarboxylic acid (650 mg, 3.14 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 427 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 9.65 (d, J = 7.3 Hz, 1H), 8.58 (s, 1H), 8.31 (br s, 2H), 7.99 (s, 1H), 7.42-7.51 (m, 2H), 7.72-7.80 (m, 2H), 7.20-7.31 (m, 1H), 6.51 (s, 1H), 3.52 (s, 1H), 5.25-5.35 (m, 1H), 3.51 (s, 3H), 3.32-3.48 (m, 1H), 3.15-3.21 (m, 1H).

Example 6



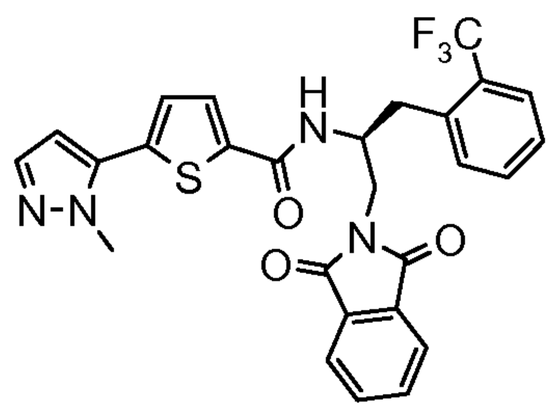
Preparation of N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 5-bromo-2-thiophenecarboxylic acid (100 mg, 0.48 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (267 mg, 1.93 mmol), tetrakistriphenylphosphine Pd(0) (28 mg, 24 umol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (94 mg, 0.48 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h and was then partitioned between 6N NaOH and DCM. The pH of the aqueous phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~100 mg, quant.): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (100 mg, 0.48 mmol), PyBrOP (270 mg, 0.58 mmol) and diisopropylethyl amine (420 µL, 2.4 mmol) in DCM (5 mL) at 25 °C was added 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (168 mg, 0.48 mmol)[from Preparation 6]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (74 mg, 28%) as a white solid: LC-MS (ES) m/z = 539 $(M+H)^+$.

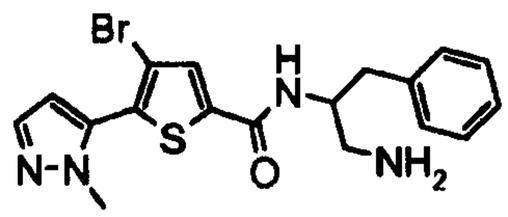
c) N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (74 mg, 0.14 mmol) in MeOH/THF (2 mL, 1:1) at RT was added hydrazine (86 µL, 2.75 mmol). After stirring for 18h at RT, the reaction

solution was concentrated under vacuum and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound.

The neutral compound from above was dissolved in MeOH (2 mL), treated with excess 4M HCl in dioxane (500 µL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z = 409 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.97 (d, J = 9.0 Hz, 1H), 8.17 (bs, 1H), 8.00 (d, 3.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.55-7.61 (m, 2H), 7.42-7.47 (m 2H), 6.56 (d, J = 2.0 Hz, 1H), 4.47-4.51 (m, 1H), 4.18 (s, 3H), 3.09-3.11 (m, 4H).

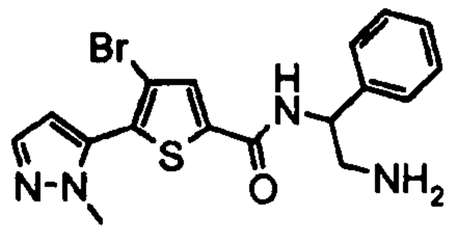
Example 7



Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 1, except substituting 4,5-dibromo thiophenecarboxylic acid (376 mg, 1.32 mmol) for 4,5-dibromo furancarboxylic acid: LC-MS (ES) m/z = 419 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.92 (d, J = 8.6 Hz, 1H), 8.03-8.06 (m, 2H), 7.56 (d, J = 1.9 Hz, 1H), 7.26-7.32 (m, 3H), 7.21-7.23 (m, 1H), 6.55 (d, J = 1.9 Hz, 1H), 4.32-4.42 (m, 1H), 3.77 (s, 3H), 3.00-3.01 (m, 2H), 2.89-2.91 (m, 2H).

Example 8

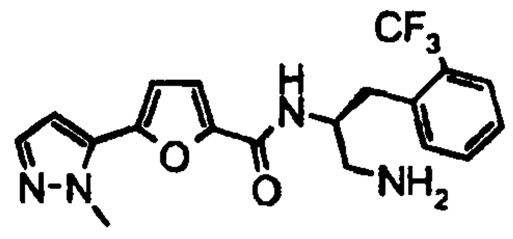


Preparation of N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 1, except substituting 4,5-dibromo thiophenecarboxylic acid (2.2 g, 7.69 mmol) for 4,5-dibromo

furancarboxylic acid and 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate (1.1 g, 4.66 mmol) for 1,1-dimethylethyl (2-amino-2-phenylpropyl)carbamate: LC-MS (ES) m/z = 406 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 9.47 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 8.17 (bs, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.38-7.46 (m, 3H), 7.30-7.34 (m, 1H), 6.56 (d, J = 1.6 Hz, 1H), 5.28-5.37 (m, 1H), 3.81 (s, 3H), 3.35-3.41 (m, 1H), 3.21-3.28 (m, 1H).

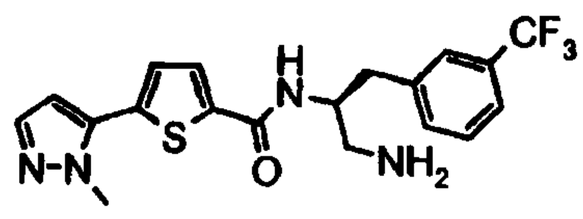
Example 9



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 5-bromo-2-furancarboxylic acid (58 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.62 (br s, 1H), 7.57 (m, 1H), 7.51 (m, 3H), 7.22 (m, 1H), 6.91 (m, 1H), 6.76 (m, 1H), 4.6 (m, 1H), 4.07 (m, 3H) and 3.15 (m, 4H).

Example 10

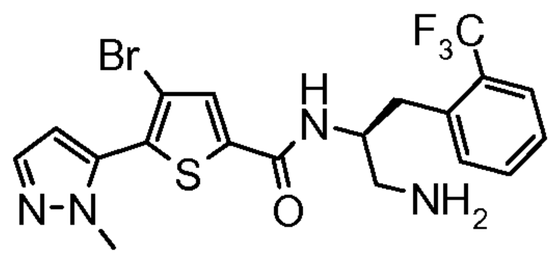


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (306 mg, 0.80 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-

HCl: LC-MS (ES) m/z = 409 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.81 - 2.88 (m, 1H) 2.93 (td, *J*= 9.03, 4.93 Hz, 2H) 3.09 (dd, *J*= 13.89, 5.31 Hz, 1H) 4.00 (s, 3H) 4.28 - 4.35 (m, 1H) 6.53 (d, *J*= 2.02 Hz, 1 H) 7.32 (d, *J*= 4.04 Hz, 1H) 7.45 - 7.52 (m, 3H) 7.54 - 7.58 (m, 1H) 7.60 (s, 1H) 7.70 (d, *J*= 4.04 Hz, 1H).

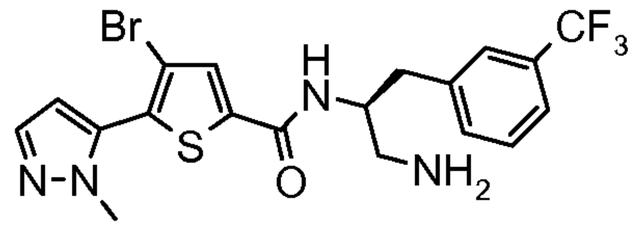
Example 11



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (237 mg, 0.83 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 488 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δppm 2.97 - 3.10 (m, 4H) 3.78 (s, 3H) 4.42 - 4.54 (m, 1H) 6.56 (d, *J*=2.02 Hz, 1H) 7.45 (t, *J*=7.58 Hz, 1H) 7.50 - 7.54 (m, 1H) 7.56 - 7.63 (m, 2H) 7.71 (d, *J*=7.58 Hz, 1H) 7.92 (s, 1H) 8.76 (d, *J*=9.09 Hz, 1H)

Example 12

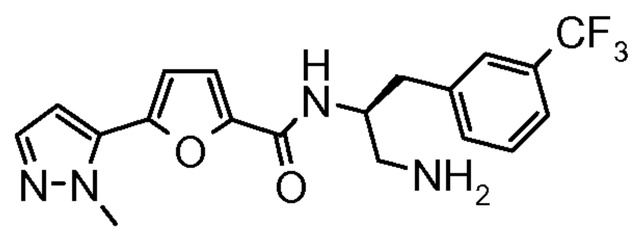


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (237 mg, 0.83 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (206 mg, 0.535 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-

isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 488 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 2.97 - 3.07 (m, 1H) 3.10 - 3.21 (m, 2H) 3.27 (d, *J*=3.54 Hz, 1H) 3.82 (s, 3H) 4.50 - 4.59 (m, 1H) 6.51 (d, *J*= 2.02 Hz, 1H) 7.50 - 7.60 (m, 4H) 7.62 (s, 1H) 7.71 (s, 1H).

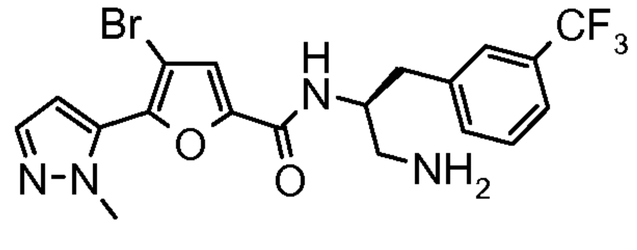
Example 13



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 5-bromo-2-furancarboxylic acid (44 mg, 0.23 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (87 mg, 0.25 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.63 (br s, 1H), 7.57 (m, 1H), 7.51 (m, 3H), 7.22 (m, 1H), 6.91 (m, 1H), 6.77 (m, 1H), 4.6 (m, 1H), 4.07 (m, 3H) and 3.14 (m, 4H).

Example 14

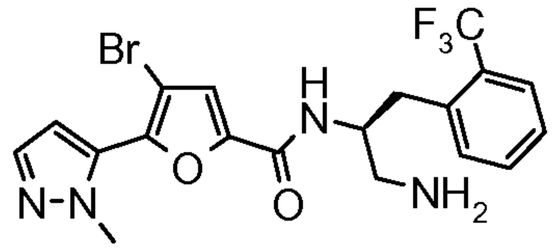


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (82 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (115 mg,

0.3 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.61 (m, 2H), 7.53 (m, 3H), 7.30 (m, 1H), 6.84 (m, 1H), 4.59 (m, 1H), 4.03 (s, 3H), 3.28 (m, 1H), 3.17 (m, 2H) and 3.01 (m, 1H)

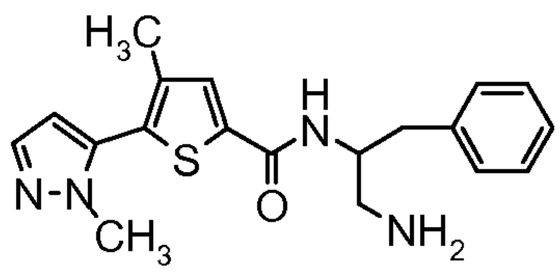
Example 15



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

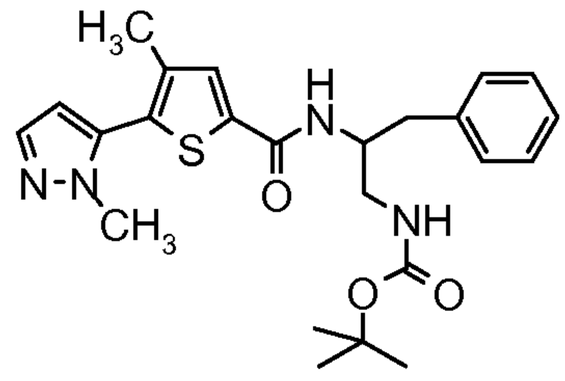
The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (82 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.71 (m, 1H), 7.60 (m, 1H), 7.53 (m, 2H), 7.44 (m, 1H), 7.33 (m, 1H), 6.88 (m, 1H), 4.7 (m, 1H), 4.06 (s, 3H), 3.25 (m, 3H) and 3.09 (m, 1H).

Example 16



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

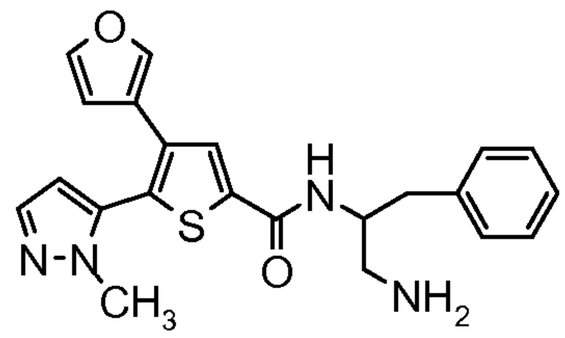


To a solution of 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.35 g, 0.67 mmol) [from Example 7] in dioxane/H_2O (5:1, 25:5 mL) was added K_2CO_3 (0.28 mg, 2.0 mmol), tetrakistriphenylphosphine Pd(0) (77 mg, 0.06 mmol), and trimethylboroxine (0.17 mL, 1.2 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (0.10 g, 33%) as a white solid: LC-MS (ES) m/z = 455 $(M+H)^+$.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl [2-({[4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.10 g, 0.22 mmol) was dissolved in MeOH (10 mL) and THF (5 mL) and treated with 4 M HCl in dioxane (5 mL). After 4 h, the solution was concentrated affording the HCl salt of the title compound (68 mg, 91%) as a white powder: LC-MS (ES) m/z = 355 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.79 (s, 1H), 7.68 (s, 1H), 7.31 (m, 4H), 7.25 (m, 1H), 6.56 (s, 1H), 4.54 (m, 1H), 3.87 (s, 3H), 3.69 (s, 2H), 3.34 (m, 2H), 3.03 (d, J = 7.6 Hz, 2H) and 2.21 (s, 3H).

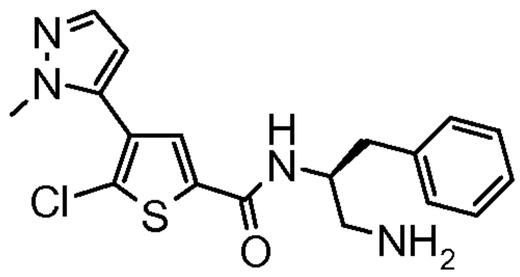
Example 17



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(3-furanyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

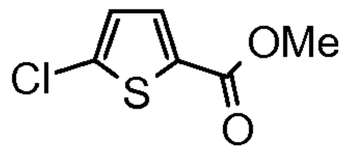
The title compound was prepared as a white solid according to the procedure of Example 16, except substituting 3-furan boronic acid (0.13 g, 1.2 mmole) for trimethylboroxine: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.53 (m, 2H), 7.34 (m, 4H), 7.26 (m, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 4.57 (m, 1H), 3.68 (s, 2H), 3.63 (s, 3H), 3.24 (m, 2H) and 3.07 (m, 2H)

Example 18



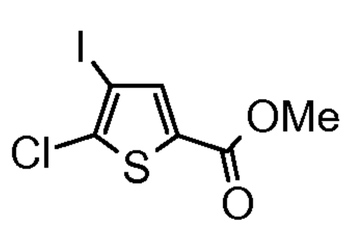
Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-2-thiophenecarboxylate



To a solution of 5-chloro-2-thiophenecarboxylic acid (2.0 g, 12.3 mmol) in dry MeOH (75 mL) was added H_2SO_4 (1 mL). The reaction mixture was heated to 50° C for 20h and was then concentrated under vacuum. The residue was dissolved in DCM and washed several times with saturated NaHCO3 solution. The organic fraction was dried (Na_2SO_4), concentrated under vacuum and used directly without further purification 21.3g, quant.): LC-MS (ES) m/z = 177 $(M+H)^+$.

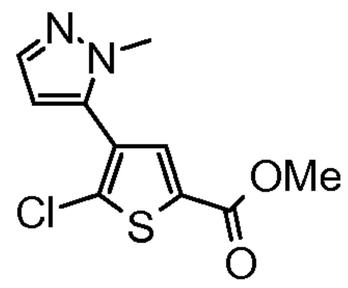
b) methyl 5-chloro-4-iodo-2-thiophenecarboxylate



To a solution of 5-chloro-2-thiophenecarboxylic acid (5.0 g, 28.0 mmol) in acetic acid (150 mL) was added $ZnCl_2$ (38g, 280 mmoles) and benzyltrimethylammonium dichloroiodate (20.5 g, 58.8 mmole) [*Bull. Chem. Soc.*

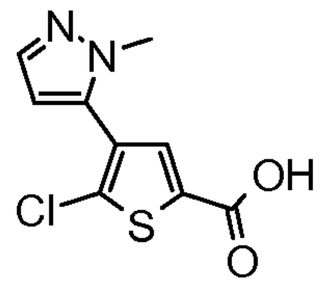
Jpn. **64**, 2566-2568 (1991)]. The reaction mixture was heated to 70° C for 48h and was then concentrated under vacuum. The residue was extracted with hexanes (2 x 200 mL) and the hexane solution washed with saturated $NaHCO_3$ solution. The organic fractions were dried (Na_2SO_4), concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 4:1) to give the title compound (3.8 g, 45%) as a light yellow solid: LC-MS (ES) m/z = 302 $(M+H)^+$.

c) methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



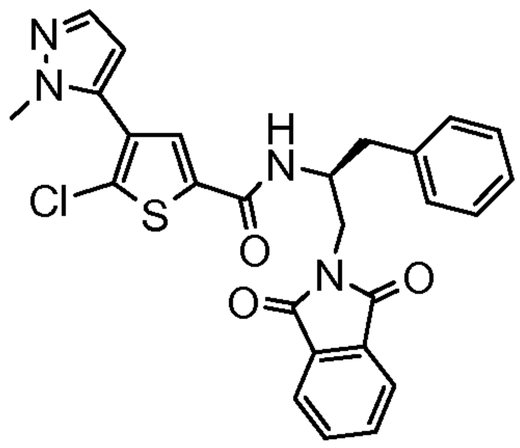
To a solution of methyl 5-chloro-4-iodo-2-thiophenecarboxylate (1.75 g, 5.8 mmol) in dioxane/H_2O (50:5 mL) was added K_2CO_3 (3.4 g, 24.9 mmol), tetrakistriphenylphosphine Pd(0) (0.96 g, 0.83 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (3.4 g, 16.5 mmol). The reaction mixture was heated to 80° C in a sealed tube for 15h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 4:1) to give the title compound (0.35 g, 24%) as a yellow oil: LC-MS (ES) m/z = 257 $(M+H)^+$.

d) 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.30 g, 1.17 mmole) in THF (10 mL) and MeOH (10 mL) was added 6N NaOH (5 mL). The reaction solution was heated to 50°C for 2hrs. The reaction solution was concentrated under vacuum, made acidic (pH ~ 2) with 3N HCl, and extracted with DCM. The organic solution was dried (Na_2SO_4) and concentrated to a solid (0.22 g) which was used without further purification. LC-MS (ES) m/z = 243 $(M+H)^+$.

e) 5-chloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



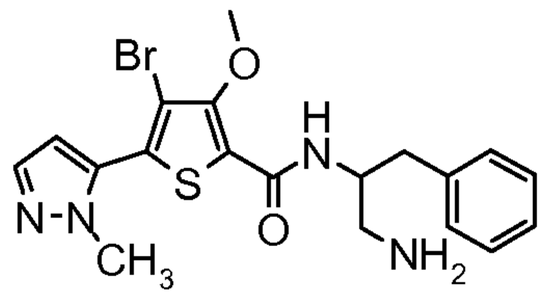
To a solution of 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (0.21 g, 0.87 mmol), PyBrOP (610 mg, 1.3mmol) and diisopropylethyl amine (0.76 mL, 4.35 mmol) in DCM (20 mL) at 25 °C was added 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione HCl (380 mg, 0.96 mmol)[prepared according to Preparation 5]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (200 mg, 46%) as a white solid: LC-MS (ES) m/z = 505 $(M+H)^+$.

f) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 5-chloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (200 mg, 0.40 mmol) in MeOH/THF (10 mL, 1:1) at RT was added hydrazine hydrate (0.20 mL, 4.0 mmol). After stirring for 24h at RT, the reaction solution was concentrated under vacuum and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound as a light yellow solid.

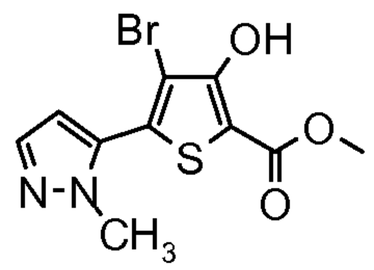
The neutral compound from above was dissolved in DCM (2 mL), treated with excess 4M HCl in dioxane (1mL) and concentrated affording the HCl salt (102 mg) of the title compound: LC-MS (ES) m/z = 375 $(M+H)^+$, 7.78 (s, 1H), 7.63 (s, 1H), 7.31 (m, 4H), 7.26 (m, 1H), 6.55 (s, 1H), 4.54 (m, 1H), 3.91 (s, 3H), 3.24 (m, 2H) and 3.03 (m, 2H).

Example 19



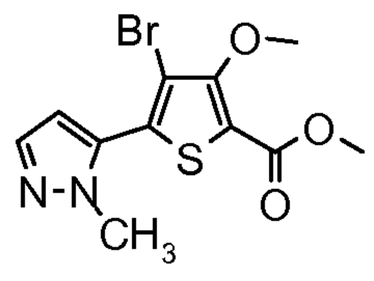
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-3-hydroxy-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



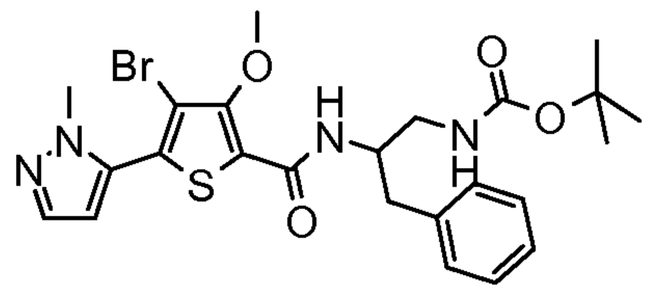
Methyl 4,5-dibromo-3-hydroxy-2-thiophenecarboxylate (500 mg, 1.59 mmol), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (339 mg, 1.75 mmol), $Pd(PPh_3)_4$ (92 mg, 79.4 µmol) and K_2CO_3 (876 mg, 6.35 mmol) in dioxane (6.6 mL) and H_2O (1.3 mL) were combined in a sealed tube. After 12h at 80 °C, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH in DCM) affording the title compound (75 mg, 15%) as a brown residue: LCMS (ES) m/z = 318 $(M+H)^+$.

b) methyl 4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-3-hydroxy-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (175 mg, 0.554 mmol), MeOH (26 µL, 0.609 mmol), PPh_3 (189 mg, 0.720 mmol) in THF (6 mL) at 25 °C was added DEAD (113 µL, 0.720 mmol) in one portion. After 30 min, the reaction was concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) affording the title compound (135 mg, 74%) as a white solid: LC-MS (ES) m/z = 332 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



i) A solution of methyl 4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (135 mg, 0.410 mmol) in 6N NaOH (4 mL) and THF (4 mL) was stirred in a sealed tube at 80 °C. After 2h, the solution was acidified to pH 3 using 1N HCl then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 318 $(M+H)^+$.

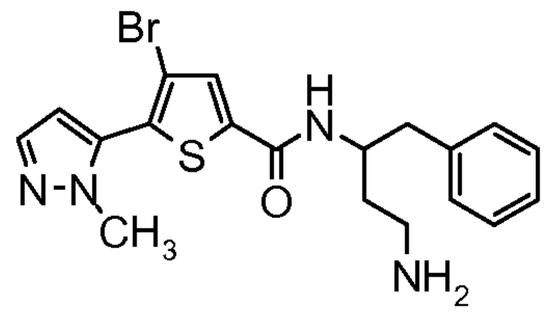
ii) To a solution of the crude acid, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (88 mg, 0.351 mmol)[from Preparation 2], diisopropylethyl amine (305 µL, 1.76 mmol) in DCM (3.5 mL) was added PyBrop (196 mg, 0.422 mmol) in one portion. After 12h, additional diisopropylethyl amine (305 µL, 1.76 mmol) and PyBrop (196 mg, 0.422 mmol) were added. After 2h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 550 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part e) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

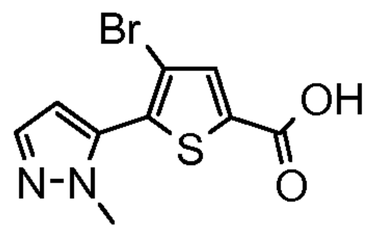
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound as the HCl salt: LC-MS (ES) m/z 450 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (br. s., 3 H) 7.85 (d, J=8.84 Hz, 1 H) 7.58 (d, J=2.02 Hz, 1 H) 7.32 (d, J=7.07 Hz, 2 H) 7.26 - 7.29 (m, 2 H) 7.20 - 7.24 (m, 1 H) 6.54 (d, J=2.02 Hz, 1 H) 4.50-4.55 (m, 1H) 3.79 (d, J=6.82 Hz, 3 H) 3.74 (d, J=6.57 Hz, 1 H) 3.17 (s, 1 H) 2.98-3.10 (m, 4 H).

Example 20



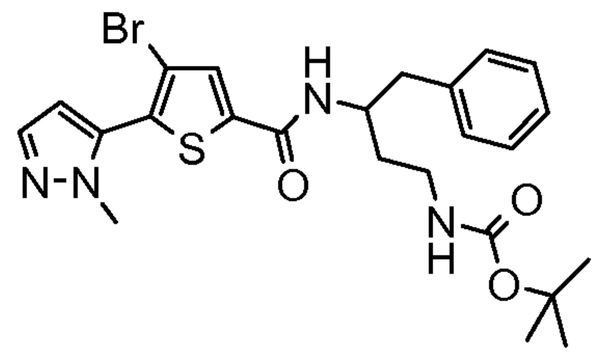
Preparation of *N*-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4,5-dibromo-2-thiophenecarboxylic acid (1 g, 3.5 mmol) in dioxane/H_2O (5:1, 18 mL) was added K_2CO_3 (1.9 g, 13.98 mmol), tetrakistriphenylphosphine Pd(0) (201 mg, 0.175 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (678 mg, 3.5 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h and was then partitioned between 6N NaOH and DCM. The pH of the aqueous phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~1 g, quant.): LC-MS (ES) m/z = 288 $(M+H)^+$.

b) 1,1-dimethylethyl [3-({[4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-4-phenylbutyl]carbamate



To a solution of 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (250 mg, 0.874 mmol), PyBrOP (489 mg, 8.74 mmol) and diisopropylethyl amine (762 µL, 4.37 mmol) in DCM (8 mL) at 25 °C was added 1,1-dimethylethyl (3-

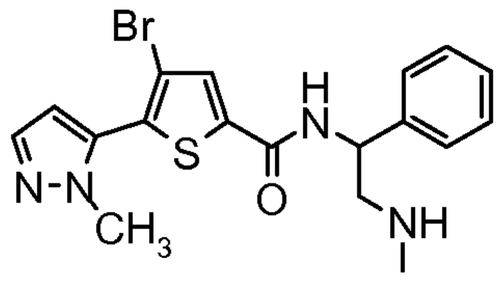
amino-4-phenylbutyl)carbamate (230 mg, 0.874 mmol)[prepared according to Preparation 8]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (130 mg, 29%) as a white solid: LC-MS (ES) m/z = 533 $(M+H)^+$.

c) N-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [3-({[4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-4-phenylbutyl]carbamate (130 mg, 0.24 mmol) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (40 mg, 40%) as the HCl salt: LC-MS (ES) m/z 433 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 (d, J=8.59 Hz, 1 H) 7.97 (s, 1 H) 7.77 (br s, 3 H) 7.57 (d, J=2.02 Hz, 1 H) 7.28 (d, J=2.27 Hz, 3 H) 7.25 - 7.32 (m, 2 H) 6.55 (d, J=2.02 Hz, 1 H) 4.17 - 4.24 (m, 1 H) 3.78 (s, 3 H) 2.77 - 2.89 (m, 4 H) 1.85 - 1.92 (m, 1 H) 1.81 (td, J=9.54, 4.93 Hz, 1 H).

Example 21

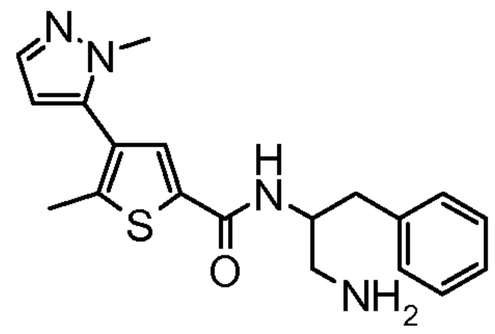


Preparation of 4-bromo-N-[2-(methylamino)-1-phenylethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 1, except substituting 1,1-dimethylethyl (2-amino-2-phenylethyl)methylcarbamate (1 g, 4.02 mmol) [Prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate and substituting 4,5-dibromo-2-thiophenecarboxylic acid (1.89 g, 6.6 mmol) for 4,5-

dibromo-2-furancarboxylic acid: LCMS (ES) m/z 420 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.64 (d, J=8.34 Hz, 1 H) 8.91 (br. s., 1 H) 8.33 (s, 1 H) 7.58 (d, J=2.02 Hz, 1 H) 7.42 - 7.50 (m, 2 H) 7.38 - 7.42 (m, 2 H) 7.34 (d, J=7.07 Hz, 1 H) 6.56 (d, J=2.02 Hz, 1 H) 5.37 - 5.44 (m, 1 H) 3.79 (s, 3 H) 3.47 - 3.54 (m, 1 H) 3.33 (td, J=8.46, 3.79 Hz, 1 H) 2.63 (t, J=5.31 Hz, 3 H).

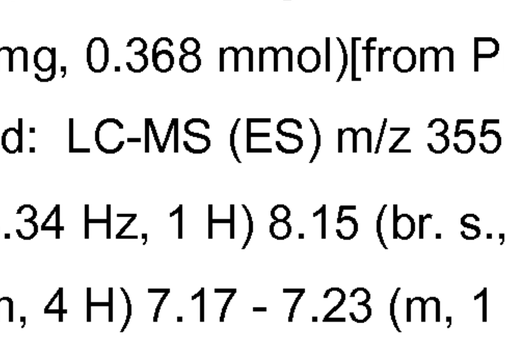
Example 22



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (81 mg, 0.368 mmol)[from Preparation 10] for 4,5-dibromo-2-furancarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=8.34 Hz, 1 H) 8.15 (br. s., 3 H) 8.00 (s, 1 H) 7.52 (d, J=1.77 Hz, 1 H) 7.24 - 7.31 (m, 4 H) 7.17 - 7.23 (m, 1 H) 6.36 (d, J=1.77 Hz, 1 H) 4.35 (d, J=3.03 Hz, 1 H) 3.78 (s, 3 H) 3.03 (dd, J=6.82, 2.53 Hz, 1 H) 2.93 - 2.99 (m, 2 H) 2.90 (d, J=6.06 Hz, 1 H) 2.38 (s, 3 H).

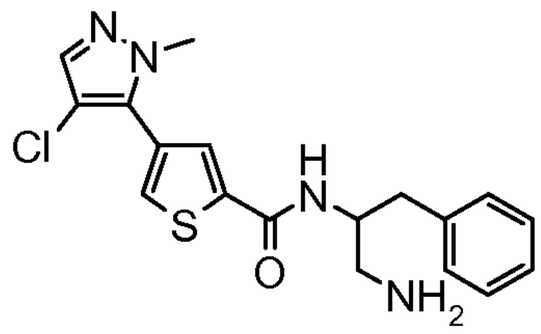
Example 23



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

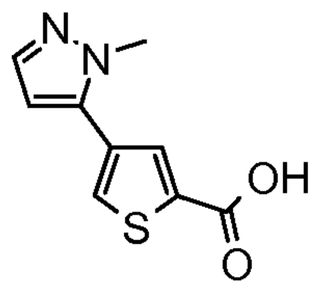
The title compound was prepared as a white solid according to the procedure of Example 1, except substituting 4-bromo-5-chloro-2-thiophenecarboxylic acid (250 mg, 1.04 mmol)[from Preparation 11] for 4,5-dibromo-2-furancarboxylic acid: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 (d, J=8.59 Hz, 1 H) 8.14 (s, 3 H) 8.10 (br. s., 1 H) 7.55 (d, J=1.77 Hz, 1 H) 7.25 - 7.32 (m, 4 H) 7.21 (dd, J=6.19, 2.40 Hz, 1 H) 6.48 (d, J=2.02 Hz, 1 H) 4.35 (d, J=8.59 Hz, 1 H) 3.84 (s, 3 H) 2.99 (d, J=10.86 Hz, 1 H) 2.89 - 2.96 (m, 3 H).

Example 24



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

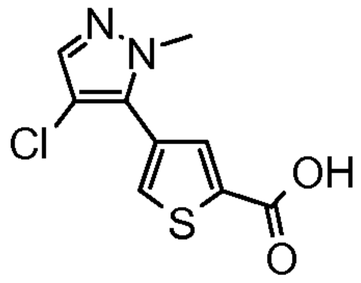
a) 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (1 g, 4.83 mmol) in dioxane/H_2O (5:1, 16 mL) was added K_2CO_3 (2.7 g, 19 mmol), tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between 6N NaOH and DCM. The pH of the aqueous

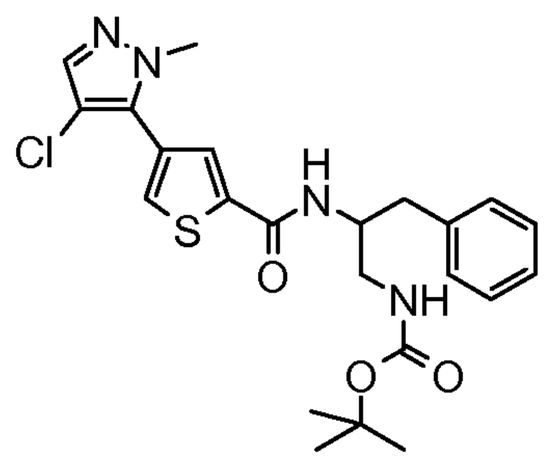
phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~1 g, quant.): LCMS (ES) m/z = 209 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (600 mg, 2.88 mmol) and N-chlorosuccinimide (384 mg, 2.88 mmol) in THF (14 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM, the aqueous phase was adjusted to pH 3 and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (698 mg, quant.): LCMS (ES) m/z = 243 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid
(350 mg, 1.45 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (362 mg, 1.45 mmol)[from Preparation 2] and diisopropylethyl amine (1.3 mL, 7.23 mmol) in DCM (7 mL) was added PyBrop (809 mg, 1.74 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase

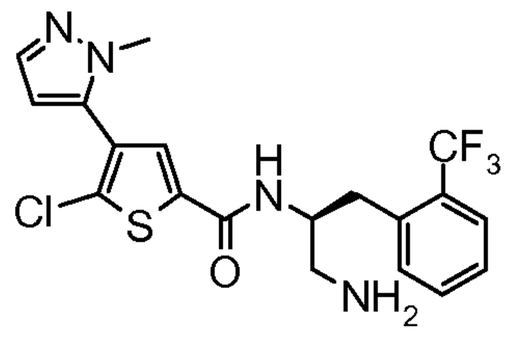
was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 476 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part c) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30 min, the solution was concentrated and the residue neutralized through a silica plug (4% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

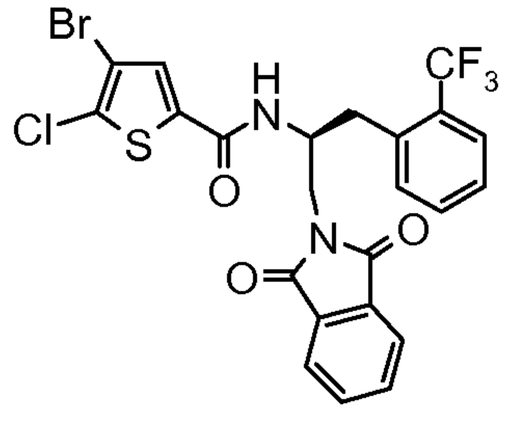
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (90 mg, 17%-2steps) as the HCl salt: LCMS (ES) m/z 476 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, J=8.08 Hz, 1 H) 8.10 (d, J=1.52 Hz, 2 H) 8.08 (s, 3 H) 7.68 (s, 1 H) 7.26 - 7.32 (m, 4 H) 7.22 (dd, J=6.06, 2.53 Hz, 1 H) 4.39 (br. s., 1 H) 3.87 (s, 3 H) 2.91 (d, J=7.33 Hz, 4 H).

Example 25



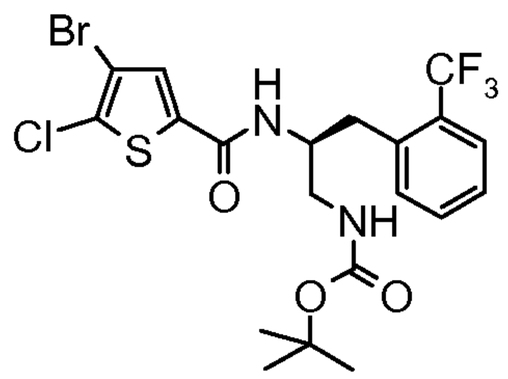
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



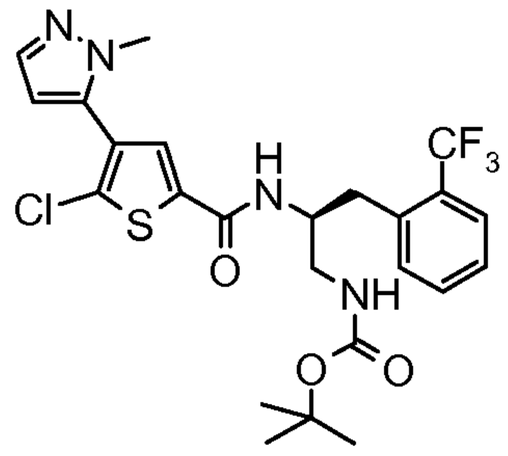
To a solution of 4-bromo-5-chloro-2-thiophenecarboxylic acid (1.3 g, 5.42 mmol), PyBrOP (3 g, 6.5 mmol) and diisopropylethyl amine (4.7 mL, 27.1 mmol) in DCM (54 mL) at 25 °C was added 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (2.0 g, 5.42 mmol)[prepared in Preparation 6]. After 1h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and used directly: LCMS (ES) m/z = 572 $(M+H)^+$.

b) 1,1-dimethylethyl {(2S)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



To a solution of 4-bromo-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (crude from part a) in THF-MeOH (1:1, 20 mL) was added hydrazine (1.59 mL, 54.2 mmol). After 12h, the solution was filtered and the filtrate concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base which was dissolved in THF (25 mL) and treated with Boc_2O (1.2 g, 5.31 mmol). After 30 min the solution was concentrated affording a white powder of the title compound (800 mg, 27%-3 steps): LCMS (ES) m/z = 542 $(M+H)^+$.

c) 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



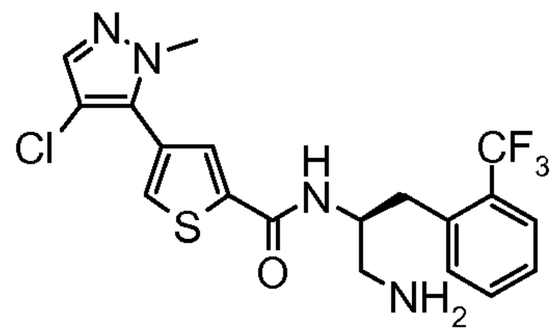
To a solution of 1,1-dimethylethyl {(2S)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (750 mg, 1.38 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (762 mg, 5.52 mmol), tetrakistriphenylphosphine Pd(0) (80 mg, 69 umol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (373 mg, 1.8 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h where additional tetrakistriphenylphosphine Pd(0) (80 mg, 69 umol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (373 mg, 1.8 mmol) were added. After 12h, the solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (194 mg, 26%) as a white solid: LC-MS (ES) m/z = 544.

c) *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (194 mg, 0.357 mmol) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30min, the solution was concentrated with a toluene azeotrope and the residue neutralized through a silica plug (2-5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

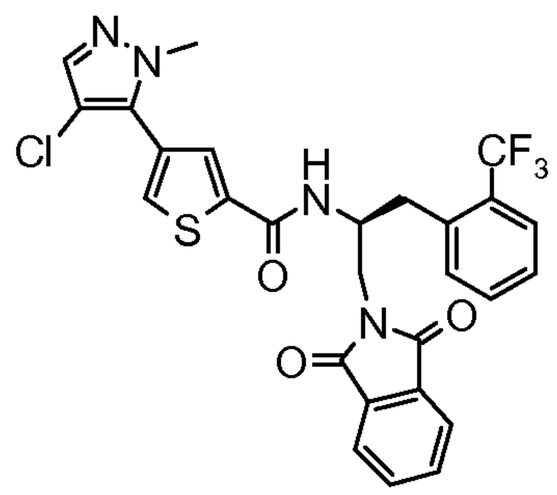
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (134 mg, 85%) as the HCl salt: LCMS (ES) m/z 444 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.10 (d, J=9.09 Hz, 1 H) 8.11 (s, 1 H) 8.10 (bs, 3 H) 7.70 (d, J=8.08 Hz, 1 H) 7.57 (d, J=2.02 Hz, 2 H) 7.43 (s, 1 H) 6.49 (d, J=2.02 Hz, 1 H) 4.47 (br. s., 1 H) 3.85 (s, 3 H) 3.06 (d, J=8.34 Hz, 4 H).

Example 26



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



The title compound was prepared as white solid according to the procedure of Example 24, except substituting 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (288 mg, 0.826 mmol)[from Preparation 6] for 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate: LCMS (ES) m/z 444 $(M+H)^+$.

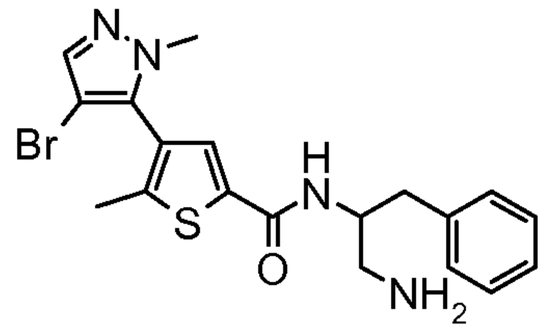
b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (150 mg, 0.262 mmol) in THF-MeOH (1:1, 2 mL) was added hydrazine (123 uL, 2.62 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (30 mg, 26%) as the HCl salt: LCMS (ES) m/z 444 $(M+H)^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.69 (s, 1 H) 8.11 (d, *J*=1.26

Hz, 1 H) 8.03 (d, *J*=1.26 Hz, 1 H) 7.93 (bs, 3H) 7.69 (s, 2 H) 7.53 - 7.59 (m, 2 H) 7.44 (d, *J*=4.80 Hz, 1 H) 4.49 (br. s., 1 H) 3.87 (s, 3 H) 2.99 - 3.12 (m, 4 H).

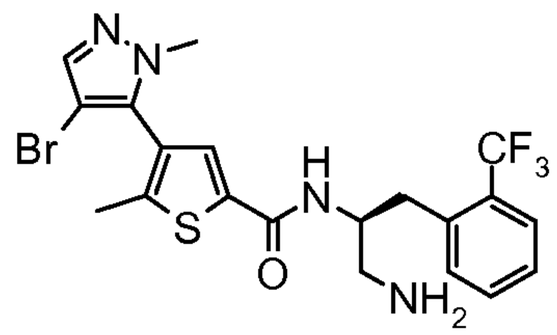
Example 27



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting NBS (325 mg, 2.43 mmol) for NCS: LCMS (ES) m/z 434 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (br. s., 1 H) 8.01 (br. s., 3 H) 7.80 (s, 1 H) 7.70 (s, 1 H) 7.25 - 7.32 (m, 4 H) 7.21 (td, J=6.19, 2.78 Hz, 1 H) 4.31 - 4.35 (m, 1 H) 3.71 (s, 3 H) 2.86 - 2.92 (m, 4 H) 2.33 (s, 3 H).

Example 28

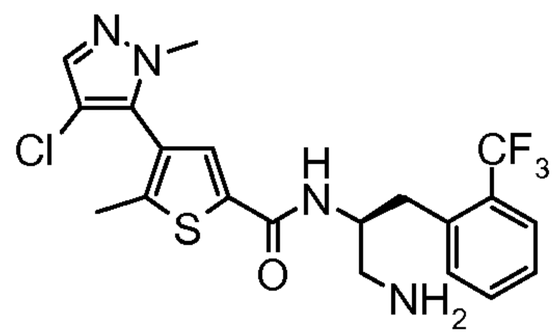


Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-bromo-5-methyl-2-

thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting NBS (325 mg, 2.43 mmol) for NCS: LCMS (ES) m/z 502 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (br. s., 1 H) 8.05 (br. s., 3 H) 7.83 - 7.90 (m, 1 H) 7.67 - 7.74 (m, 2 H) 7.53 - 7.60 (m, 2 H) 7.39 - 7.47 (m, 1 H) 4.48 (d, J=5.05 Hz, 1 H) 3.68 - 3.76 (m, 3 H) 3.01 - 3.08 (m, 4 H) 2.33 (s, 3 H).

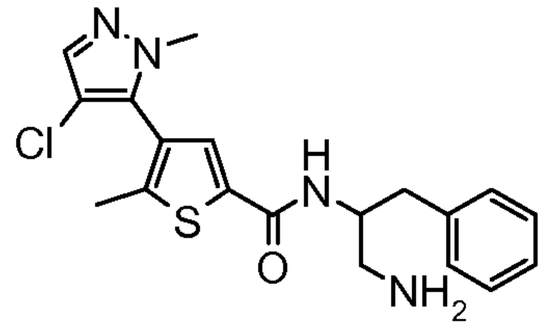
Example 29



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. s., 1 H) 8.03 (br. s., 3 H) 7.86 (s, 1 H) 7.70 (s, 2 H) 7.53 - 7.60 (m, 2 H) 7.39 - 7.47 (m, 1 H) 4.46 (d, J=9.35 Hz, 1 H) 3.72 (s, 3 H) 3.03 - 3.10 (m, 4 H) 2.34 (s, 3 H).

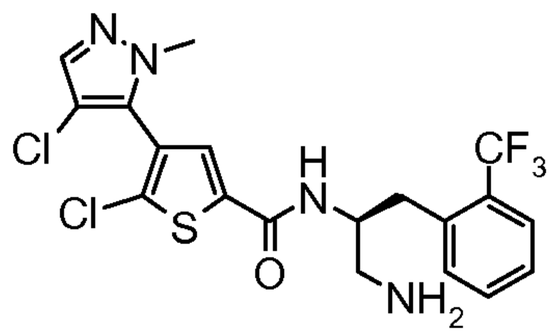
Example 30



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

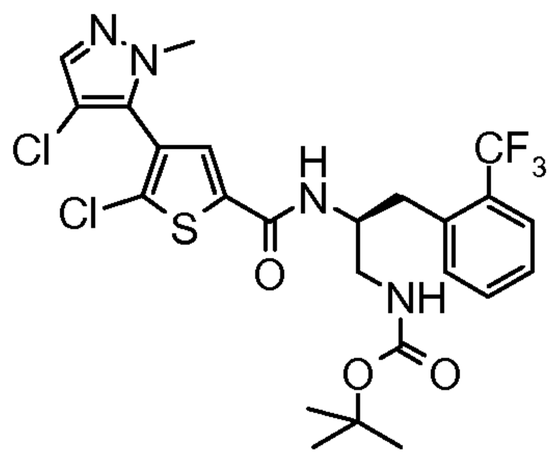
The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 389 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (br. s., 1 H) 8.01 (br. s., 3 H) 7.82 (s, 1 H) 7.70 (s, 1 H) 7.25 - 7.32 (m, 4 H) 7.19 - 7.23 (m, 1 H) 4.31 - 4.38 (m, 1 H) 3.71 (s, 3 H) 2.97 (br. s., 2 H) 2.89 (t, J=6.19 Hz, 2 H) 2.34 (s, 3 H).

Example 31



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



A solution of 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (110 mg, 0.202 mmol)[prepared in Example 25] and N-chlorosuccinimide (35 mg, 0.263 mmol) in THF (2 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4),

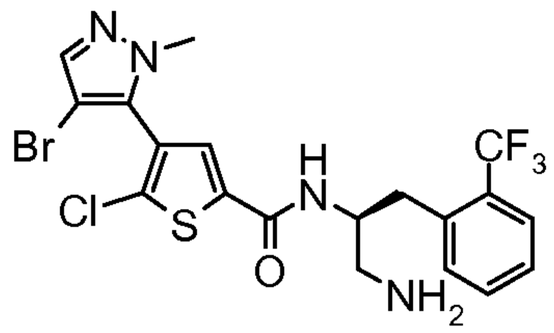
concentrated under vacuum and used directly without further purification: LCMS (ES) m/z = 578 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (crude from part a) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

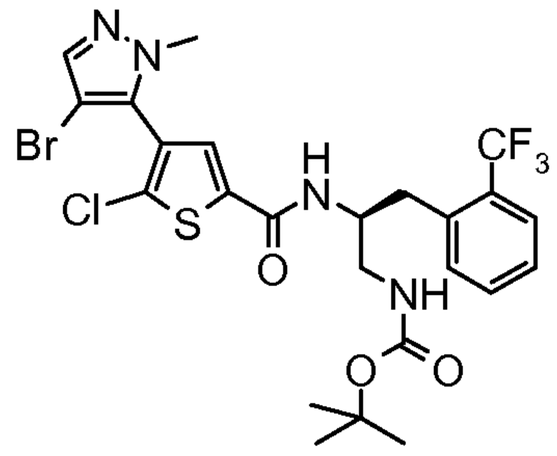
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (43 mg, 44%-2 steps) as the HCl salt: LCMS (ES) m/z 478 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.10 (d, J=8.84 Hz, 1 H) 8.06 (s, 4 H) 7.75 (s, 1 H) 7.70 (d, J=7.83 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.43 (t, J=7.45 Hz, 1 H) 4.47 (t, J=8.84 Hz, 1 H) 3.78 (s, 3 H) 2.98 – 3.12 (m, 4 H).

Example 32



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 1,1-dimethylethyl {(2S)-2-({[4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



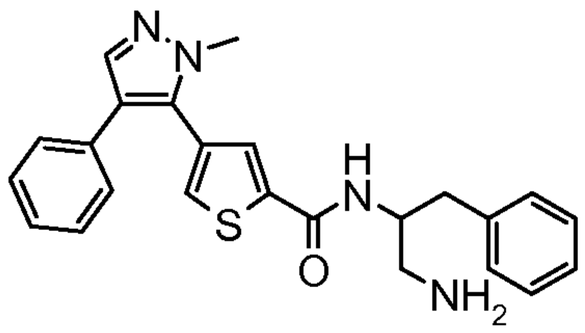
A solution of 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (121 mg, 0.22 mmol)[prepared in Example 25] and N-bromosuccinimide (52 mg, 0.290 mmol) in THF (2 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification: LCMS (ES) m/z = 622 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (crude from part a) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30 min, the solution was concentrated and the residue neutralized through a silica plug (5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

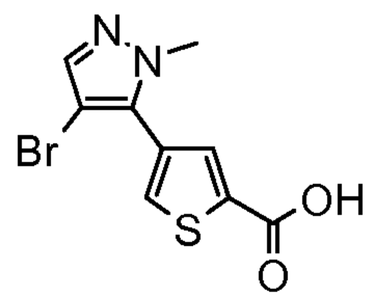
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (42 mg, 44%-2 steps) as the HCl salt: LCMS (ES) m/z 522 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (d, J=9.09 Hz, 1 H) 8.17 (br. s., 1 H) 8.05 (s, 3 H) 7.75 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.43 (t, J=7.58 Hz, 1 H) 4.46 (d, J=9.60 Hz, 1 H) 3.78 (s, 3 H) 2.99 – 3.13 (m, 4 H).

Example 33



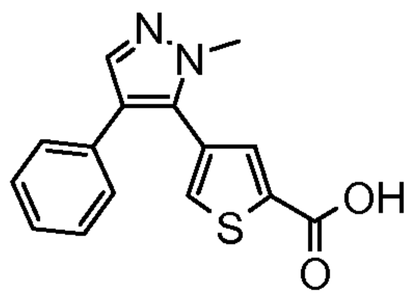
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



The title compound was prepare as an orange oil according to Example 24, except substituting N-bromosuccinimide (1 g, 5.77 mmol) for N-chlorosuccinimide: LCMS (ES) m/z 288 $(M+H)^+$.

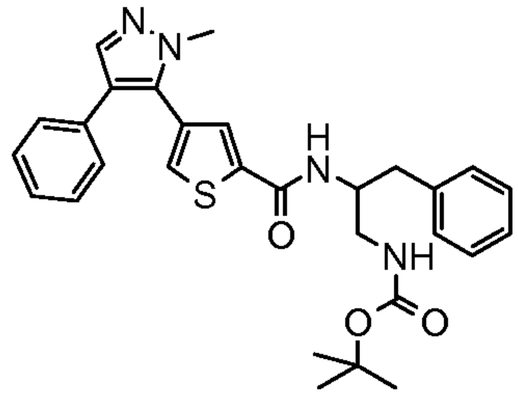
b) 4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (688 mg, 2.41 mmol) in dioxane/H_2O (5:1, 12 mL) was added K_2CO_3 (1.3 g, 9.6 mmol), tetrakistriphenylphosphine Pd(0) (139 mg, 0.120 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (293 mg, 2.41 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h where additional tetrakistriphenylphosphine Pd(0) (139 mg, 0.120 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (293 mg, 2.41 mmol) were added. After 12h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title

compound white was used directly without further purification: LC-MS (ES) m/z = 284 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



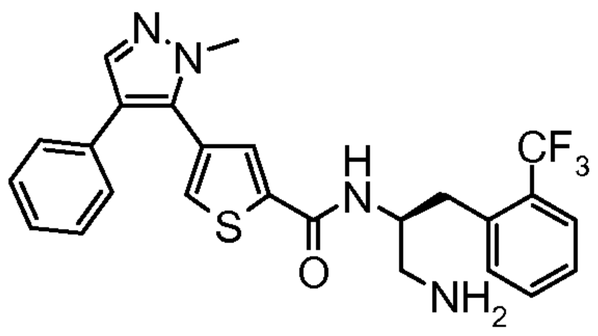
To a solution of 4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (341 mg, 1.2 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (300 mg, 1.2 mmol)[from Preparation 2], diisopropylethyl amine (1 mL, 6.01 mmol) in DCM (6 mL) was added PyBrop (673 mg, 1.44 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 517 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part c) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (4% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

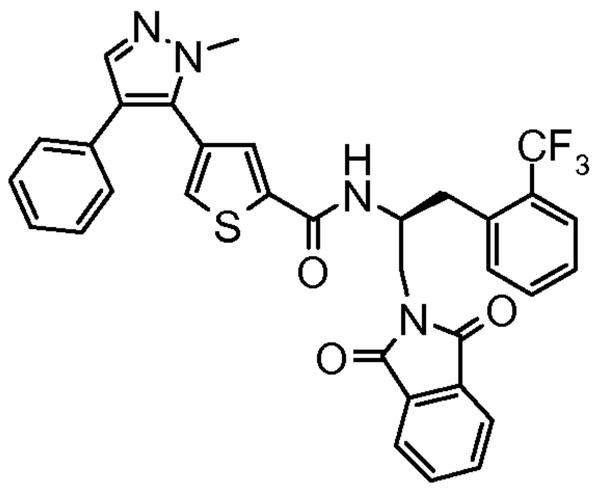
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (105 mg, 21%-3steps) as the HCl salt: LCMS (ES) m/z 417 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (d, J=8.34 Hz, 1 H) 8.14 (br. s., 3 H) 7.96 (s, 1 H) 7.90 (d, J=1.26 Hz, 1 H) 7.82 (s, 1 H) 7.29 (s, 1 H) 7.25 (t, J=8.46 Hz, 9 H) 4.34 (dd, J=7.45, 5.68 Hz, 1 H) 3.75 (s, 3 H) 2.94 - 3.00 (m, 2 H) 2.89 (dd, J=6.82, 5.31 Hz, 2 H).

Example 34



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



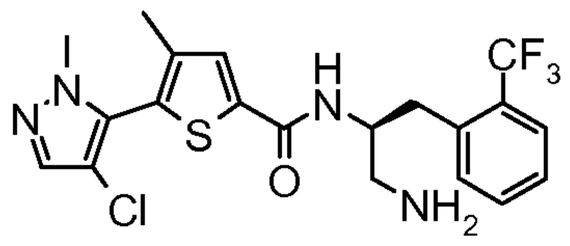
The title compound was prepared as a white solid according to the procedure of Example 33, except substituting 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (420 mg, 1.2 mmol) [from Preparation 6] for 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate: LCMS (ES) m/z 615 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (crude from part a) in THF-MeOH (1:1, 10 mL) was added hydrazine (384 uL, 12 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

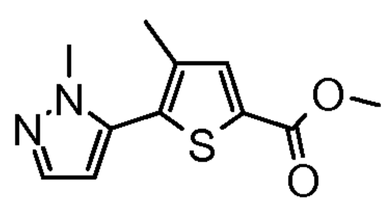
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (40 mg, 7%) as the HCl salt: LCMS (ES) m/z 485 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (d, J=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.91 (dd, J=9.09, 1.26 Hz, 2 H) 7.83 (s, 1 H) 7.69 (d, J=7.33 Hz, 1 H) 7.50 - 7.53 (m, 1 H) 7.43 (d, J=7.58 Hz, 1 H) 7.47 (t, J=6.82 Hz, 1 H) 7.23 - 7.30 (m, 4 H) 7.22 (s, 1 H) 4.47 (br. s., 1 H) 3.75 (s, 3 H) 3.01 (d, J=8.08 Hz, 4 H).

Example 35



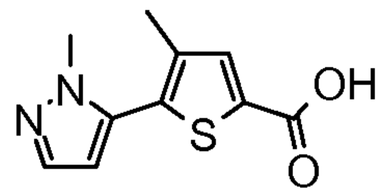
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

a) methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 5-bromo-4-methyl-2-thiophenecarboxylate (1 g, 4.25 mmol) in dioxane/H_2O (5:1, 20 mL) was added K_2CO_3 (2.3 g, 17 mmol), bis(tri-t-butylphosphine)palladium(0) (108 mg, 0.213 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.52 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification: LCMS (ES) m/z = 237 $(M+H)^+$.

b) 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid

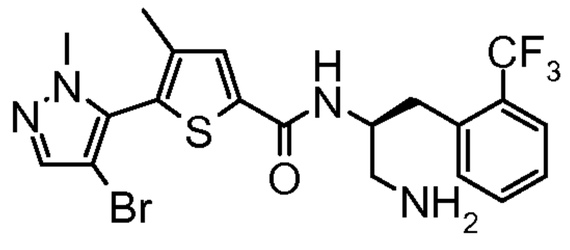


A solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (crude from part a) in THF (4 mL) and 6N NaOH (4 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound as a white solid which was used directly without further purification: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

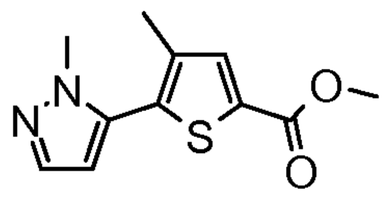
The title compound was prepared as a white solid according to the procedure of Example 27, except substituting 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (424 mg, 1.92 mmol) for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=8.84 Hz, 1 H) 8.05 (br. s., 3 H) 7.84 (s, 1 H) 7.74 (s, 1 H) 7.71 (d, J=8.08 Hz, 1 H) 7.56 - 7.63 (m, 2 H) 7.44 (t, J=7.20 Hz, 1 H) 4.47 - 4.54 (m, 1 H) 3.70 (s, 3 H) 2.93 - 3.12 (m, 4 H) 2.10 (s, 3 H).

Example 36



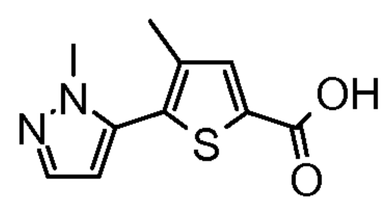
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

a) methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 5-bromo-4-methyl-2-thiophenecarboxylate (1 g, 4.25 mmol) in dioxane/H_2O (5:1, 20 mL) was added K_2CO_3 (2.3 g, 17 mmol), bis(tri-t-butylphosphine)palladium(0) (108 mg, 0.213 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.52 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.24 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification: LCMS (ES) m/z = 237 $(M+H)^+$.

b) 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



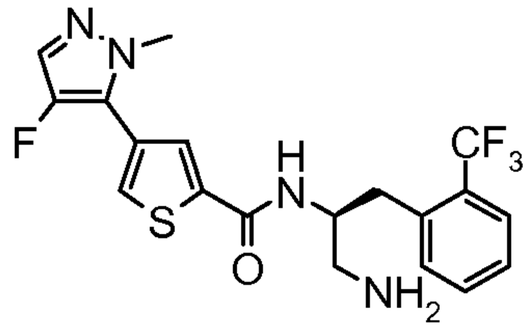
A solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (crude from part a) in THF (4 mL) and 6N NaOH (4 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound white was used directly without further purification: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (424 mg, 1.92 mmol) for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting N-bromosuccinimide (376 mg, 2.11 mmol) for N-chlorosuccinimide: LCMS (ES) m/z 502 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.83 (s, 1 H) 7.67 - 7.74

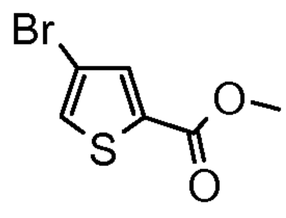
(m, 2 H) 7.60 (q, J=7.83 Hz, 2 H) 7.40 - 7.47 (m, 1 H) 4.50 (d, J=4.04 Hz, 1 H) 3.71 (s, 3 H) 2.98-3.12 (m, 4 H) 2.09 (s, 3 H).

Example 37



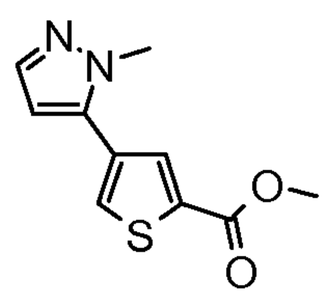
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-2-thiophenecarboxylate



To a solution of 4-bromo-2-thiophenecarboxylic acid (4g, 19 mmol) in MeOH (100 mL) was added H_2SO_4 (5 mL) dropwise at 25 °C. The solution was stirred for 12 h at 50 °C and was poured into ice-H_2O and the pH was adjusted to ~11 with aqueous NaOH. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly (4.27g, quant.): LCMS (ES) m/z 222 $(M+H)^+$.

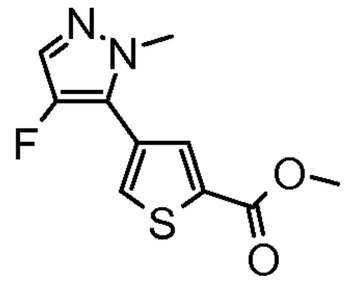
b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1 g, 4.52 mmol) in dioxane/H_2O (5:1, 16 mL) was added K_2CO_3 (2.7 g, 19 mmol), bis(tri-t-butylphosphine)palladium(0) (116 mg, 0.226 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.88 mmol). The reaction mixture was heated to 80° C in a sealed tube. After 1h, the reaction was partitioned

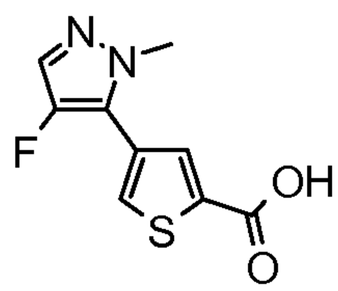
between H_2O-DCM and the aqueous phase was extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z 223 $(M+H)^+$.

c) methyl 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



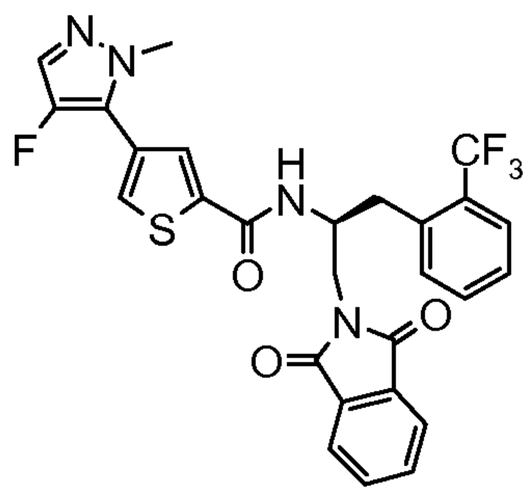
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (330 mg, 1.49 mmol) and selectfluor ® (793 mg, 2.23 mmol) in THF (7 mL) and H_2O (500 uL) was stirred in a sealed tube at 70 °C. After 1h, additional selectfluor (793 mg, 2.23 mmol) was added and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM, the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) affording the title compound (126 mg, 33%) as a white solid: LCMS (ES) m/z = 241 $(M+H)^+$.

d) 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate
(126 mg, 0.53 mmol) in THF (1 mL) and 6N NaOH (1 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound white was used directly without further purification: LCMS (ES) m/z = 227 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



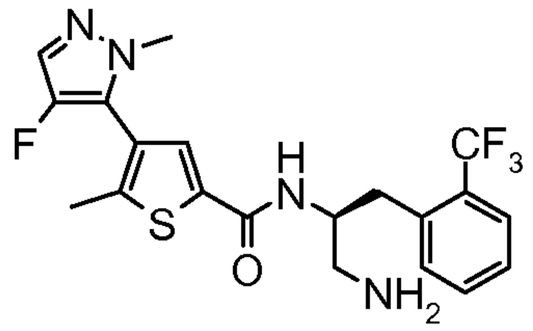
To a solution of 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (84 mg, 0.372 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (130 mg, 0.372 mmol)[from Preparation 6], diisopropylethyl amine (323 uL, 1.86 mmol) in DCM (4 mL) was added PyBrop (208 mg, 0.446 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH-DCM) affording the title compound (135 mg, 65%) as a white solid: LCMS (ES) m/z = 557 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (135 mg, 0.242 mmol) in THF-MeOH (1:1, 2 mL) was added hydrazine (75 uL, 2.42 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (3% MeOH in DCM (1% NH_4OH)). The title compound was further purified via Gilson reverse phase chromatography using 5-95% mobile phase gradient affording the TFA-salt of the title compound which was neutralized through a silica plug ((5% MeOH in DCM (1% NH_4OH)) then transferred to the HCl salt using excess 4M HCl in dioxane (40 mg, 26%): LCMS (ES) m/z 427 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 8.88 (d, J=8.84 Hz, 1 H) 8.13 (s, 1 H) 8.06 (bs, 3 H) 7.70 (d, J=7.83 Hz, 1

H) 7.55 - 7.62 (m, 3 H) 7.54 (br. s., 1 H) 7.41 (d, J=2.53 Hz, 1 H) 4.49 (d, J=5.05 Hz, 1 H) 3.92 (s, 3 H) 2.99 - 3.11 (m, 4 H).

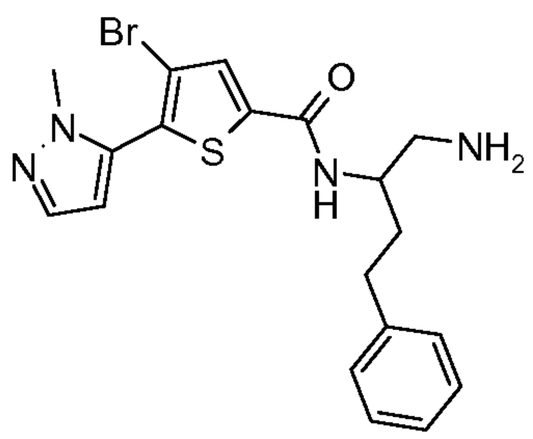
Example 38



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 37, except substituting methyl 4-bromo-5-methyl-2-thiophenecarboxylate (1g, 4.26 mmol)[from Preparation 11] for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z 441 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.78 (d, J=9.60 Hz, 1 H) 8.03 (br s, 3 H) 7.91 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.62 (d, J=4.55 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 7.39 - 7.46 (m, 1 H) 4.47 (br. s., 1 H) 3.74 (s, 3 H) 3.06 (br. s., 4 H) 2.36 (s, 3 H).

Example 39

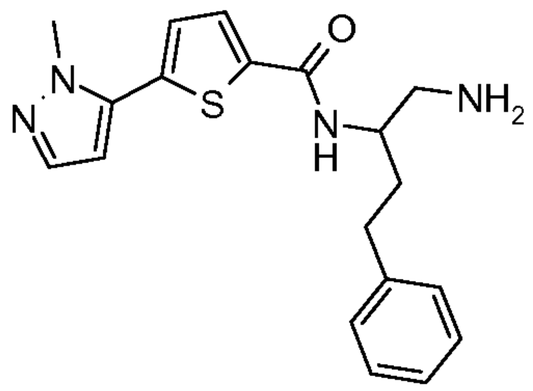


Preparation of *N*-[1-(aminomethyl)-3-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-4-

phenylbutyl)carbamate (0.44 g, 1.7 mmol) [from Preparation 4] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z = 435 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 1.92 - 2.22 (m, 2 H) 2.71 - 2.82 (m, 2 H) 3.02 - 3.11 (m, 1 H) 3.12 - 3.24 (m, 1 H) 3.88 (s, 3 H) 4.30 (s, 1 H) 6.59 (d, *J*=1.77 Hz, 1 H) 7.17 (t, *J*=7.07 Hz, 1 H) 7.22 - 7.29 (m, 4 H) 7.67 (d, *J*=1.77 Hz, 1 H) 7.85 (s, 1 H).

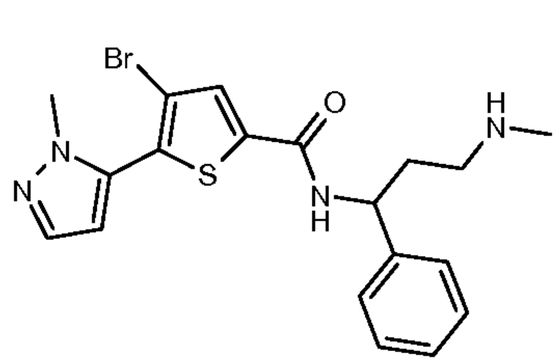
Example 40



Preparation of *N*-[1-(aminomethyl)-3-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (223 mg, 1.07 mmol) for 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (0.51 g, 1.9 mmol) [from Preparation 4] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 1.87 - 1.99 (m, 2 H) 2.69 - 2.91 (m, 4 H) 4.00 - 4.07 (m, 3 H) 4.08 - 4.16 (m, 1 H) 6.56 (d, *J*=2.02 Hz, 1 H) 7.15 (t, *J*=6.95 Hz, 1 H) 7.20 - 7.28 (m, 4 H) 7.35 (d, *J*=3.79 Hz, 1 H) 7.51 (d, *J*=1.77 Hz, 1 H) 7.79 (d, *J*=3.79 Hz, 1 H).

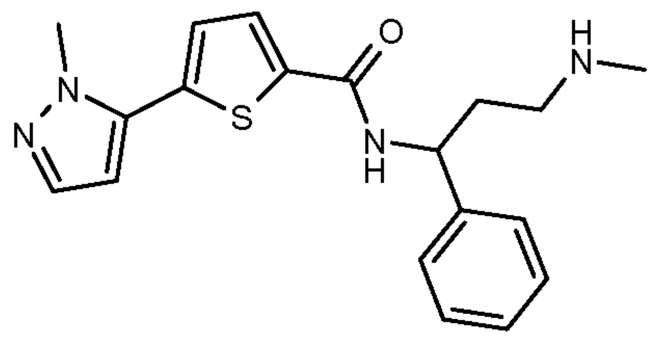
Example 41



Preparation of 4-bromo-*N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate (289 mg, 1.09 mmol) [from Preparation 12] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.12 - 2.23 (m, 2 H) 2.45 - 2.52 (m, 3 H) 2.64 - 2.74 (m, 1 H) 2.76 (dd, *J*=8.72, 5.94 Hz, 1 H) 3.77 - 3.88 (m, 3 H) 5.10 - 5.20 (m, 1 H) 6.52 (d, *J*=2.02 Hz, 1 H) 7.30 (d, *J*=6.82 Hz, 1 H) 7.35 - 7.45 (m, 4 H) 7.57 (d, *J*=1.77 Hz, 1 H) 7.89 (s, 1 H).

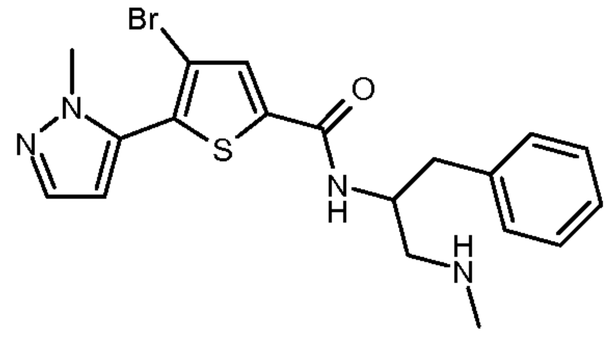
Example 42



Preparation of *N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate (430 mg, 1.63 mmol) [from Preparation 12] for 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate and substituting 5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (224 mg, 1.08 mmol) for 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.18 - 2.28 (m, 2 H) 2.55 (s, 3 H) 2.77 - 2.85 (m, 1 H) 2.87 (dd, *J*=8.84, 5.81 Hz, 1 H) 4.01 (s, 3 H) 5.19 (dd, *J*=8.59, 6.57 Hz, 1 H) 6.55 (d, *J*=2.02 Hz, 1 H) 7.31 (d, *J*=7.07 Hz, 1 H) 7.34 - 7.41 (m, 3 H) 7.44 - 7.47 (m, 2 H) 7.50 (d, *J*=2.02 Hz, 1 H) 7.85 (d, *J*=4.04 Hz, 1 H).

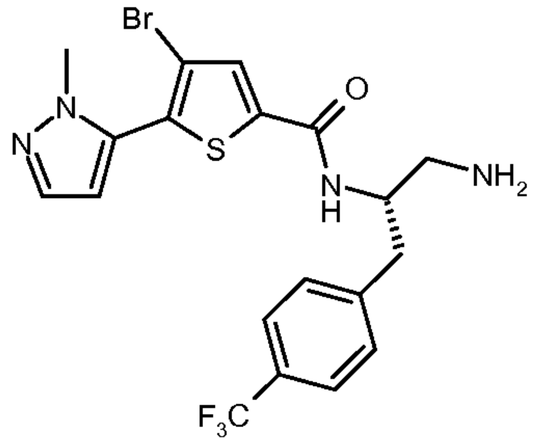
Example 43



Preparation of 4-bromo-*N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate (0.26 g, 1.09 mmol) [from Preparation 12] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.60 (s, 3 H) 2.90 - 3.01 (m, 2 H) 3.06 (d, *J*=6.57 Hz, 2 H) 3.83 (s, 3 H) 4.48 - 4.58 (m, 1 H) 6.52 (d, *J*=1.77 Hz, 1 H) 7.17 - 7.27 (m, 1 H) 7.27 - 7.33 (m, 4 H) 7.57 (d, *J*=2.02 Hz, 1 H) 7.77 (s, 1 H).

Example 44

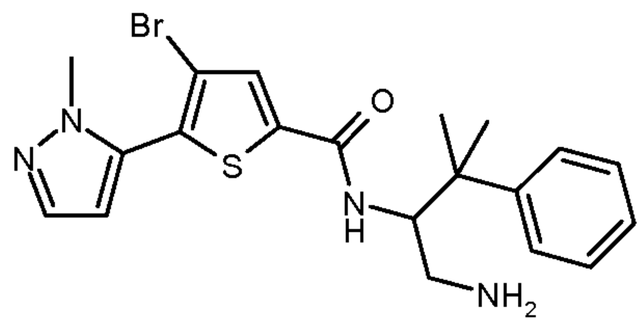


Preparation of *N*-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 6, except substituting 2-{(2*S*)-2-amino-3-[4-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.22 g, 0.62 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was absorbed onto silica and purified via column chromatography to yield the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 489 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.04 - 3.30 (m, 4 H) 3.81 - 3.85 (m, 3 H) 4.59 (dd,

J=6.32, 3.28 Hz, 1 H) 6.52 (d, *J*=2.02 Hz, 1 H) 7.50 (d, *J*=8.08 Hz, 2 H) 7.58 (d, *J*=2.02 Hz, 1 H) 7.64 (d, *J*=8.08 Hz, 2 H) 7.73 (s, 1 H).

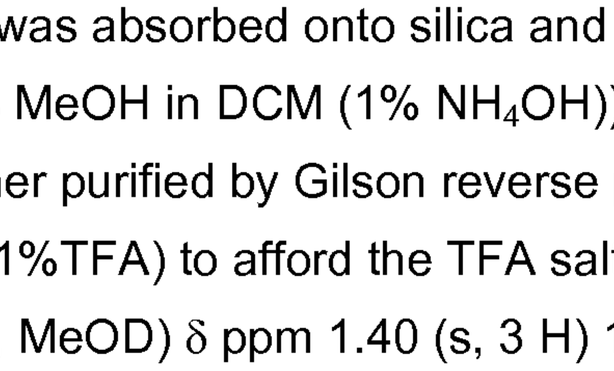
Example 45



Preparation of *N*-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (194 mg, 0.68mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2 -(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione (0.20 g, 0.58 mmol) [prepared according to preparation 16] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 448 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.40 (s, 3 H) 1.47 (s, 3 H) 2.85 - 2.92 (m, 1 H) 3.01 (d, *J*=11.37 Hz, 1 H) 3.83 - 3.86 (m, 3 H) 4.74 (dd, *J*=11.37, 2.27 Hz, 1 H) 6.54 (d, *J*=2.02 Hz, 1 H) 7.28 (t, *J*=7.33 Hz, 1 H) 7.41 (t, *J*=7.71 Hz, 3 H) 7.52 (d, *J*=7.58 Hz, 2 H) 7.59 (d, *J*=2.02 Hz, 1 H) 7.89 (s, 1 H).

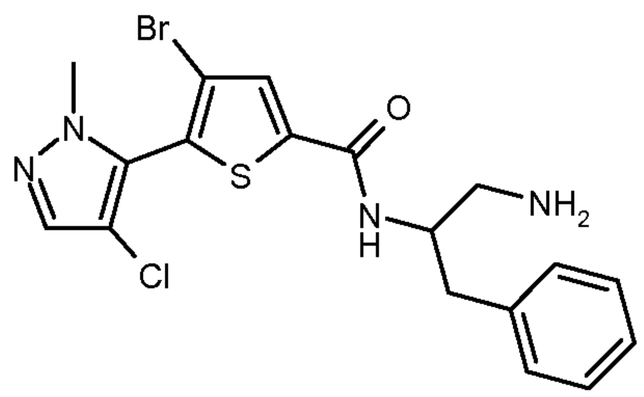
Example 46



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (135 mg, 0.47mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (153 mg, 0.44 mmol) [prepared according to the procedure of Preparation 6] for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 491 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.03 (dd, *J*=13.89, 9.35 Hz, 1 H) 3.14 - 3.21 (m, 1 H) 3.21 - 3.29 (m, 2 H) 3.84 (s, 3 H) 4.62 - 4.70 (m, 1 H) 6.53 (d, *J*=2.02 Hz, 1 H) 7.28 - 7.32 (m, 1 H) 7.33 - 7.37 (m, 1 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.58 (d, *J*=2.02 Hz, 1 H) 7.73 - 7.76 (m, 1 H).

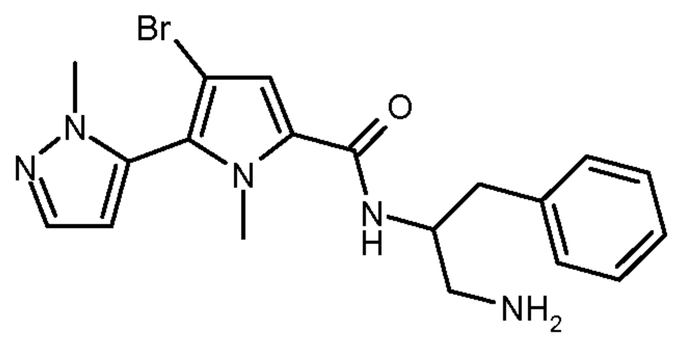
Example 47



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

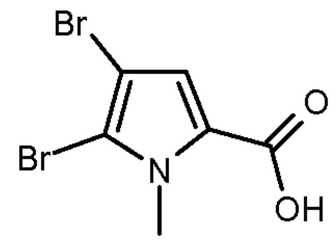
The title compound was prepared as a pale yellow solid according to the procedure of Example 30, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (2.84 g, 9.9mmol) for 4-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.95 - 3.07 (m, 4 H) 3.75 (s, 3 H) 4.44 (dd, *J*=6.44, 4.93 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 7.27 - 7.32 (m, 4 H) 7.59 (s, 1 H) 7.86 (s, 1 H) .

Example 48



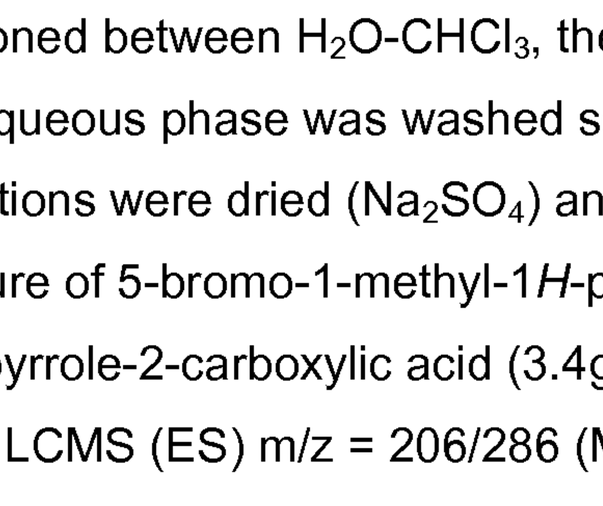
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

a) 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid



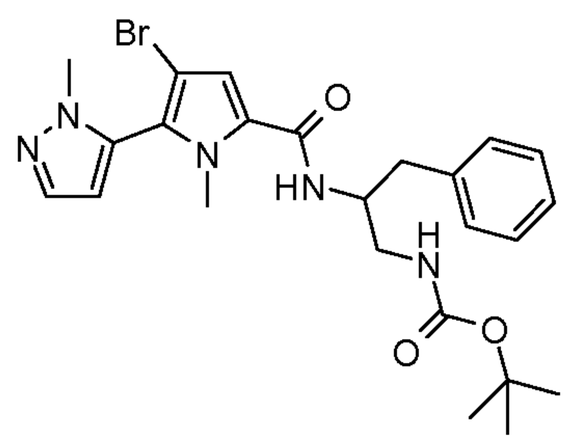
NBS (6.3 g, 35.4 mmol) was added in portions over 15 minutes to a stirred solution of 1-methyl-1*H*-pyrrole-2-carboxylic acid (2.1 g, 16.78 mmol) in DMF (30 mL) at 0 °C. Upon complete addition the mixture was slowly brought to 70°C. After 1h, the solution was partitioned between H_2O-$CHCl_3$, the aqueous phase was adjusted to pH 3 and the aqueous phase was washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4) and concentrated under vacuum to yield a 3:4 mixture of 5-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid and 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (3.4g) which was used directly without further purification: LCMS (ES) m/z = 206/286 $(M+H)^+$.

b) 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 5-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid and 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (1.3 g), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (1.2 g, 4.8 mmol) [from Preparation 2] and PyBrop (2.6 g, 5.6 mmol) in $CHCl_3$ (30 mL) was added diisopropylethyl amine (2.8 mL, 16.1 mmol). The reaction mixture was stirred overnight, adsorbed onto silica and purified via column chromatography [1:3 EtOAc/hexanes] to give a 1:1 mixture of 1,1-dimethylethyl (2-{[(5-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate and 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (800 mg): LCMS (ES) m/z = 438/518 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate



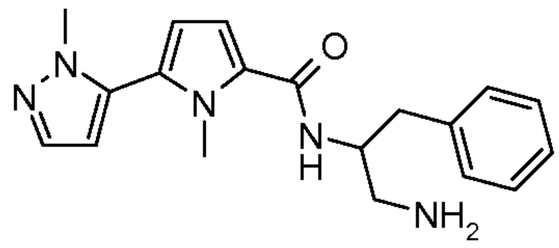
To a solution of a 1:1 mixture of 1,1-dimethylethyl (2-{[(5-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate and 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (307 mg) in dioxane/H_2O (5:1, 5.6 mL) was added Cs_2CO_3 (800 mg, 2.5 mmol), tetrakistriphenylphosphine Pd(0) (44 mg, 0.04 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (157 mg, 0.75 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h after which additional tetrakistriphenylphosphine Pd(0) (20 mg, 0.02 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (177 mg, 0.85 mmol) were added. After 12h, the reaction mixture was adsorbed onto silica and purified via column chromatography to give two isomers: the title compound 1,1-dimethylethyl [2-({[4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (17 mg, 0.033 mmol) and 1,1-dimethylethyl [2-({[1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (20 mg, 0.05 mmol).

d) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

1,1-dimethylethyl [3-{[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]amino}-3-oxo-2-(phenylmethyl)propyl]carbamate (0.045 g, 0.09 mmol) dissolved in $CHCl_3$ (4 mL) and MeOH (1 mL) was treated with 4 M HCl in dioxane (2 mL). After stirring for 18h at RT, the reaction solution was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound as a white solid.

The neutral compound from above was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (150 μL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z 418 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.76 - 2.98 (m, 4 H) 3.57 (d, *J*=2.78 Hz, 3 H) 3.71 (d, *J*=1.26 Hz, 3 H) 4.28 (ddd, *J*=8.27, 5.12, 2.78 Hz, 1 H) 6.44 (dd, *J*=7.58, 2.02 Hz, 1 H) 6.85 (s, 1 H) 7.18 - 7.24 (m, 1 H) 7.27 - 7.32 (m, 4 H) 7.61 (d, *J*=2.02 Hz, 1 H).

Example 49



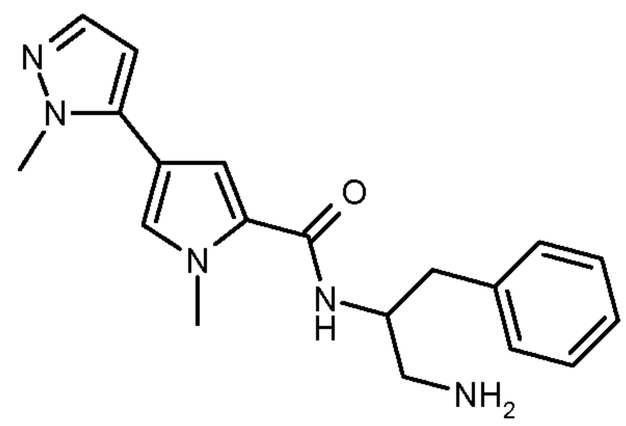
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

1,1-dimethylethyl [2-({[1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (20 mg, 0.05 mmol) [prepared in Example 48] in $CHCl_3$ (4 mL) and MeOH (1 mL) was treated with 4 M HCl in dioxane (2 mL). After stirring for 18h at RT, the reaction solution was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound.

The above compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (150 μL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z 338 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.74 - 2.81 (m, 1 H) 2.83 - 2.90 (m, 2 H) 2.92 - 2.98 (m, 1 H) 3.63 (s, 3 H) 3.76 (s, 3 H)

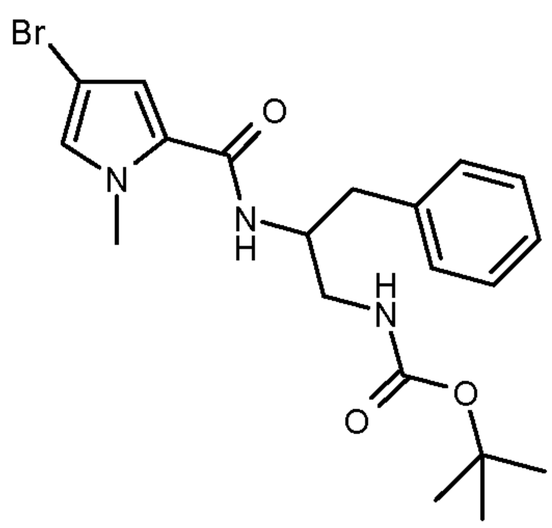
4.29 (ddd, *J*=8.02, 5.12, 2.53 Hz, 1 H) 6.27 (d, *J*=4.04 Hz, 1 H) 6.39 (d, *J*=2.02 Hz, 1 H) 6.80 (d, *J*=4.04 Hz, 1 H) 7.20 (td, *J*=5.87, 2.65 Hz, 1 H) 7.26 - 7.31 (m, 4 H) 7.57 (d, *J*=2.02 Hz, 1 H) .

Example 50



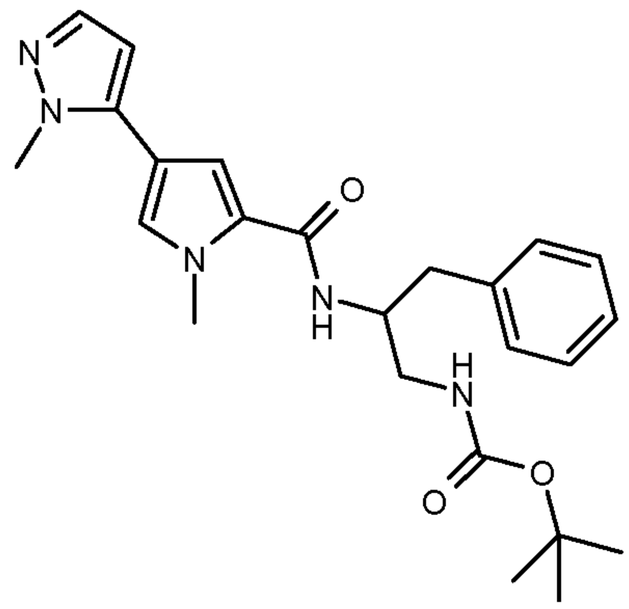
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

a) 1,1-dimethylethyl (2-{[(4-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate



To a 50 mL round-bottomed flask was added 4-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (610 mg, 3.0 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (748 mg, 2.99 mmol) [prepared according to the procedure of Preparation 2] and PyBrop (1.71 g, 3.67 mmol) in Chloroform (15 mL). DIEA (1.8 mL, 10.3 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (Hex/EtOAc) affording the title compound (335 mg, 26%): LC-MS (ES) m/z = 438 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate

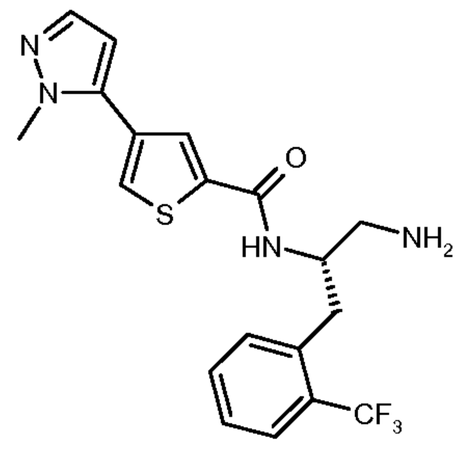


To a solution of 1,1-dimethylethyl (2-{[(4-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (313 mg, 0.717 mmol) in dioxane/H_2O (4:1, 6.25 mL) was added Cs_2CO_3 (840 mg, 2.6 mmol), tetrakistriphenylphosphine Pd(0) (62 mg, 0.05 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (202 mg, 1.04 mmol). The reaction mixture was heated to 80 °C in a sealed tube for 12h and was then partitioned between H_2O and $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum, adsorbed onto silica gel and purified via column chromatography (35% EtOAc/Hex) affording the title compound (285 mg, 91%): LC-MS (ES) m/z = 438 $(M+H)^+$.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

HCl in Dioxane (4M, 2mL) was added to a solution of 1,1-dimethylethyl [2-({[1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (285 mg, 0.65 mmol) in CHCl3/MeOH (10:1, 10 mL) affording the title compound as a white solid (71 mg, 0.21 mmol, 32%): LC-MS (ES) m/z 338 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.77 - 2.93 (m, 4 H) 3.86 (s, 3 H) 3.92 (s, 3 H) 4.29 (ddd, *J*=8.15, 4.74, 2.02 Hz, 1 H) 6.30 (d, *J*=2.02 Hz, 1 H) 6.94 (d, *J*=1.77 Hz, 1 H) 7.14 (d, *J*=1.77 Hz, 1 H) 7.19 (td, *J*=5.56, 3.03 Hz, 1 H) 7.25 - 7.30 (m, 4 H) 7.41 (d, *J*=1.77 Hz, 1 H).

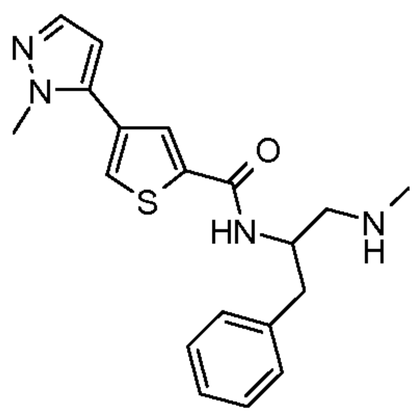
Example 51



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (232 mg, 1.11mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.09 - 3.30 (m, 4 H) 3.97 - 4.00 (m, 3 H) 4.62 - 4.72 (m, 1 H) 6.48 (d, *J*=2.02 Hz, 1 H) 7.43 (ddd, *J*=8.08, 4.42, 4.17 Hz, 1 H) 7.51 - 7.56 (m, 3 H) 7.72 (d, *J*=7.83 Hz, 1 H) 7.89 - 7.93 (m, 2 H).

Example 52

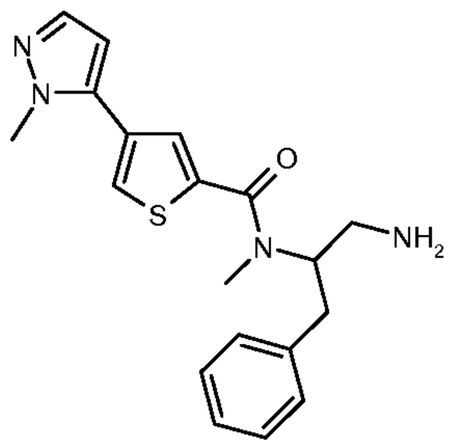


Preparation of *N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate (0.32 g, 1.2 mmol) [from Preparation 13] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate and substituting 4-(1-methyl-1*H*-

pyrazol-5-yl)-2-thiophenecarboxylic acid (220 mg, 1.06 mmol) for 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.41 (s, 3 H) 2.81 (td, *J*=11.81, 7.96 Hz, 2 H) 2.87 - 2.97 (m, 2 H) 3.96 (s, 3 H) 4.43 - 4.52 (m, 1 H) 6.45 (d, *J*=1.52 Hz, 1 H) 7.16 - 7.23 (m, 1 H) 7.25 - 7.30 (m, 4 H) 7.50 (d, *J*=1.52 Hz, 1 H) 7.85 (d, *J*=13.14 Hz, 2 H).

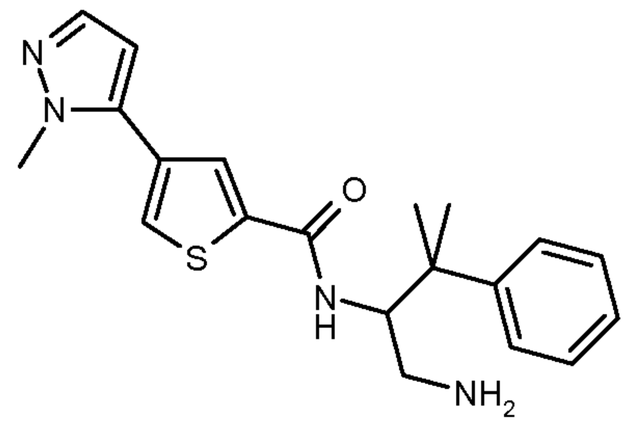
Example 53



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-*N*-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 2-[2-(methylamino)-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.7 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl and substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.72 mmol) for 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.86 (s, 3 H) 2.97 (dd, *J*=14.02, 8.72 Hz, 2 H) 3.12 - 3.23 (m, 2 H) 3.70 (m, 1 H) 3.97 (s, 3 H) 6.47 (d, *J*=2.02 Hz, 1 H) 7.30 - 7.35 (m, 1 H) 7.37 - 7.43 (m, 5 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.88 (d, *J*=1.52 Hz, 1 H) 7.94 (d, *J*=1.52 Hz, 1 H).

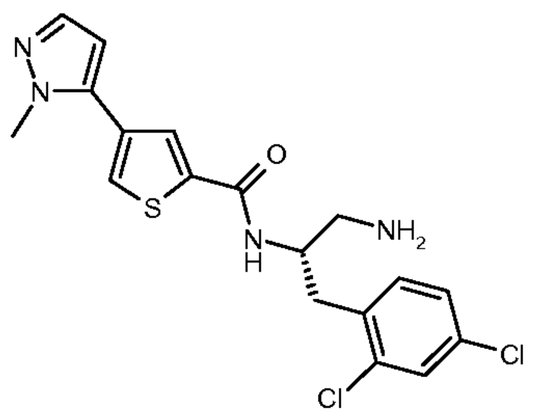
Example 54



Preparation of *N*-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (129 mg, 0.62 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2 -(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione (0.20 g, 0.58 mmol) [prepared according to the procedure of Preparation 14] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 369 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 1.36 (s, 3 H) 1.41 (s, 3 H) 2.61 (d, *J*=6.82 Hz, 2 H) 3.99 (s, 3 H) 4.49 (t, *J*=6.95 Hz, 1 H) 6.49 (d, *J*=1.77 Hz, 1 H) 7.23 (t, *J*=7.33 Hz, 1 H) 7.36 (t, *J*=7.71 Hz, 2 H) 7.47 - 7.52 (m, 3 H) 7.89 (d, *J*=1.26 Hz, 1 H) 8.00 (d, *J*=1.52 Hz, 1 H)).

Example 55

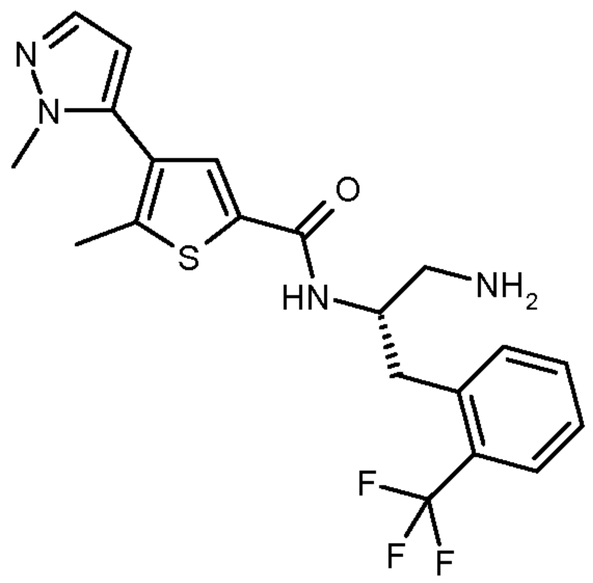


Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (99 mg, 0.48mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (155 mg, 0.44 mmol) [prepared

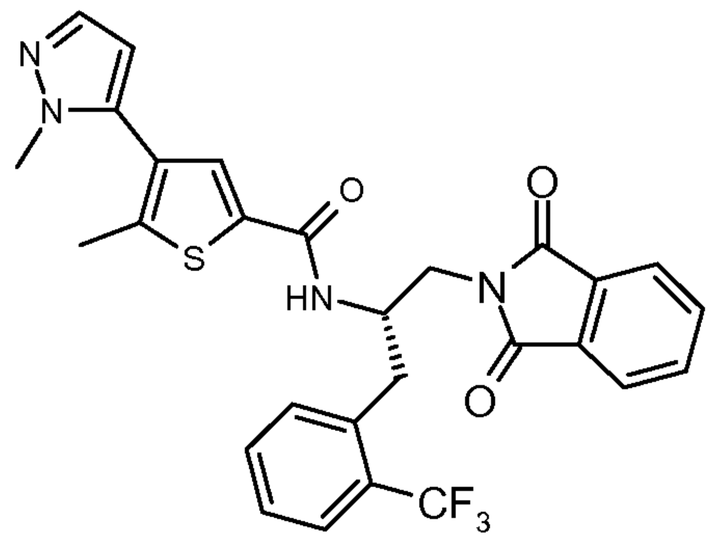
according to procedure of Preparation 6] for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 411 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.05 - 3.28 (m, 4 H) 3.97 (s, 3 H) 4.63 - 4.72 (m, 1 H) 6.47 (d, *J*=2.02 Hz, 1 H) 7.26 - 7.29 (m, 1 H) 7.34 - 7.37 (m, 1 H) 7.49 (d, *J*=2.27 Hz, 1 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.86 (d, *J*=1.52 Hz, 1 H) 7.90 (d, *J*=1.52 Hz, 1 H).

Example 56



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (206 mg, 0.93 mmol) [prepared according

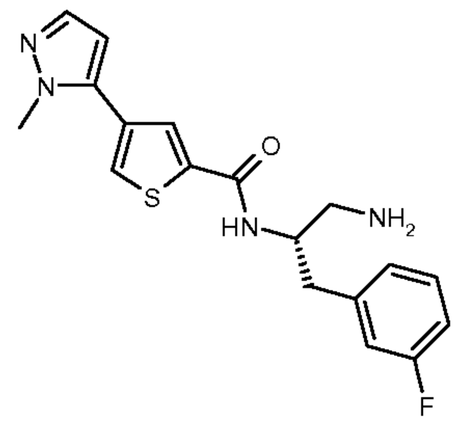
to the procedure of Preparation 9], 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (209 mg, 0.60 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (340 mg, 0.73 mmol) in Chloroform (15 mL). DIEA (0.81 mL, 4.65 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (112 mg, 0.203 mmol, 22%): LC-MS (ES) m/z = 553 $(M+H)^+$

b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (112 mg, 0.203 mmol) in Tetrahydrofuran (THF) (6 mL) and Methanol (1 mL). Hydrazine (40 µL, 1.3 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (43 mg, 0.102 mmol, 50 % yield): LC-MS (ES) m/z 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 3.01 (m, 1 H) 3.08 (d, *J*=6.57 Hz, 3 H) 3.76 - 3.83 (m, 3 H) 4.47 (m, 1 H) 6.37 (d, *J*=2.02 Hz, 1 H) 7.41 (t, *J*=7.58 Hz, 1 H) 7.50 - 7.57 (m, 2 H) 7.57 - 7.63 (m, 1 H) 7.68 (d, *J*=7.58 Hz, 1 H) 8.04 (d, *J*=9.09 Hz, 1 H) 8.15 (s, 3 H) 8.96 (s, 1 H).

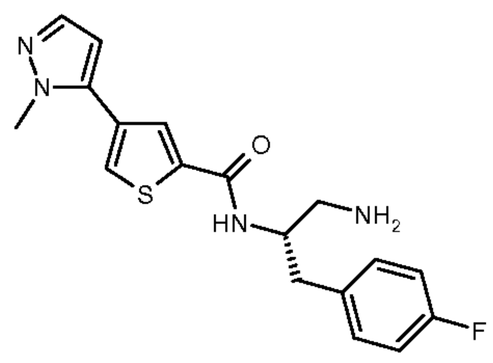
Example 57



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (222 mg, 1.07mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (357 mg, 1.2 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 359 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.96 - 3.06 (m, 4 H) 3.92 - 3.98 (m, 3 H) 4.40 (dd, *J*=8.08, 5.56 Hz, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.02 (td, *J*=8.46, 2.02 Hz, 1 H) 7.14 (t, *J*=8.08 Hz, 2 H) 7.26 - 7.35 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.16 - 8.27 (m, 3 H) 8.34 (d, *J*=1.26 Hz, 1 H) 9.08 (d, *J*=8.34 Hz, 1 H).

Example 58

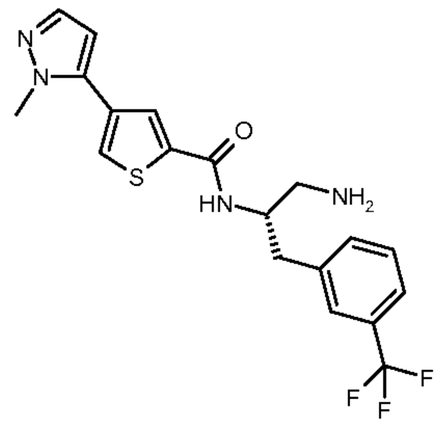


Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (138 mg, 0.66 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (196 mg, 0.66 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-

1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 - 3.03 (m, 4 H) 3.89 - 3.97 (m, 3 H) 4.30 - 4.40 (m, 1 H) 6.45 (d, *J*=1.77 Hz, 1 H) 7.12 (t, *J*=8.84 Hz, 2 H) 7.29 (dd, *J*=8.34, 5.56 Hz, 2 H) 7.48 (d, *J*=1.77 Hz, 1 H) 7.92 (br. s, 3 H) 7.96 (d, *J*=1.26 Hz, 1 H) 8.02 (d, *J*=1.26 Hz, 1 H) 8.58 (d, *J*=8.84 Hz, 1 H).

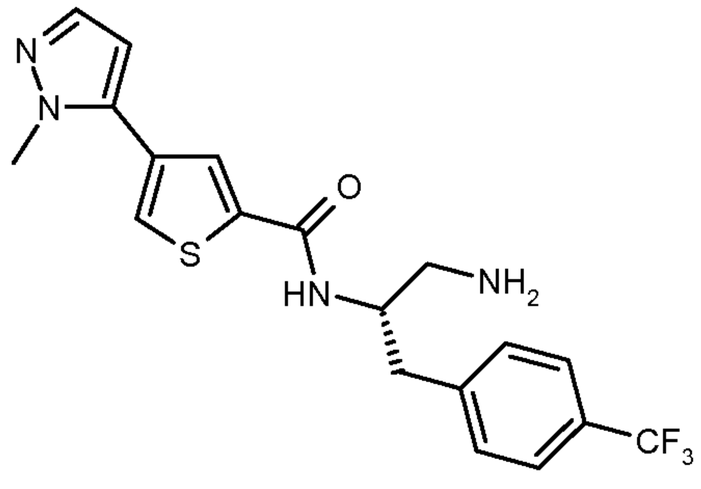
Example 59



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (189 mg, 0.91mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (297 mg, 0.85 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (d, *J*=7.07 Hz, 4 H) 3.91 - 3.98 (m, 3 H) 4.35 - 4.45 (m, 1 H) 6.46 (d, *J*=1.77 Hz, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.49 - 7.57 (m, 2 H) 7.58 - 7.63 (m, 1 H) 7.69 (s, 1 H) 7.98 (d, *J*=1.52 Hz, 1 H) 8.23 (s, 3 H) 8.32 (d, *J*=1.26 Hz, 1 H) 9.11 (d, *J*=8.84 Hz, 1 H).

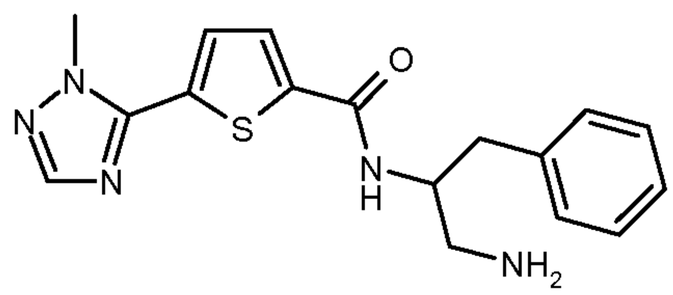
Example 60



Preparation of *N*-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

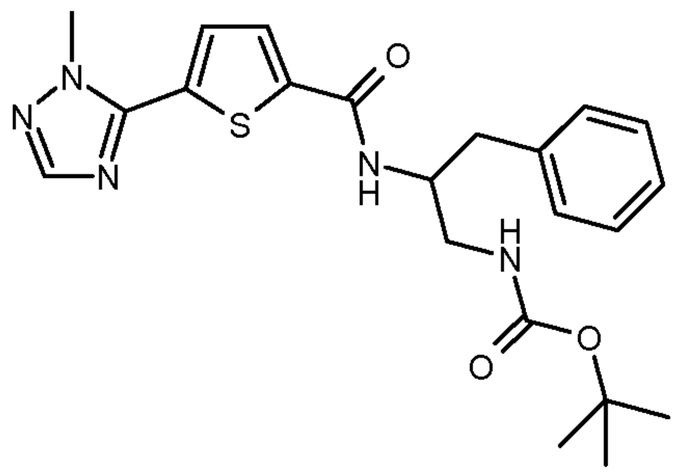
The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (240 mg, 0.9 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substitiuting 2-{(2*S*)-2-amino-3-[4-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (278 mg, 0.80 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 409 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.04 (m, 4 H) 3.96 (s, 3 H) 4.42 (s, 1 H) 6.44 - 6.49 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.52 (d, *J*=7.83 Hz, 2 H) 7.66 (d, *J*=8.08 Hz, 2 H) 8.01 (s, 1 H) 8.05 – 8.32 (br. m, 3H) 8.34 (m, 1H) 8.9 – 9.2 (br. s, 1 H).

Example 61



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

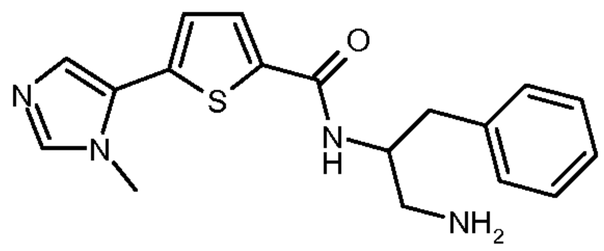


To a solution of 1,1-dimethylethyl [3-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)propyl]carbamate (154 mg, 0.32 mmol) [prepared according to the procedure of Example 3] in Dioxane / H_2O (5:1, 3.1 mL) was added Cs_2CO_3 (415 mg, 1.27 mmol), tetrakistriphenylphosphine Pd(0) (29 mg, 0.03 mmol), and 5-iodo-1-methyl-1*H*-1,2,4-triazole (95 mg, 0.46 mmol) [prepared according to the procedure of Preparation 15]. The reaction mixture was heated to 85 °C in a sealed tube for 12 hours. The reaction was partitioned between H_2O and $CHCl_3$, the organic layer dried with Na_2SO_4, absorbed onto silica and purified via column chromatography (35-50% EtOAc/Hexanes) affording the title compound as a yellow solid (61 mg, 28%): LC-MS (ES) m/z = 521.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

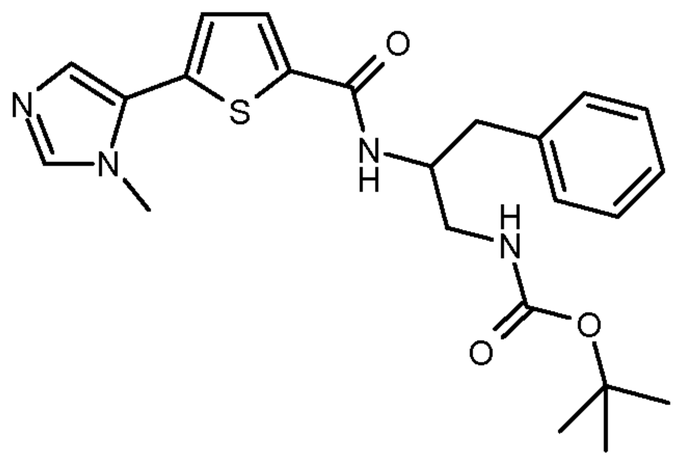
HCl in Dioxane (4M, 1mL) was added to a solution of 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (61 mg, 0.12 mmol) in $CHCl_3$/MeOH (10:1, 10 mL) and the mixture stirred overnight. Upon completion, the mixture was adsorbed onto silica gel and purified via chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound as a white solid (30 mg, 0.09 mmol, 77%): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.79 - 2.91 (m, 3 H) 2.94 (t, *J*=5.56 Hz, 1 H) 4.10 (s, 3 H) 4.25 - 4.34 (m, 1 H) 7.18 (ddd, *J*=8.27, 5.75, 3.16 Hz, 1 H) 7.24 - 7.29 (m, 4 H) 7.63 (d, *J*=4.04 Hz, 1 H) 7.75 (d, *J*=4.04 Hz, 1 H) 7.95 (s, 1 H).

Example 62



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-imidazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



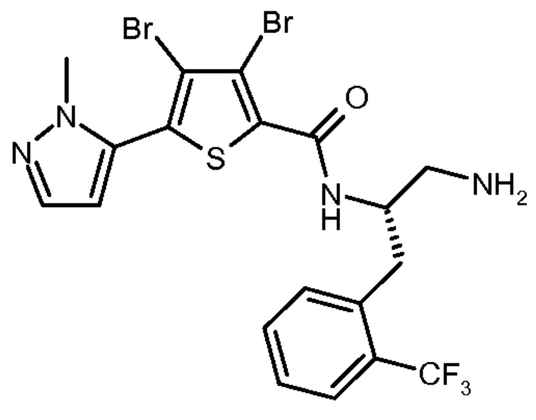
To a solution of 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate (72 mg, 0.15 mmol) [prepared according to the procedure of Example 3] in dioxane/H_2O (5:1, 1.4 mL) was added Cs_2CO_3 (200 mg, 0.61 mmol), tetrakistriphenylphosphine Pd(0) (8.5 mg, 0.01 mmol), and 5-bromo-1-methyl-1*H*-imidazole (64 mg, 0.40 mmol). The reaction mixture was heated to 85 °C in a sealed tube for 12h. Upon completion, the reaction mixture was partitioned between H_2O (25 mL) and $CHCl_3$. The organics were dried (Na_2SO_4), concentrated under vacuum, adsorbed onto silica gel and purified via column chromatography (35 – 50% EtOAc / Hexanes) to give the title compound (19.6 mg, 31%) as a yellow solid: LC-MS (ES) m/z = 441.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide

HCl in Dioxane (4M, 1mL) was added to a solution of 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-imidazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (19.6 mg, 0.04 mmol) in $CHCl_3$/MeOH (10:1, 5 mL). Upon completion of the reaction, the mixture was adsorbed onto silica gel and purified via chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound as a white solid (19 mg, 0.05 mmol, quant.): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.77 - 2.83 (m, 1 H) 2.85 - 2.91 (m, 2 H) 2.93 - 2.99 (m, 1 H) 3.82 (s, 3 H) 4.30 (ddd, *J*=8.08, 4.80, 1.77 Hz, 1 H) 7.15 - 7.31 (m, 7 H) 7.69 (d, *J*=4.04 Hz, 1 H) 7.76 (s, 1 H).

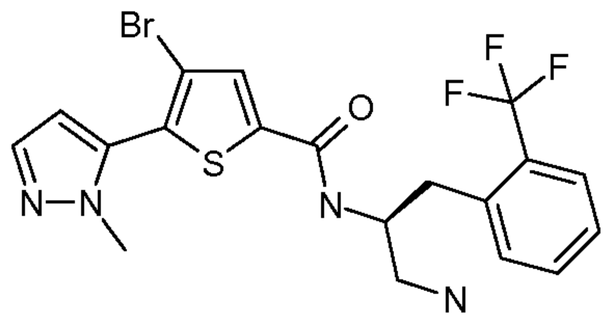
Example 63



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (253 mg, 0.69mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 569 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.14 - 3.30 (m, 4 H) 3.82 (s, 3 H) 4.73 (dd, *J*=9.47, 4.67 Hz, 1 H) 6.54 (d, *J*=2.02 Hz, 1 H) 7.44 - 7.50 (m, 1 H) 7.56 - 7.62 (m, 3 H) 7.74 (d, *J*=7.83 Hz, 1 H).

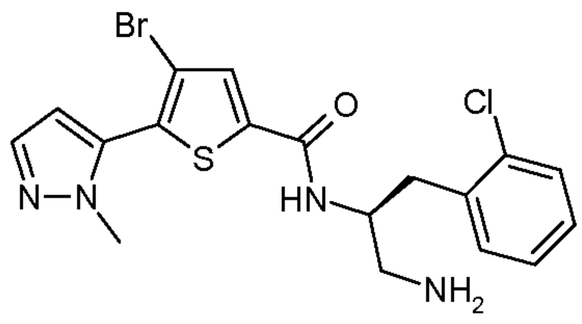
Example 64



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.50 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 488 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.15 (s, 2 H) 3.23 (s, 2 H) 3.84 (s, 3 H) 4.65 (s, 1 H) 6.52 - 6.57 (m, 1 H) 7.46 (s, 1 H) 7.52 - 7.61 (m, 3 H) 7.72 (s, 1 H) 7.81 (s, 1 H).

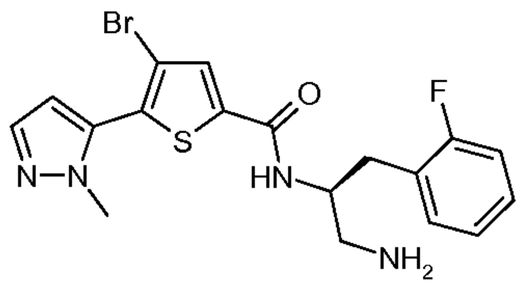
Example 65



Preparation of *N*-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (157 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 455 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.11 (s, 1 H) 3.22 (s, 1 H) 3.27 (s, 2 H) 3.85 (s, 3 H) 4.70 (s, 1 H) 6.57 (s, 1 H) 7.26 (s, 2 H) 7.41 (s, 2 H) 7.66 (s, 1 H) 7.88 (s, 1 H).

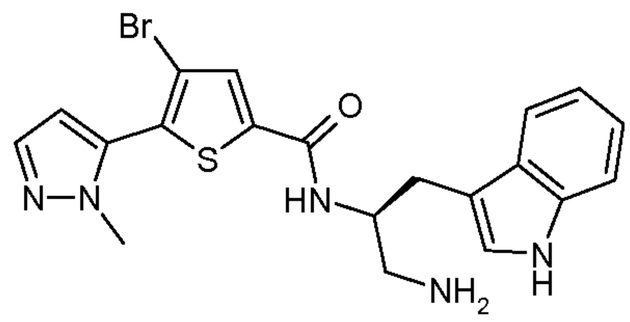
Example 66



Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (149 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 438 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.00 (s, 1 H) 3.09 (s, 1 H) 3.15 (dd, J=3.41, 1.64 Hz, 2 H) 3.83 (s, 4 H) 4.58 (s, 1 H) 6.52 (d, J=2.02 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 7.27 - 7.37 (m, 3 H) 7.59 (d, J=2.02 Hz, 1 H) 7.74 (d, J=3.54 Hz, 1 H).

Example 67

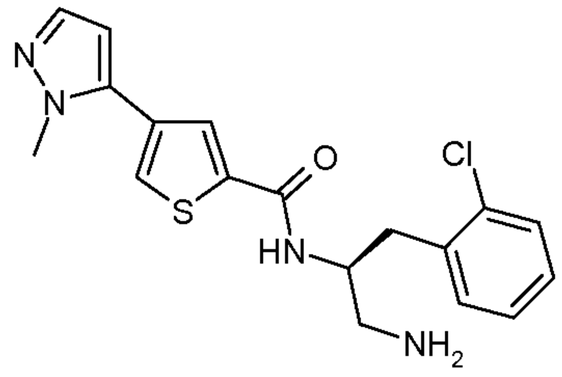


Preparation of *N*-[(1*S*)-2-amino-1-(1*H*-indol-3-ylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-dione-HCl (160 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 459 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.15 (dt, J=10.42, 6.79 Hz,

3 H) 3.27 (dd, J=4.04, 2.27 Hz, 1 H) 3.84 (s, 3 H) 4.63 (d, J=6.82 Hz, 1 H) 6.54 (d, J=2.02 Hz, 1 H) 7.05 (t, J=7.45 Hz, 1 H) 7.13 (t, J=7.07 Hz, 1 H) 7.19 (s, 1 H) 7.37 (d, J=8.08 Hz, 1 H) 7.64 - 7.73 (m, 2 H) 7.77 (s, 1 H).

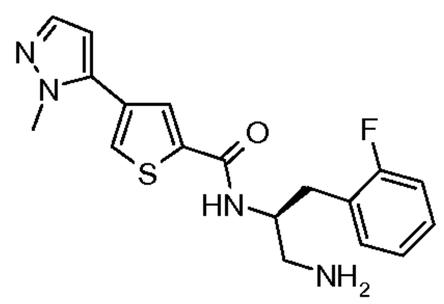
Example 68



Preparation of *N*-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (157 mg, 0.5 mmol) [prepared according to Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.11 - 3.20 (m, 1 H) 3.22 - 3.31 (m, 3 H) 4.23 (s, 3 H) 4.75 (s, 1 H) 6.96 (s, 1 H) 7.18 - 7.26 (m, 2 H) 7.38 (d, J=6.06 Hz, 1 H) 7.46 (d, J=4.55 Hz, 1 H) 8.22 (s, 2 H) 8.32 (s, 1 H).

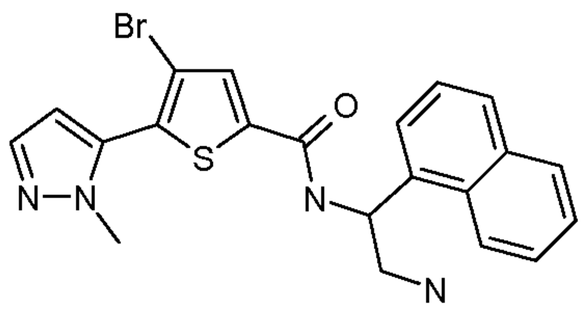
Example 69



Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (149 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.06 - 3.17 (m, 2 H) 3.25 - 3.31 (m, 2 H) 4.18 (s, 3 H) 4.59 - 4.67 (m, 1 H) 6.88 (s, 1 H) 7.05 - 7.12 (m, 2 H) 7.23 - 7.30 (m, 1 H) 7.36 - 7.42 (m, 1 H) 8.12 (d, J=1.01 Hz, 1 H) 8.17 (s, 1 H) 8.21 (s, 1 H).

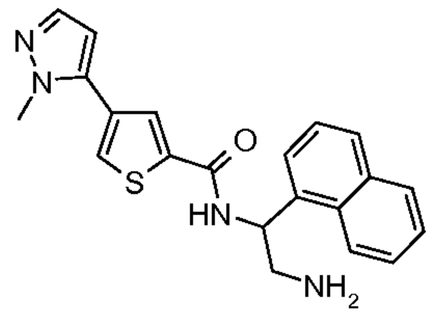
Example 70



Preparation of *N*-[2-amino-1-(1-naphthalenyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate (143 mg, 0.5 mmol) [from Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 456 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.60 (s, 1 H) 3.72 (s, 1 H) 3.84 (s, 3 H) 6.33 (d, J=10.11 Hz, 1 H) 6.55 (s, 1 H) 7.55 - 7.61 (m, 3 H) 7.64 (d, J=8.34 Hz, 1 H) 7.74 (s, 1 H) 7.92 - 7.99 (m, 2 H) 8.09 (s, 1 H) 8.26 (s, 1 H).

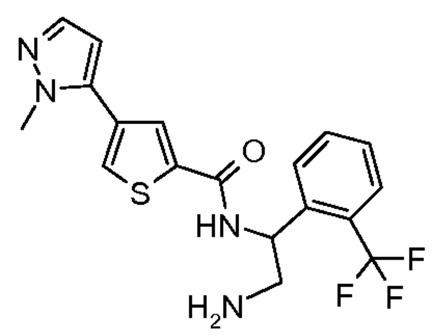
Example 71



Preparation of *N*-[2-amino-1-(1-naphthalenyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate (143 mg, 0.5 mmol) [from Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 377 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.62 (d, J=4.04 Hz, 1 H) 3.67 - 3.78 (m, 1 H) 4.08 - 4.10 (m, 3 H) 6.35 (s, 1 H) 6.73 (d, J=2.27 Hz, 1 H) 7.55 - 7.60 (m, 2 H) 7.62 - 7.67 (m, 1 H) 7.76 (d, J=7.33 Hz, 1 H) 7.88 (d, J=2.53 Hz, 1 H) 7.93 - 7.99 (m, 2 H) 8.10 (d, J=1.52 Hz, 1 H) 8.23 - 8.27 (m, 2 H).

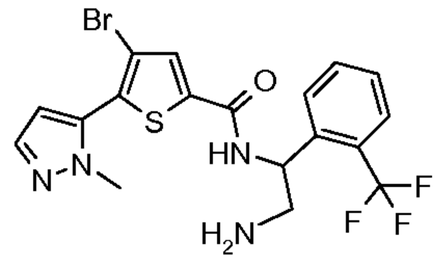
Example 72



Preparation of *N*-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl {2-amino-2-[2-(trifluoromethyl)phenyl]ethyl}carbamate (152 mg, 0.5 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.36 - 3.39 (m, 1 H) 3.46 - 3.53 (m, 1 H) 3.98 (s, 3 H) 5.86 - 5.91 (m, 1 H) 6.48 (s, 1 H) 7.51 (d, J=2.02 Hz, 1 H) 7.60 (s, 1 H) 7.76 (s, 1 H) 7.83 (d, J=8.08 Hz, 2 H) 7.94 (s, 1 H) 8.05 (s, 1 H).

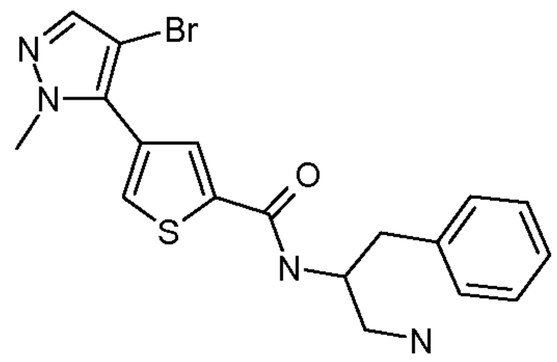
Example 73



Preparation of *N*-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl {2-amino-2-[2-(trifluoromethyl)phenyl]ethyl}carbamate (152 mg, 0.5 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 474 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.37 (s, 1 H) 3.65 (s, 1 H) 3.89 - 4.00 (m, 3 H) 5.88 (s, 1 H) 6.76 (d, J=2.27 Hz, 1 H) 7.58 (s, 1 H) 7.77 (d, J=9.60 Hz, 2 H) 7.91 - 8.03 (m, 2 H) 8.26 (d, J=2.27 Hz, 1 H).

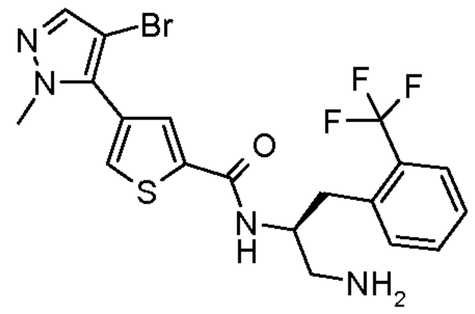
Example 74



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 24, except substituting NBS (194 mg, 1.09 mmol) for NCS: LC-MS (ES) m/z 418 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.03 (d, J=7.33 Hz, 2 H) 3.23 (s, 2 H) 3.90 (s, 3 H) 4.56 (d, J=1.77 Hz, 1 H) 7.20 - 7.27 (m, 1 H) 7.28 - 7.34 (m, 4 H) 7.58 (s, 1 H) 7.96 (s, 2 H).

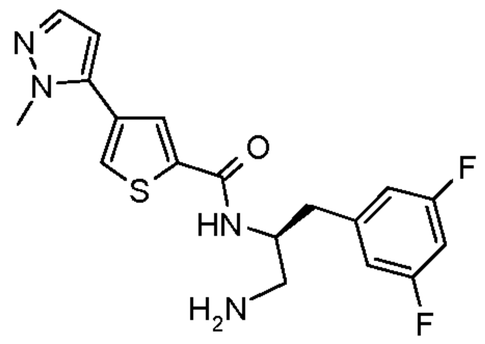
Example 75



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 25, except substituting NBS (67 mg, 0.5 mmol) for NCS: LC-MS (ES) m/z 488 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.10 - 3.19 (m, 1 H) 3.20 - 3.28 (m, 3 H) 3.91 (s, 3 H) 4.66 (dd, J=8.59, 3.03 Hz, 1 H) 7.39 - 7.47 (m, 1 H) 7.51 - 7.58 (m, 2 H) 7.59 (s, 1 H) 7.72 (d, J=8.08 Hz, 1 H) 7.98 (s, 2 H).

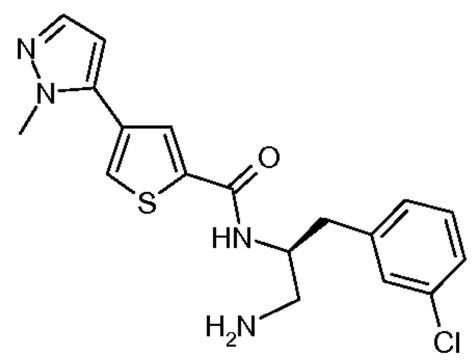
Example 76



Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (158 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.94 - 3.06 (m, 4 H) 3.95 (s, 3 H) 4.40 (d, J=6.06 Hz, 1 H) 6.46 (d, J=1.77 Hz, 1 H) 7.00 - 7.10 (m, 3 H) 7.47 (d, J=1.77 Hz, 1 H) 7.99 (d, J=1.26 Hz, 1 H) 8.10 (s, 2 H) 8.21 (s, 1H) 8.92 (d, J=8.0 Hz, 1H).

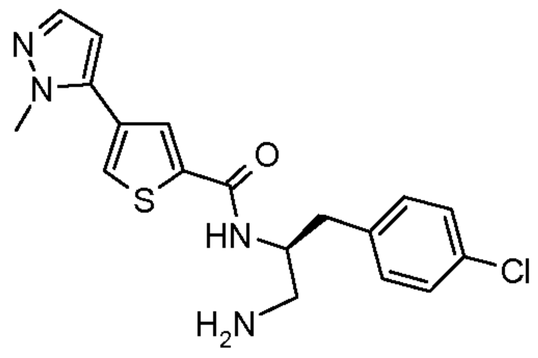
Example 77



Preparation of *N*-{(1*S*)-2-amino-1-[(3-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-chlorophenyl)propyl]-*1H*-isoindole-1,3(2*H*)-dione (157 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.92 - 3.04 (m, 4 H) 3.92 - 3.98 (m, 3 H) 4.36 (d, J=5.56 Hz, 1 H) 6.47 (s, 1H) 7.19 - 7.29 (m, 2 H) 7.29 - 7.35 (m, 1 H) 7.37 - 7.42 (m, 1 H) 7.47 (s, 1H) 8.17 (s, 3 H) 8.85-9.07 (m, 1H).

Example 78

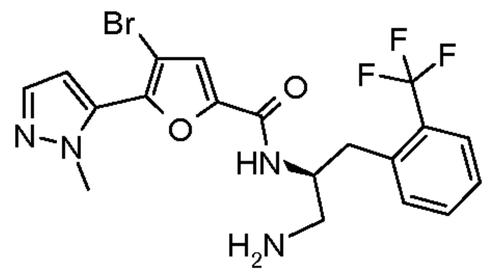


Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(4-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (157 mg, 0.5

mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.92 - 2.97 (m, 2 H) 2.99 - 3.04 (m, 2 H) 4.01 (s, 3 H) 4.32 - 4.42 (m, 1 H) 6.43 - 6.50 (m, 1 H) 7.27 - 7.37 (m, 4 H) 7.47 (d, J=1.77 Hz, 1 H) 7.99 (d, J=1.26 Hz, 1 H) 8.21 (s, 3 H) 8.94-9.10 (m, 1H).

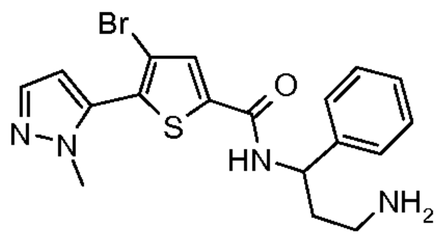
Example 79



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (135 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 472 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 3.11 (d, J=9.85 Hz, 1 H) 3.21 - 3.31 (m, 3 H) 4.06 (s, 3 H) 4.70 (s, 1 H) 6.87 (d, J=2.02 Hz, 1 H) 7.33 (s, 1 H) 7.41 - 7.48 (m, 1 H) 7.50 - 7.57 (m, 2 H) 7.60 (d, J=2.02 Hz, 1 H) 7.71 (d, J=7.83 Hz, 1 H).

Example 80



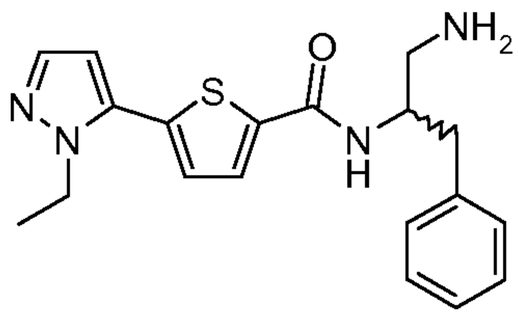
Preparation of *N*-(3-amino-1-phenylpropyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl [3-(methylamino)-3-

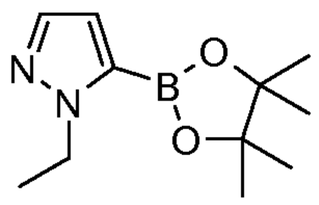
phenylpropyl]carbamate (125 mg, 0.5 mmoles) [from Preparation 3] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 420 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.25 - 2.37 (m, 2 H) 2.96 (d, J=8.08 Hz, 1 H) 3.04 - 3.13 (m, 1 H) 3.84 (s, 3 H) 5.22 (t, J=7.58 Hz, 1 H) 6.53 (d, J=1.52 Hz, 1 H) 7.35 (d, J=6.57 Hz, 1 H) 7.44 (dt, J=15.09, 7.48 Hz, 4 H) 7.58.

Example 81

Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

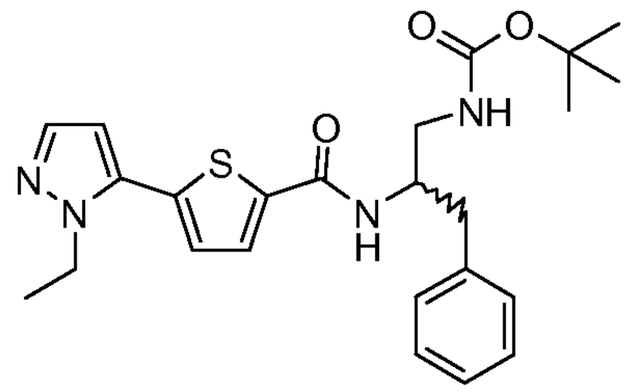


To a suspension of NaH (60% in mineral oil, 2.2 g, 55 mmol) in THF (50 mL) was added pyrazole (3.4 g, 50 mmol) in THF (10 mL) at room temperature. After 30 min, to above suspension was added EtI (7.75 g, 50 mmol) dropwise. After the reaction was complete (20 h), the suspension was filtered, and the resulting solution was used directly with further purification.

At 0°C, to above solution of 4-methyl pyrazole (~50 mmol) was added n-BuLi (2.5M in hexane, 22 mL, 55 mmol). The reaction solution was stirred for 1 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem*. **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.2 g, 55 mmol). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford a tan solid (9.8 g, 89%) which was used without further purification. LCMS (ES) m/z 141 $(M+H)^+$ for $[RB(OH)_2]$; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.52 (d, J =

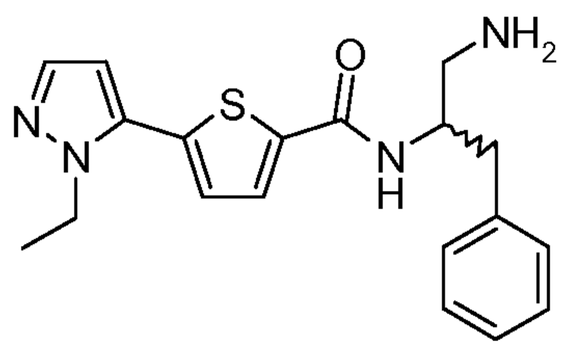
2 Hz, 1H), 6.36 (d, J = 2 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2Hz, 3H), 1.36 (s, 12 H)

b) 1,1-dimethylethyl [2-({[5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (100 mg, 0.23 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (100 mg, 0.72 mmol), tetrakistriphenylphosphine Pd(0) (30 mg, 26 µmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (64 mg, 0.29 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 12h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 40-60%) to afford the title compound (0.074 g, 71%) as a light yellow solid: LC-MS (ES) m/z 455 $(M+H)^+$.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

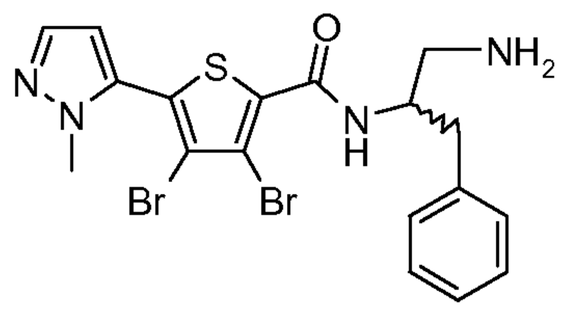


1,1-Dimethylethyl [2-({[5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (74 mg, 0.16 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). After 1 h, the solution was concentrated and neutralized through silica using 4% MeOH in DCM (1% NH_4OH). The title compound was further purified using reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) affording the bis-TFA salt of the title compound (47 mg, 50%) as a white solid: LCMS (ES) m/z 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.71 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.34-7.22 (m, 6H), 6.51 (d. J = 1.8 Hz, 1H), 4.55

(m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 3.5, 13.1 Hz, 1H), 3.13 (dd, J = 10.1, 13.1 Hz, 1H), 3.00 (m, 2H), and 1.42 (t, J = 7.1 Hz, 3H).

Example 82

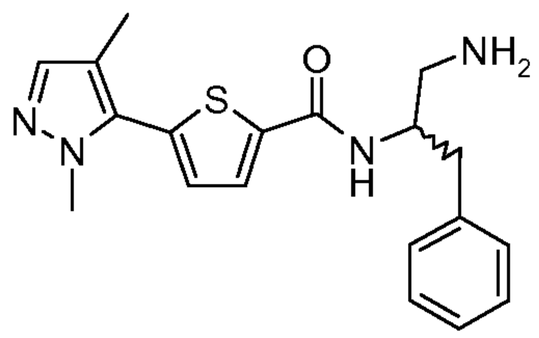
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,1-dimethylethyl (3-phenyl-2-{[(3,4,5-tribromo-2-thienyl)carbonyl]amino}propyl)carbamate (120 mg, 0.20 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z 499 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.59 (d, J = 2.0 Hz, 1H), 7.37-7.24 (m, 5H), 6.53 (d, J = 2.0 Hz, 1H), 4.62 (m, 1H), 3.27 (d, J = 13.1, 4.3 Hz, 1H), 3.21 (dd, J = 13.1, 9.4 Hz, 1H), 3.09 (dd, J = 14.2, 6.1 Hz, 1H), 3.02 (dd, J = 13.9, 9.1 Hz, 1H), and 1.96 (s, 3H).

Example 83

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



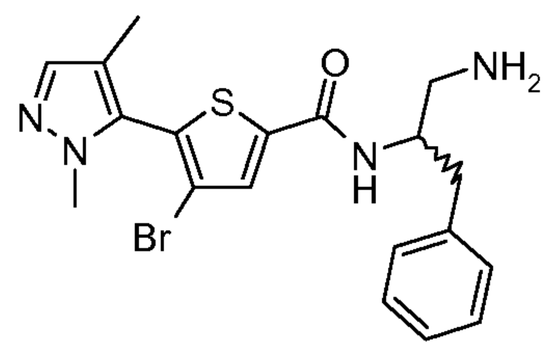
a) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (64.0 mg, 0.23 mmol) [from Preparation 17] for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate, and substituting 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (110 mg, 0.25 mmol) for 1,1-dimethylethyl (2-{[(5-bromo-3-thienyl)carbonyl]amino}-2-phenylethyl)carbamate: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.75 (d, J= 3.8 Hz, 1H), 7.40 (br s, 1H), 7.32-7.23 (m, 5H), 7.21 (d, J = 3.8 Hz, 1H), 4.56 (m, 1H), 3.86 (s, 3H), 3.23 (dd, J = 13.1, 3.8 Hz, 1H), 3.15 (dd, J = 12.9, 10.1 Hz,1H), 3.01 (m, 2H) and 2.10 (s, 3H).

Example 84

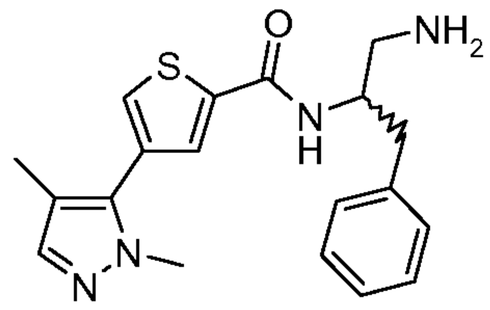
N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (77 mg, 0.23 mmol) [from Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, and substituting 1,1-dimethylethyl (2-{[(4,5-dibromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (150 mg, 0.29 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z 434 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.77 (s, 1H), 7.43 (s, 1H), 7.35-7.23 (m, 5H), 4.55 (m, 1H), 3.72 (s, 3H), 3.23 (dd, J = 3.5 Hz, 1H), 3.13 (dd, J = 10.6, 13.1 Hz, 1H), 3.02 -2.95 (m, 2H), and 1.99 (s, 3H).

Example 85

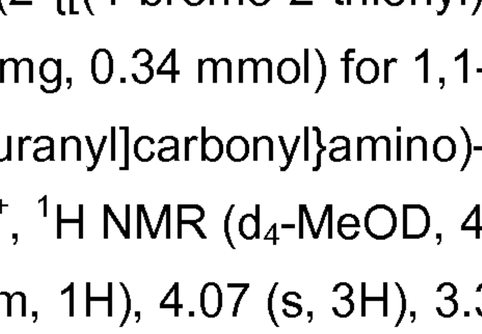
N-[2-amino-1-(phenylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



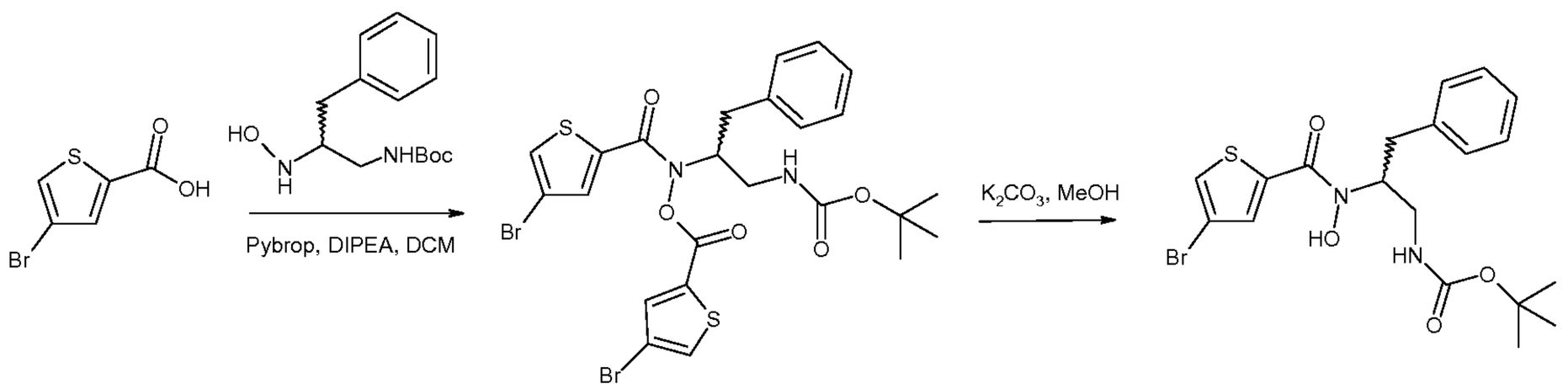
The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (220 mg, 1.0 mmol) [from Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, and substituting 1,1-dimethylethyl (2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (150 mg, 0.34 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z = 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.14-8.13 (m, 3H), 7.35-7.20 (m, 5H), 4.58 (m, 1H), 4.07 (s, 3H), 3.36-3.22 (m, 2H), 3.12-3.01 (m, 2H), and 2.21 (s, 3H).

Example 86

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



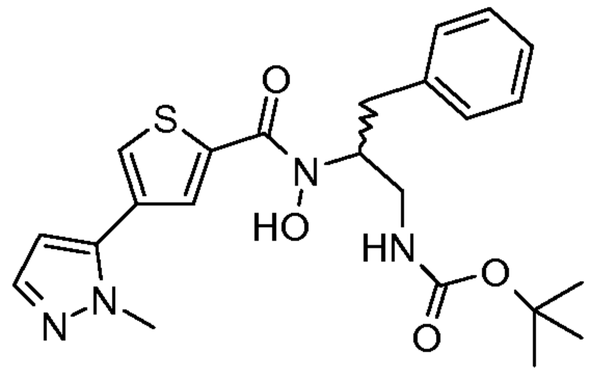
a) 1,1-dimethylethyl {2-[[(4-bromo-2-thienyl)carbonyl](hydroxy)amino]-3-phenylpropyl}carbamate



To a solution of 4-bromo-2-thiophenecarboxylic acid (1.0 g, 4.83 mmol) in DCM (10 mL) was added PyBrop (3.4 g, 7.24 mmol) and Hunig's base (2 mL, 12.6 mmol). After 15 min, 1,1-dimethylethyl [2-(hydroxyamino)-3-phenylpropyl]carbamate (641 mg, 2.41 mmol) was added to the reaction mixture in DCM (2 mL) and stirred for 2h at RT. The reaction solution was concentrated to give crude 1,1-dimethylethyl [2-([(4-bromo-2-thienyl)carbonyl]{[(4-bromo-2-thienyl)carbonyl]oxy}amino)-3-phenylpropyl]carbamate. LC-MS (ES) m/z = 645 $(M+H)^+$.

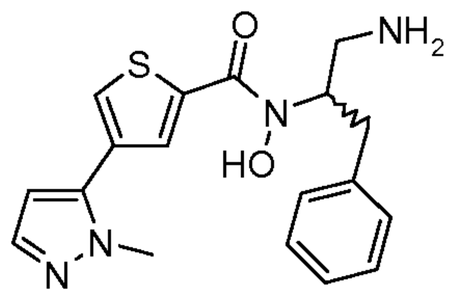
To a solution of 1,1-dimethylethyl [2-([(4-bromo-2-thienyl)carbonyl]{[(4-bromo-2-thienyl)carbonyl]oxy}amino)-3-phenylpropyl]carbamate in MeOH (5 mL) was added K_2CO_3 (1.0 g, 7.3 mmol). The mixture was stirred at RT for 2h. The mixture was concentrated under vacuum and purified on silica gel (EtOAc/Hexane, 30%) to give the the title compound (410 mg, 37 % for two steps) as an off white solid: LC-MS (ES) m/z = 456 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(hydroxy{[4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl {2-[[(4-bromo-2-thienyl)carbonyl](hydroxy)amino]-3-phenylpropyl}carbamate (100 mg, 0.22 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (91 mg, 0.66 mmol), tetrakistriphenylphosphine Pd(0) (23 mg, 0.022 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (68 mg, 0.33 mmol). The reaction mixture was heated to 75° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (87 mg, 87%).: LC-MS (ES) m/z = 456 $(M+H)^+$.

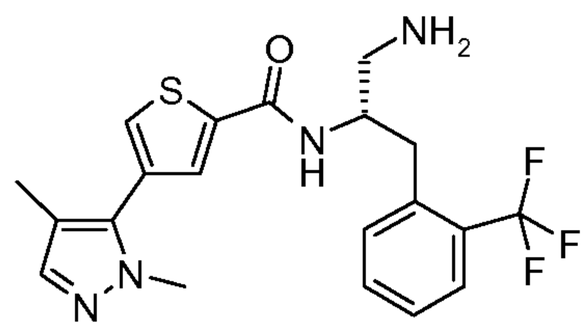
c) *N*-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



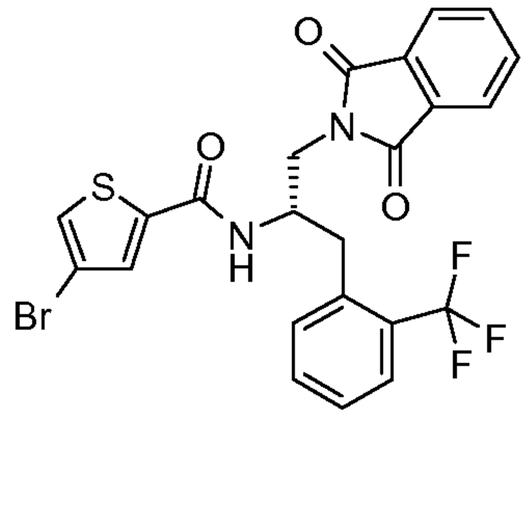
1,1-Dimethylethyl [2-(hydroxy{[4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (84 mg, 0.19 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). The reaction was stirred over 1h, and concentrated, and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40 -10%), and concentrated to afford the bis-TFA salt of the title compound (51.2 mg, 64.8%). LC-MS (ES) m/z 357 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.03 (s, 1H), 7.94 (d, J = 1.8Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 7.34-7.18 (m, 5H), 5.16 (m, 1H), 3.95 (s, 3H), 3.38 (dd, J = 13.1, 10.6 Hz, 1H), 3.17-3.11 (m, 2H), and 2.95 (dd, J = 13.6, 6.6 Hz, 1H)

Example 87

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

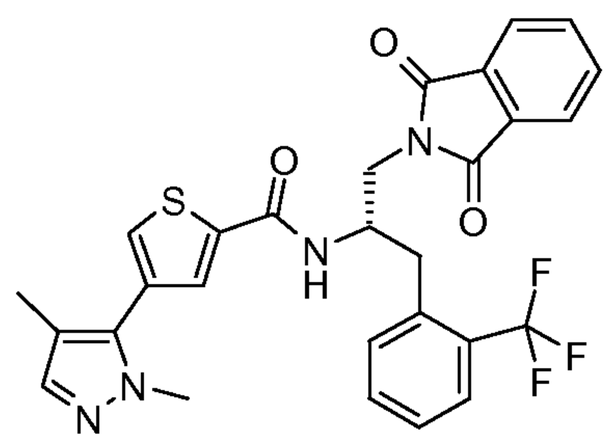


a) 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



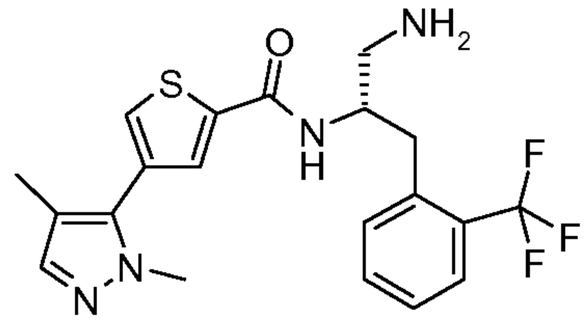
Ta a solution of 4-bromo-2-thiophenecarboxylic acid (80 mg, 0.39 mmol) in DCM (2 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (218 mg, 0.47 mmol) in one portion, followed by addition of DIPEA (0.2 mL, 1.14 mmol). After stirring for 10 min, diamine 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (165mg, 0.43 mmol) was added to above solution. After 2h, the solution was concentrated and purified via column chromatography (silica, 10% MeOH in CH_3Cl) affording the title compound (206 mg, 99%) as a white solid: LC-MS (ES) m/z 538 $(M+H)^+$.

b) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (200 mg, 0.37 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (0.17g, 1.23 mmol), tetrakistriphenylphosphine Pd(0) (42 mg, 0.036mmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (413 mg, 1.86 mmol) [from Preparation 17] . The reaction mixture was heated to 80° C in a sealed tube for 2h. The reaction solution was concentrated under vacuum, and purified on silica gel (10-50% EtOAc/Hex) to give the title compound (192 mg, 94%) as a white solid: LC-MS (ES) m/z 553 $(M+H)^+$.

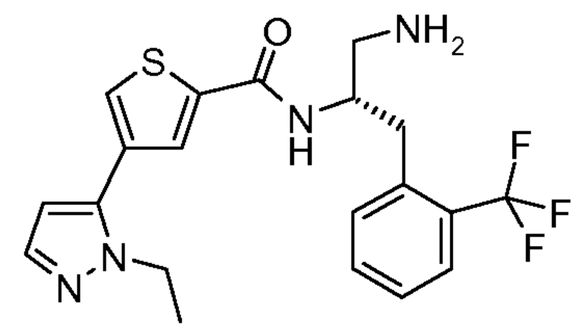
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



4-(1,4-Dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (110 mg, 0.198 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.93 mmol). The reaction was stirred over 10 h, concentrated and the residue in DCM (2 mL) was treated with TFA (1.0 mL). After stirring for 2 h, the solvent was removed and the residue was purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%), and concentrated to afford the bis-TFA salt of the title compound. The bis-TFA salt was neutralized through a silica plug (90:9:1 $CHCl_3$/MeOH/NH_4OH) affording the free base of the title compound. The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (62 mg, 34.6%) as the HCl salt: LC-MS (ES) m/z 423 $(M+H)^+$, ^1H NMR (d4-MeOD, 400 MHz) δ ppm 8.27 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.70 (d, 7.8 Hz,1H), 7.64 (d, J = 7.6 Hz,1H), 7.51 (dd, J = 7.3, 7.3 Hz, 1H), 7.41 (dd, J = 7.6, 7.3 Hz, 1H), 4.69 (m, 1H), 4.12 (s, 3H), 3.41-3.19 (m, 4H), and 2.24 (s, 3H).

Example 88

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

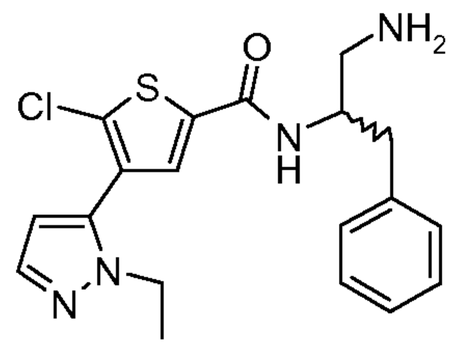


The title compound was prepared as a white solid according to the procedure of Example 87, except substituting 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (104 mg, 0.47 mmol) for 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.35-8.31 (m, 2H), 8.21 (br s, 1H), 7.70 (d, J =

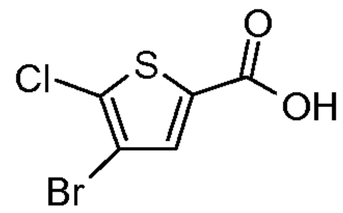
7.8 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.51 (dd, J = 7.3, 7.3 Hz, 1H), 7.42 (dd J = 7.6, 7.3 Hz, 1H), 7.00 (m, 1H), 4.70-4.61 (m, 3H), 3.40-3.17 (m, 4H), and 1.57 (t, J = 6.8 Hz, 3H).

Example 89

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

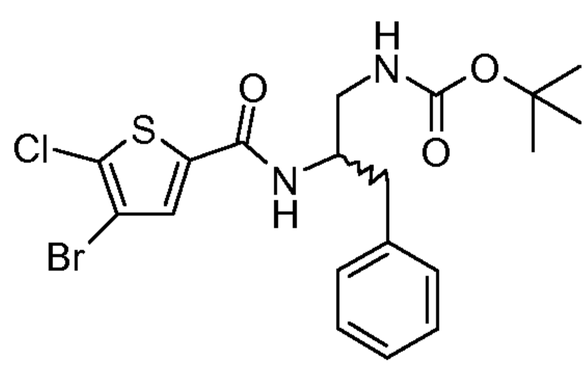


a) 5-chloro-4-methyl-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (2.07 g, 10 mmol) in DMF (5 mL) was added NCS (2.7 g, 15 mmol) in one portion. The reaction mixture was stirred at 50 °C for 10 h, and then cooled to room temperature. The desired product precipitated after water (5 mL) was added. The white solid was filtered and dried under high vacuum to give 1.9 g (79%). LC-MS (ES) m/z =242 $(M+H)^+$,

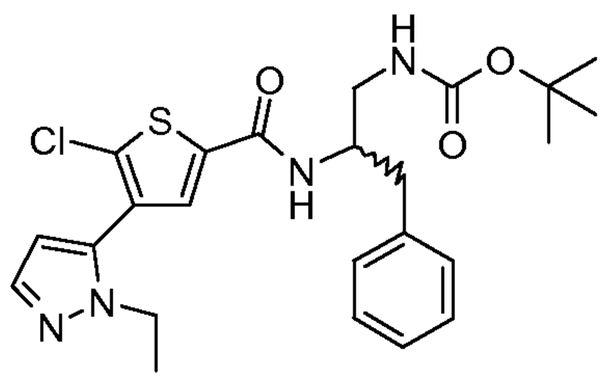
b) 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 5-chloro-4-methyl-2-thiophenecarboxylic acid (242 mg, 1.0 mmol) and diisopropylethyl amine (2.5 mL, 14.60 mmol) in DCM (50 mL) at 25 °C

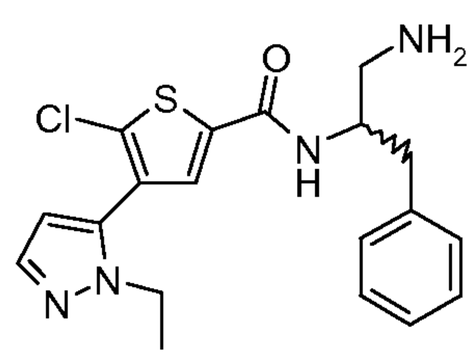
was added PyBrOP (2.5 g, 5.30 mmol) in one portion. After 30 min, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (250 mg, 1.0 mmol) was added at one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 10-40% EtOAc in Hexane) affording the title compound (460 mg, 97%) as a white solid: LC-MS (ES) m/z = 474 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (100 mg, 0.21 mmol) in THF (5 mL) was added Na_2CO_3 (2N, 0.3 mL, 0.6 mmol), $Pd(dppf)Cl_2$ (20 mg, 24 μmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (92 mg, 0.42 mmol). The reaction mixture was heated to 80 °C in a sealed tube under N_2. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 20-50%) to afford the title compound (74 mg, 72%) as a light yellow solid: LC-MS (ES) m/z 489 $(M+H)^+$.

d) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

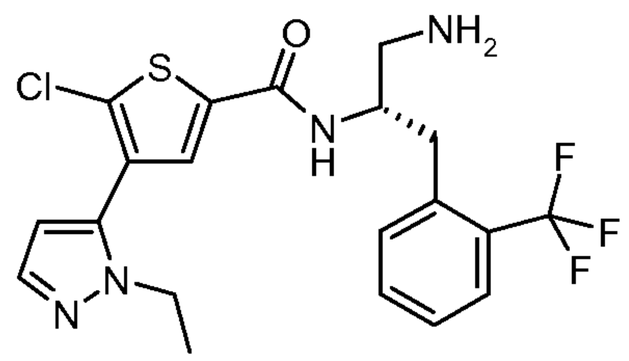


1,1-dimethylethyl [2-({[5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (61 mg, 0.12 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). After 0.5h, the solution was concentrated and neutralized through silica using 4% MeOH in DCM (1% NH_4OH).

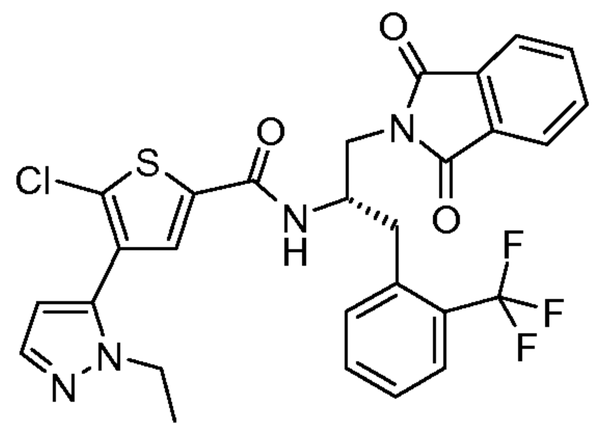
The title compound was further purified using reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) affording the bis-TFA salt of the title compound (41 mg, 53%) as a white solid. LC-MS (ES) m/z = 389 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.61(d, J = 2.0Hz, 1H), 7.59 (s, 1H), 7.33-7.21 (m, 5H), 6.41 (d, J = 2.0Hz, 1H), 4.52 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 12.9, 3.5 Hz, 1H), 3.12 (dd, J = 12.6, 10.1 Hz, 1H), 2.98 (m, 2H), and 1.35 (t, J = 7.1Hz, 3H).

Example 90

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

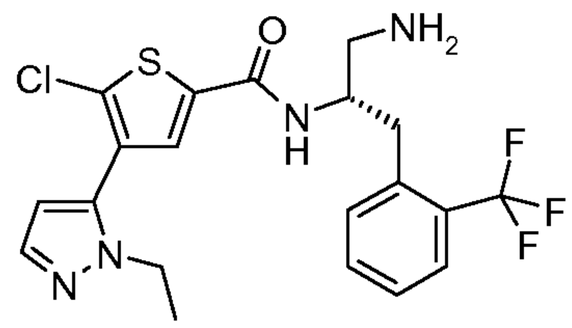


a) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 89(c), except substituting 4-bromo-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (150 mg, 0.26 mmol) for 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate: LC-MS (ES) m/z 587 $(M+H)^+$.

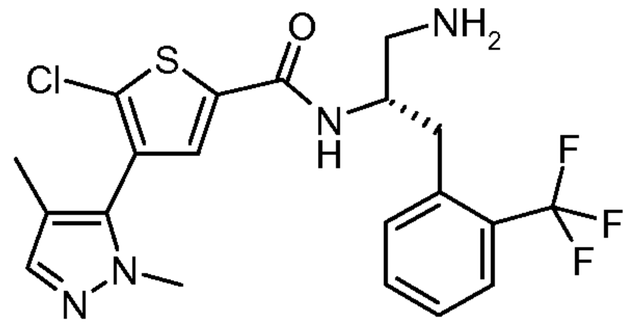
b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



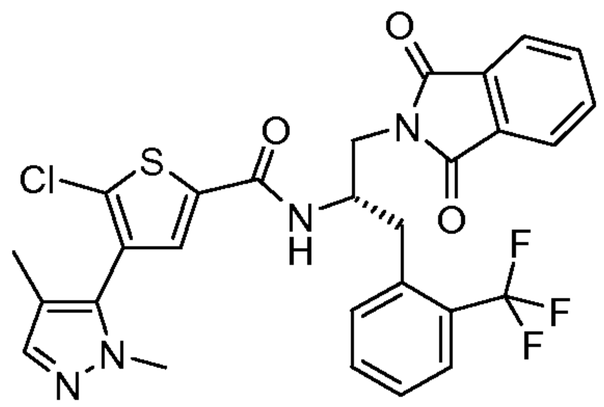
To a solution of 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (110 mg, 0.19 mmol) in MeOH/THF(5 mL/0.5 mL) was added hydrazine (0.5 mL, 15.9 mmol). After stirring overnight at RT, the reaction mixture was concentrated, and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and neutralized by ammonium hydroxide. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4, and concentrated to give a free base of the title compound, which was dissolved in MeOH (2 mL), and treated with HCl (aq, 37%). After stirring overnight, the reaction solution was concentrated to give the title compound (26 mg, 26 %) as a di-HCl salt: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.28 (d, J = 2.5Hz, 1H), 8.07 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 7.3, 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 4.66 (m, 1H), 4.43 (q, J = 7.3 Hz, 2H), 3.37-3.16 (m, 4H), and 1.50 (t, J = 7.3 Hz, 3H).

Example 91

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

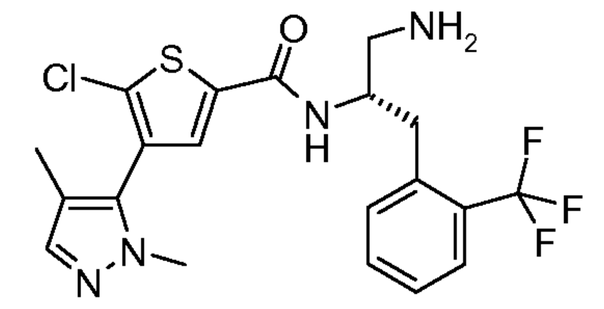


a) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-bromo-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (260 mg, 0.46 mmol) in THF (5 mL) was added Na_2CO_3 (2N, 0.7 mL, 1.4 mmol), $Pd(dppf)Cl_2$ (40 mg, 48 µmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (303 mg, 1.38 mmol). The reaction mixture was heated to 75 °C in a sealed tube under N_2. After 8h, the reaction mixture was concentrated under vacuum and purified on silica (10:1 CHCl3/MeOH) to afford the title compound (196 mg, 73.4%): LC-MS (ES) m/z = 587 $(M+H)^+$.

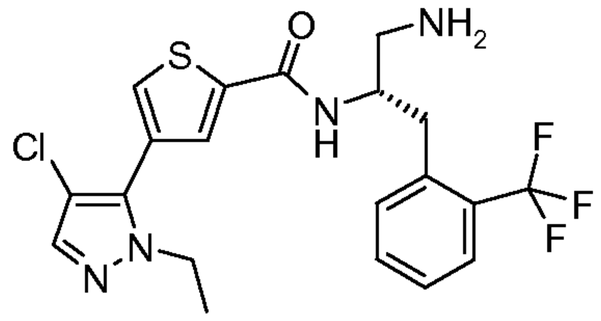
b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



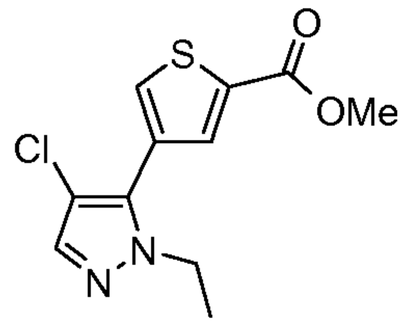
To a solution of 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (196 mg, 0.34 mmol) in MeOH/THF(2 mL/0.5 mL) was added hydrazine (0.5 mL, 15.9 mmol). After stirring overnight at RT, the reaction mixture was concentrated, and purified on silica (50% MeOH in $CHCl_3$ (0.5% NH_4OH) to give a free base of the tile compound, which was dissolved in MeOH (2 mL), and treated with HCl (aq, 37%). After stirring overnight, the reaction solution was concentrated to give the title compound (107 mg, 51 %) as a di-HCl salt: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.96 (s, 1H), 7.90 (m, 1H), 7.70 (d, J =7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 4.66 (m, 1H), 3.91 (s, 3H), 3.33-3.14 (m, 4H), and 2.10 (s, 3H).

Example 92

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



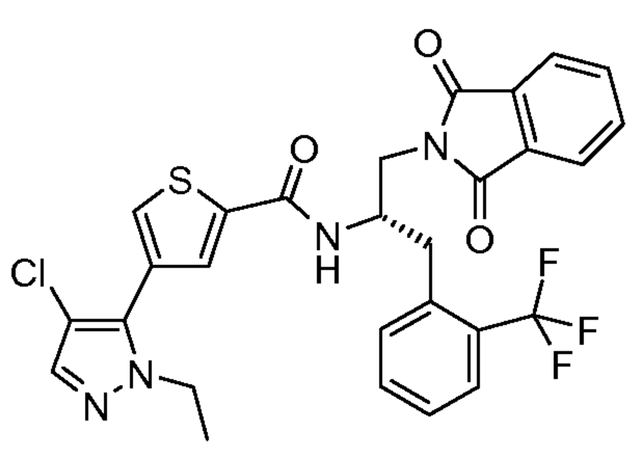
a) methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1.0 g, 4.52 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (1.86 g, 13.5 mmol), tetrakistriphenylphosphine Pd(0) (260 mg, 0.23 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole(1.3 g, 5.85 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 20-40%) to afford methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.7 g, 66%) as a light yellow solid: LC-MS (ES) m/z = 237 $(M+H)^+$.

To a solution of the above compound (0.5 g, 2.11 mmol) in THF (10 mL) was added NCS (0.364g, 2.74 mmol). The reaction mixture was heated to 70° C under nitrogen. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (Hexanes/EtOAc, 10-20%) to afford the title compound (0.45 g, 78%) as a light yellow solid: LC-MS (ES) m/z 271 $(M+H)^+$.

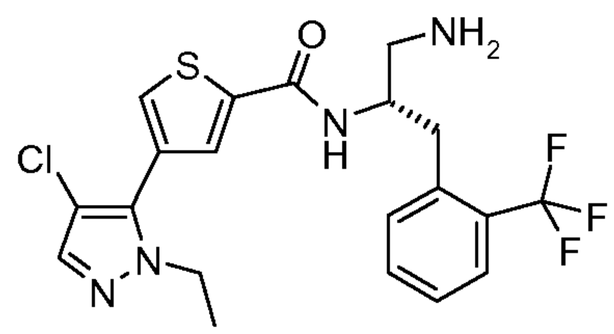
(b) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.3 g, 1.1 mmol) in THF/H_2O (5 mL/0.5 mL) was added KOH (0.2 g, 3.4 mmol). The reaction mixture was heated to 50° C for 4 h and then concentrated and diluted with H_2O (2 mL). The pH was adjusted to 3 with aqueous HCl. The mixture was extracted with DCM (3 x 5 mL) and the collected organic fractions were concentrated under vacuum to give crude 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (260 mg) which was used directly without further purification. LC-MS (ES) m/z = 256 $(M+H)^+$.

To a solution of 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (0.26 g, 1.0 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.35 g, 1.1 mmol) and DIPEA (0.5 mL, 2.86 mmol) in DCM (5 mL) at 25 °C was added PyBrOP (0.6 g, 1.2 mmol) in one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/hexane) affording the title compound (0.54 g, 91%) as a white solid: LC-MS (ES) m/z = 588 $(M+H)^+$.

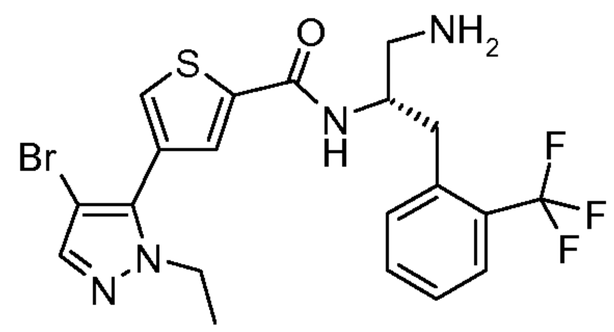
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



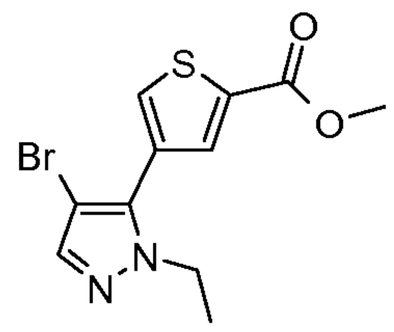
4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (350 mg, 0.60 mmol) was dissolved in MeOH (5 mL) and treated with NH_2NH_2 (0.5 mL,15.93 mmol). The mixture was stirred at RT overnight, and concentrated. The residue was purified by column chromatography (silica, 2-5% MeOH in $CHCl_3$ (0.5% NH_4OH) affording the free base of the title compound, which was treated with HCl(aq) in MeOH to give title compound (0.16 g, 51%) as a off white solid: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.97- 7.94 (m, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.61 (s, 1H), 7.56-7.51 (m, 2H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 4.67 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.36-3.12 (m, 4H), and 1.38 (t, J = 7.1 Hz, 3H).

Example 93

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

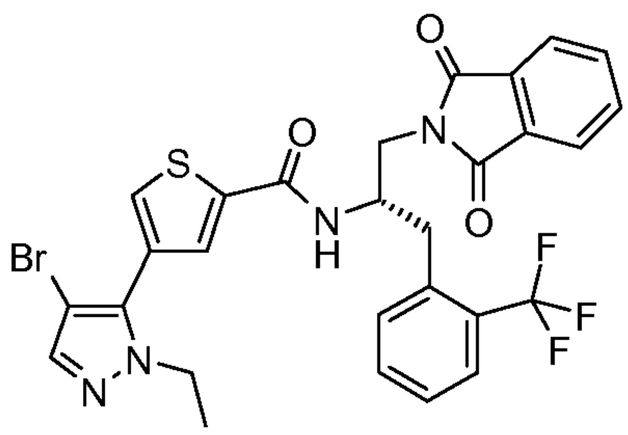


a) methyl 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.45 g, 1.9 mmol) [see example 92(a)] in THF (5 mL) was added NBS (0.33 g, 2.5 mmol). The reaction mixture was heated to 70° C under nitrogen. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/hexanes, 10-30%) to afford the title compound (0.47 g, 78%). LC-MS (ES) m/z = 316 $(M+H)^+$.

b) 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

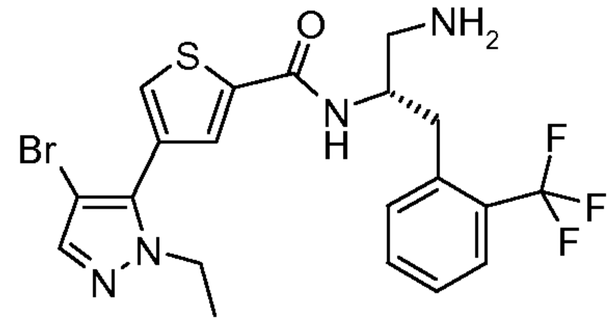


To a solution of methyl 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.2 g, 0.63 mmol) in THF/H_2O (5 mL/1 mL) was added KOH (0.15 g, 2.4 mmol). The reaction mixture was heated to 50° C for 10h and then

concentrated and diluted with H_2O (2 mL). The pH was adjusted to 6 with aqueous HCl. The mixture was extracted with DCM (3 x 5 mL) and the collected organic fractions were concentrated under vacuum to give crude 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly without further purification. LC-MS (ES) m/z = 302 $(M+H)^+$.

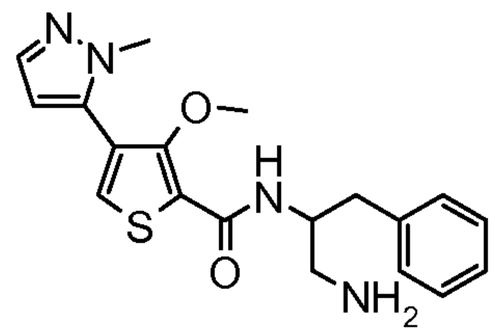
To a solution of 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid 156 mg, 0.52 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.18 g, 0.52 mmol) and DIPEA (0.5 mL, 2.86 mmol) in DCM (5 mL) at 25 °C was added PyBrOP (0.29g, 0.62 mmol) in one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-60 % EtOAc/hexane) affording the title compound (0.281 g, 86%). LC-MS (ES) m/z = 632 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



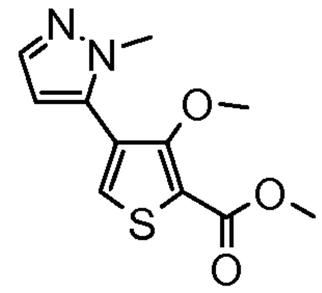
4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (250 mg, 0.39 mmol) was dissolved in MeOH (5 mL) and treated with NH_2NH_2 (0.5 mL, 15.93 mmol). The mixture was stirred at RT overnight, and concentrated. The residue was purified by column chromatography [silica, 2-10% MeOH in $CHCl_3$ (0.5% NH_4OH)] affording the free base of the title compound, which was treated with HCl(aq) in MeOH to give the title compound (144 mg, 51%) as an off white solid: LC-MS (ES) m/z 502 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.93-7.87 (m, 2H), 7.72 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.57-7.51 (m, 2H), 7.43 (t, J = 6.6 Hz, 1H), 4.67 (m, 1H), 4.25 (q, J = 7.3 Hz, 2H), 3.37-3.11(m, 4H), and 1.37 (t, J = 7.1Hz, 3H).

Example 94



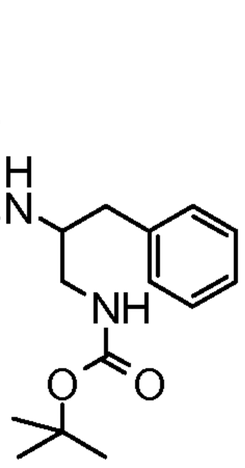
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



Methyl 4-bromo-3-(methyloxy)-2-thiophenecarboxylate (250 mg, 0.10 mmol) [prepared according to Corral, C.; El-Ashmawy, M.B.; Lissavetzky, J.; Basilio, A.; Giraldez, A.; *Eur. J. Med. Chem. Chim. Ther*. 22; **1987**; 251-254.], 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (250 mg, 1.20 mmol), $Pd(PPh_3)_4$ (58 mg, 49.8 µmol) and K_2CO_3 (550 mg, 3.98 mmol) in dioxane (5 mL) and H_2O (1 mL) were combined in a sealed tube. After 12h at 80 °C, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH in DCM) affording the title compound (215 mg, 86%) as a brown residue: LCMS (ES) m/z = 253 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



i) A solution of methyl 3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (215 mg, 0.853 mmol) in 6N NaOH (4 mL) and THF (4 mL) was stirred in a sealed tube at 70 °C. After 2h, the solution was acidified to pH 3

using 1N HCl then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 239 $(M+H)^+$.

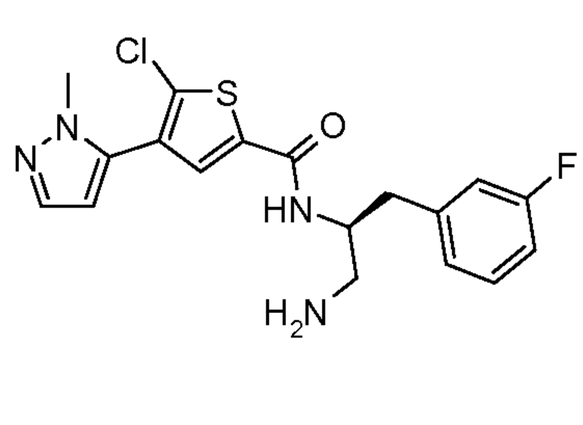
ii) To a solution of the crude acid, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (210 mg, 0.844 mmol) [from Preparation 2] and diisopropylethyl amine (735 µL, 4.22 mmol) in DCM (8 mL) was added PyBrop (472 mg, 1.01 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 471 $(M+H)^+$.

c) N-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

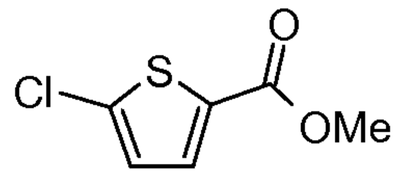
A solution of 1,1-dimethylethyl [2-({[3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part b) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated with a toluene azeotrope and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (270 mg, 86%-2steps) as the HCl salt: LCMS (ES) m/z 371 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.06 (br. s., 3 H) 7.91 (s, 1 H) 7.72 (d, J=8.59 Hz, 1 H) 7.52 (d, J=1.77 Hz, 1 H) 7.25 - 7.31 (m, 4 H) 7.18 - 7.23 (m, 1 H) 6.39 (d, J=2.02 Hz, 1 H) 4.52 (br. s., 1 H) 3.78 (s, 3 H) 3.41 (s, 3 H) 2.97 - 3.05 (m, 4 H).

Example 95



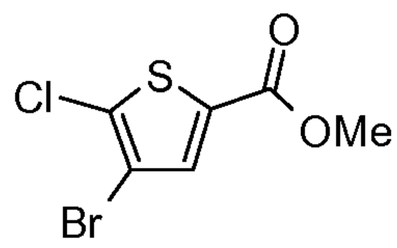
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) methyl 5-chloro-2-thiophenecarboxylate

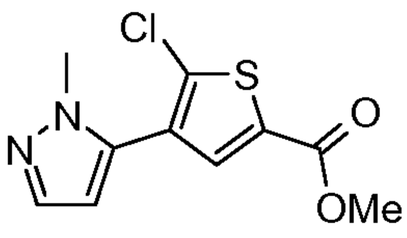
To a solution of 5-chloro-2-thiophenecarboxylic acid (20 g, 123 mmoles) in MeOH (200 mL) was added conc. H_2SO_4 (5 mL). After heating to 55°C for 12 h, the reaction solution was concentrated and diluted with DCM (250 mL). The DCM solution was washed with aqueous $NaHCO_3$, then H_2O and dried over Na_2SO_4. Concentration under vacuum gave the title compound as a yellow oil (21.5 g, 99%): LCMS (ES) m/z 178 $(M+H)^+$.

b) methyl 4-bromo-5-chloro-2-thiophenecarboxylate



To a 1 L round bottom flask was added aluminum chloride (11.32 g, 85 mmol) and methyl 5-chloro-2-thiophenecarboxylate (10 g, 56.6 mmol) dissolved in $CHCl_3$ (250 mL). Br_2 (4.08 ml, 79 mmol) was added dropwise over 10 minutes. After stirring for 6 h at 25 °C, the light orange reaction solution was washed with sat $NaHCO_3$. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [hexanes/EtOAc, 9:1] to give the product [12 g, 80%] as a white solid. LCMS (ES) m/z 256 $(M+H)^+$.

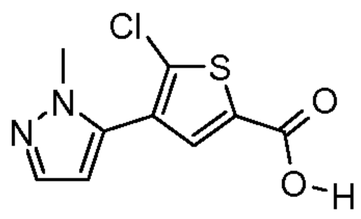
c) methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 300 mL sealed flask was added 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.14 g, 39.1 mmol), potassium carbonate (12.98 g, 94 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (8 g, 31.3 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.40 g, 0.78 mmol) in 1,4-dioxane (50 ml) and H_2O (6 ml). After stirring for 90 min at 75 °C, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered

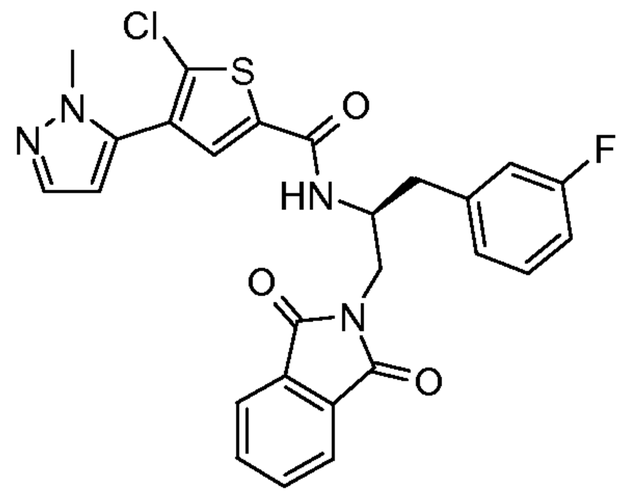
and concentrated. The reaction residue was purified on silica gel [hexanes/EtOAc, 2:1] to give the product [5.7 g, 70%] as a tan solid: LCMS (ES) m/z 258 $(M+H)^+$.

d) 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 250 mL round-bottomed flask was added methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (4.4 g, 17.14 mmol) and sodium hydroxide (28.6 ml, 171 mmol) in tetrahydrofuran (THF) (50 ml) and MeOH (50 mL). The reaction solution was stirred at RT for 12h and then made acidic (pH ~ 2) with 2.5 M HCl and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated to an off-white solid (4.2 g, 94%) which was used directly without further purification: LCMS (ES) m/z 243 $(M+H)^+$.

e) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



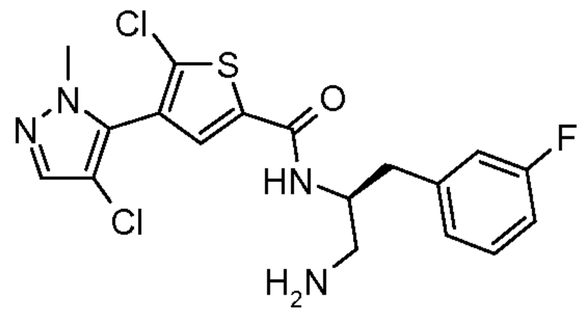
To a 500 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (4.2 g, 17.31 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (6.37 g, 19.04 mmol) [prepared according to the procedure of Preparation 6], N,N-diisopropyl ethylamine (4.53 ml, 26.0 mmol) and Pybrop (12.05 g, 26.0 mmol) in dichloromethane (DCM) (150 ml). After stirring at RT for 12 h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with [EtOAc/hexanes, 1:1] to give the product [7.8 g, 86%] as a white solid: LCMS (ES) m/z 524 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 250 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (7.8g, 14.91 mmol) and hydrazine (14.50 ml, 298 mmol) in tetrahydrofuran (THF) (75 ml) and methanol (75 mL). After 24 h at RT, the precipitate was filtered, the filtrate was concentrated. The crude product was purified on a silica gel column [$CHCl_3$/MeOH/NH_4OH, 90:9:1] to give the title compound as a white solid.

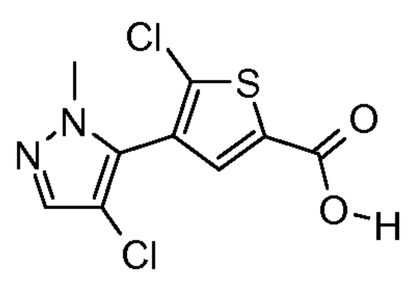
The free base product was treated with 4M HCl in dioxane (15 mL). After 5 min, the solution was concentrated and dried under vacuum to afford the product (6.8 g, 95%) as an HCl salt: LCMS (ES) m/z 467 $(M+H)^+$, ^1H NMR (400 MHz, CD3OD) δ ppm 7.97 (s, 2H), 7.31 (s, 1H), 7.14 (m, 2H), 6.98 (m, 1H), 6.75 (s, 1H), 4.54 (m, 1H), 3.98 (s, 3H), 3.24 (m, 2H), 3.04 (m, 2H).

Example 96



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

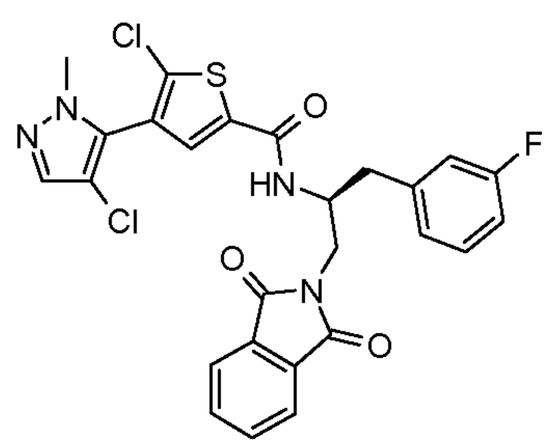
a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 500 mL flask was added methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (5 g, 19.48 mmol) [from Example 95] and NCS (3.12 g, 23.37 mmol) in tetrahydrofuran (THF) (100 ml) (50 mL). After stirring for 4 h at 70 °C, the yellow reaction solution was treated with 6M NaOH (32 mL, 195 mmole) and stirred an additional 2 hours. The reaction solution was diluted with H_2O (50 mL)

and DCM (200 mL). The organic layer was separated and the aqueous layer made acidic with 6N HCl. The acidic aqueous solution was extracted with DCM (3 x 200 mL), dried over Na_2SO_4, and concentrated to give the crude product [2.6 g, 48%] as a tan solid: LCMS (ES) m/z 277 $(M+H)^+$.

b) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



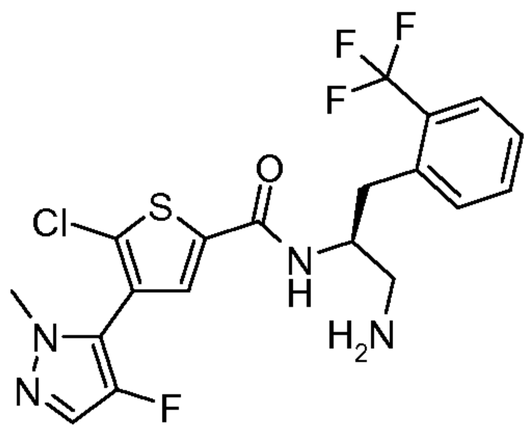
To a 500 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (6 g, 21.65 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (7.25 g, 21.65 mmol) [prepared according to the procedure of Preparation 6], N,N-diisopropyl ethylamine (5.67 ml, 32.5 mmol) and Pybrop (15.08 g, 32.5 mmol) in Dichloromethane (DCM) (150 ml). After stirring at RT for 12 h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with [EtOAc/hexanes, 1:1] to give the product [9.0g, 74%] as a white solid: LCMS (ES) m/z 558 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 250 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (9 g, 16.15 mmol) and hydrazine (15.69 ml, 323 mmol) in tetrahydrofuran (THF) (75 ml) and methanol (75 mL). After 24 h at RT, the precipitate was filtered, the filtrate was concentrated, and the crude product was purified on a silica gel column [$CHCl_3$/MeOH/NH_4OH, 90:9:1] to give the title compound as a white solid.

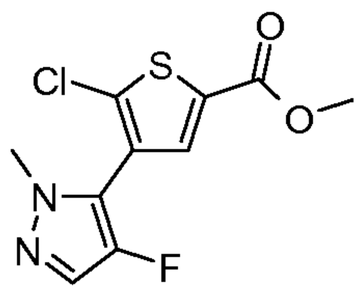
The free base product was treated with 4M HCl in dioxane (15 mL). After 5 min, the product solution was concentrated and dried under vacuum to afford the product (6.5 g, 91%) as an HCl salt: LCMS (ES) m/z 428 $(M+H)^+$, ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 (s, 1 H), 7.60 (s, 1H), 7.32 (m, 1H) 7.14 (m, 2H), 6.98 (m, 1H), 4.54 (m, 1H), 3.78 (s, 3H), 3.24 (m, 2H), 3.02 (m, 2H).

Example 97



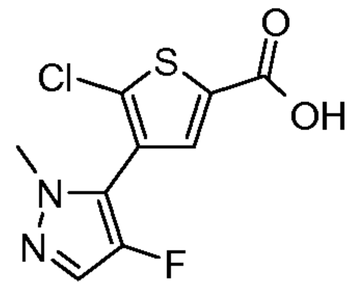
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



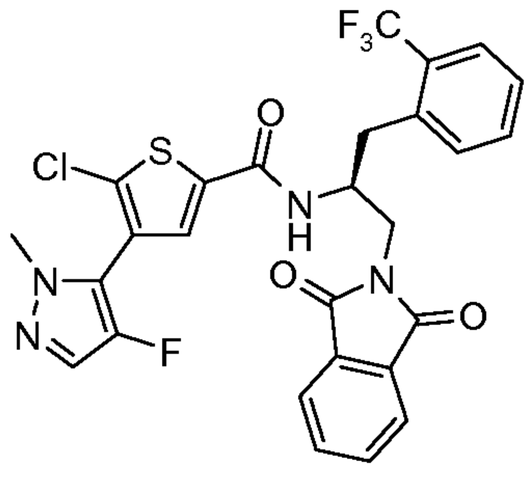
To a solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 0.974 mmol)[prepared according to the procedure in Example 95] in acetonitrile (4.864 ml) and H_2O (486 µl) was added selectfluor (449 mg, 1.27 mmol). The resulting solution was stirred at 70 ºC in a sealed tube for 1h after which additional selectfluor (449 mg, 1.266 mmol) was added in one portion. After stirring 12h, the solution was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM-THF and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 10% EtOAc in hexanes) affording methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (65 mg, 0.237 mmol, 24.30 % yield) as a yellow solid; LCMS (ES) m/z 274, 276 (M, M+H).

b) 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (65 mg, 0.237 mmol) in 6N sodium hydroxide (0.39 ml, 2.37 mmol) and tetrahydrofuran (2 ml) was stirred at 70 ºC in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (54 mg, 0.17 mmol, 72 % yield) as a yellow oil; LCMS (ES) m/e 261, 263 (M, M+2)+.

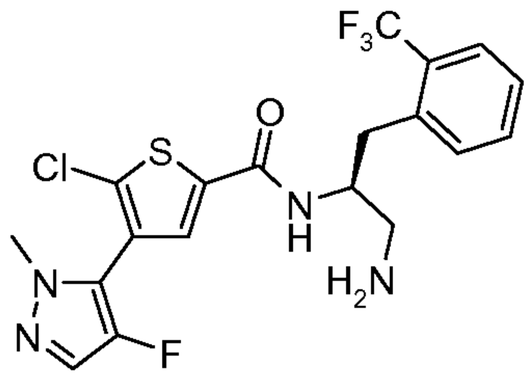
c) 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (53 mg, 0.203 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (78 mg, 0.203 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.18 ml, 1.02 mmol) in DCM at 25 ºC was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (95 mg, 0.203 mmol) in one portion. The solution stirred at 25 ºC over 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-

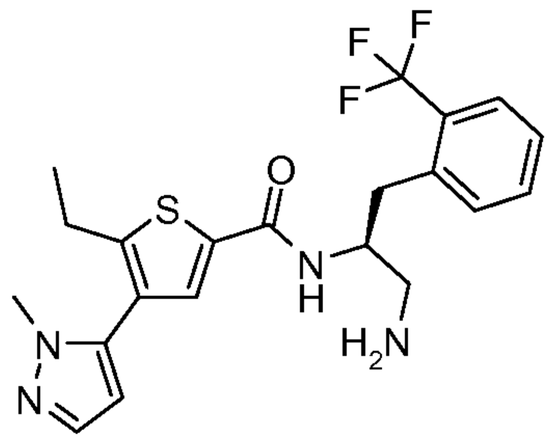
2-thiophenecarboxamide (106 mg, 0.129 mmol, 63.5 % yield) as a clear oil; LCMS (ES) m/e 591, 593 (M, M+H)+.

d) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



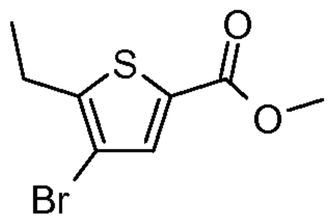
To a solution of 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (106 mg, 0.179 mmol) in tetrahydrofuran (1.095 ml) and methanol (1.095 ml) at 25 °C was added hydrazine (0.056 ml, 1.79 mmol) dropwise. After 48h, the solution was concentrated, dry loaded (silica, 5% MeOH in DCM (1% NH_4OH)) and purified initially by column chromatography. The residue was then further purified via gilson reverse phase chromatography using 2%-95% mobile phase affording the TFA salt of the title compound. This compound was neutralized through a plug of silica (5% MeOH in DCM (1% NH_4OH)) concentrated and transferred to the HCl salt adding excess 4M HCl in dioxane (500 ul) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (17 mg, 0.029 mmol, 16.16 % yield) as a white solid: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.11 (s,1 H) 8.11 (s, 1 H) 7.71 (br. s., 3 H) 7.66 - 7.70 (m, 2H) 7.54 - 7.61 (m, 2H) 7.41 - 7.44 (m, 1 H) 4.47 (br. s., 1 H) 3.79 (s, 3 H) 3.07 - 3.16 (m, 4 H).

Example 98



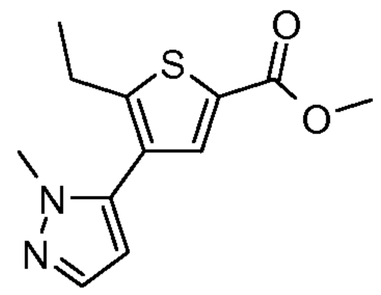
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-5-ethyl-2-thiophenecarboxylate



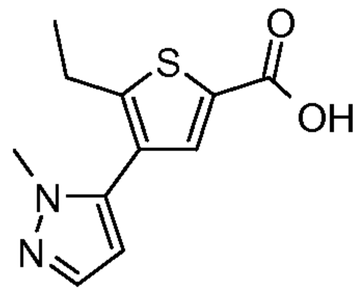
To a solution of 4-bromo-5-ethyl-2-thiophenecarboxylic acid (1 g, 4.25 mmol) in methanol (21.27 ml) was added sulfuric acid (0.23 mL, 4.25 mmol). The resulting solution was stirred at 50 °C for 48h. H_2O (50 mL) was added and the reaction was cooled to 0 °C in an ice-bath. The pH was adjusted to ~12 and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-5-ethyl-2-thiophenecarboxylate (1.060 g, 4.25 mmol, 100 % yield): LCMS (ES) m/e 248, 250 (M, M+2)+.

b) methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



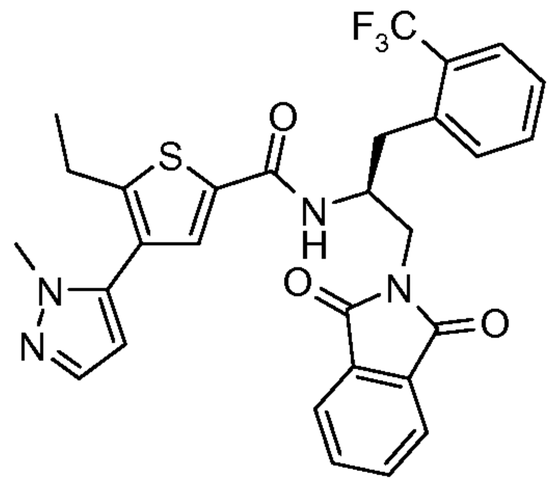
A solution of methyl 4-bromo-5-ethyl-2-thiophenecarboxylate (300 mg, 1.204 mmol), potassium carbonate (832 mg, 6.02 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (326 mg, 1.565 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (30.8 mg, 0.060 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (301 mg, 1.204 mmol, 100 % yield) as a brown oil: LCMS (ES) m/e 251 $(M+H)^+$.

c) 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



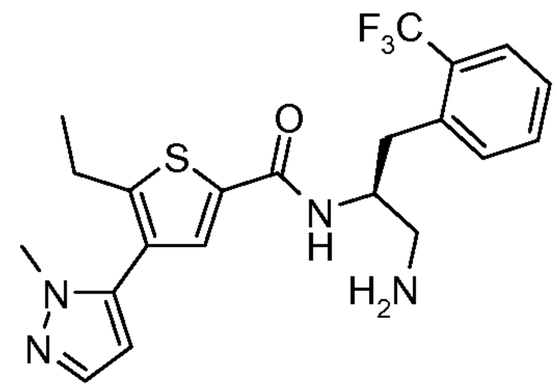
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.198 mmol) in 6N sodium hydroxide (2.397 ml, 1.198 mmol) and tetrahydrofuran (5.992 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (283 mg, 1.2 mmol, 100 % yield) as a yellow oil; LCMS (ES) m/z = 236 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



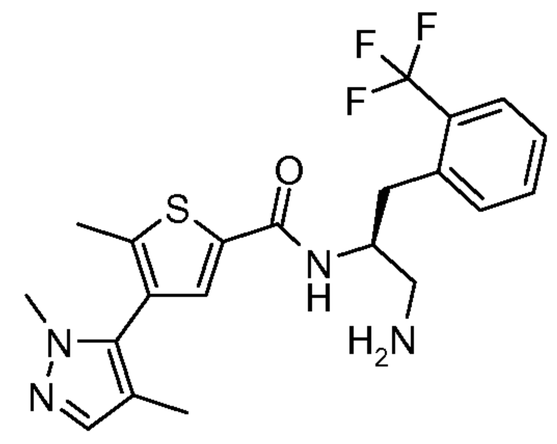
To a solution of 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (283 mg, 1.2 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (461 mg, 1.2 mmol)[prepared according to Preparation 6] and diisopropylethylamine (1.043 ml, 5.99 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (615 mg, 1.317 mmol) in one portion. The solution was stirred at 25 °C over 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (486 mg, 0.86 mmol, 71.6 % yield) as a clear oil: LCMS (ES) m/e 567 (M+H)+.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



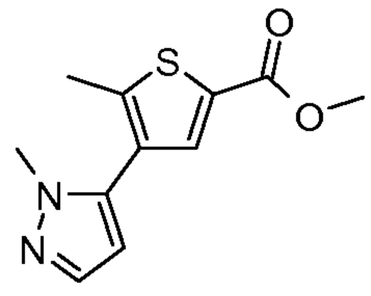
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (486 mg, 0.86 mmol) in tetrahydrofuran (2.144 ml) and methanol (2.14 ml) at 25 °C was added hydrazine (0.269 ml, 8.58 mmol) dropwise. After 12h, the solution was concentrated, dry loaded and purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (500 ul) to the residue in MeOH (2 ml) affording N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (250 mg, 0.491 mmol, 57.2 % yield)-2 HCl as a white solid: LCMS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.84 (d, J=8.84 Hz, 1 H) 8.08 (br. s., 3 H) 7.93 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.51-7.61 (m, 3 H) 7.39 - 7.46 (m, 1 H) 6.34 (d, J=2.02 Hz, 1 H) 4.48 (br. s., 1 H) 3.77 (s, 3 H) 2.99-3.11 (m, 4 H) 2.74 (q, J=7.49 Hz, 2 H) 1.16 (t, J=7.45 Hz, 3 H).

Example 99



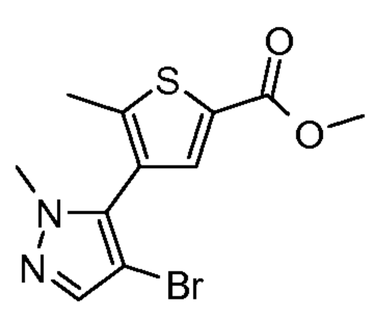
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



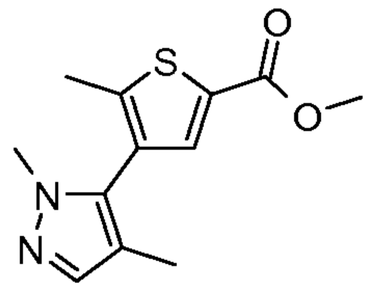
A solution of methyl 4-bromo-5-methyl-2-thiophenecarboxylate (2g, 8.51 mmol)[prepared in Preparation 10], potassium carbonate (5.88 g, 42.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.124 g, 10.21 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.217 g, 0.425 mmol) in 1,4-Dioxane (35.4 ml) and H_2O (7.09 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 25% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate. This reaction was run in several batches (1g, 3 x 2g) which were combined for workup and purification affording the title compound (5.5 g, 78% combined yield) as a viscous yellow oil: LCMS (ES) m/e 236 $(M+H)^+$.

b) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



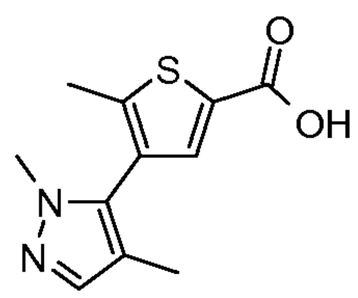
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (580 mg, 2.45 mmol) and n-bromosuccinimide (437 mg, 2.45 mmol) in tetrahydrofuran (12.300 ml) was stirred in a sealed tube for 1h at 70 °C. The solution was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAc in hexanes) yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (600 mg, 1.90 mmol, 78 % yield) as a yellow oil: LCMS (ES) m/e 314, 316 (M, $M+H)^+$.

c) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



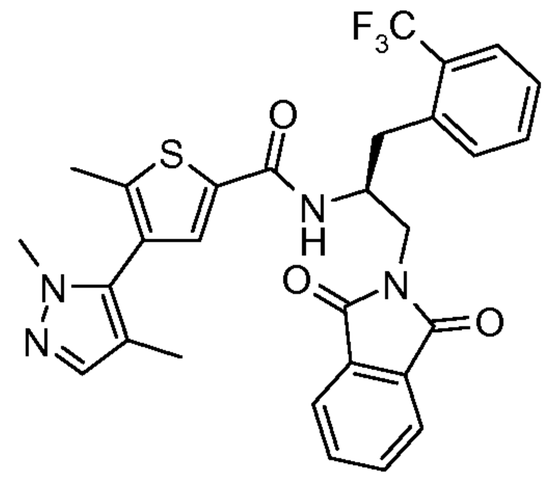
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (420 mg, 1.33 mmol), potassium carbonate (921 mg, 6.66 mmol), $PdCl_2$(dppf) (98 mg, 0.13 mmol) and trimethylboroxine (0.371 ml, 2.67 mmol) in N,N-dimethylformamide (6.663 ml) was stirred at 110 °C in a sealed tube for 2h. This reaction was run in two batches (100 mg and 420 mg) which were combined and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (240 mg, 58%) as a yellow oil: LCMS (ES) m/e 251 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



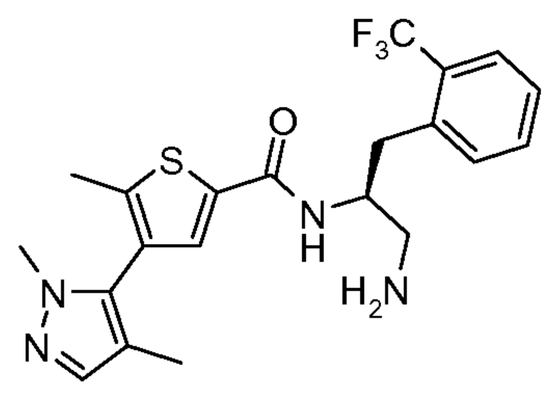
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (240 mg, 0.96 mmol) in 6N sodium hydroxide (3.20 ml, 19.18 mmol) and tetrahydrofuran (4.79 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (217 mg, 0.92 mmol, 96 % yield) as a yellow oil: LCMS (ES) m/e 236 $(M+H)^+$.

e) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



To a solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.918 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (353 mg, 0.92 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.800 ml, 4.59 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (472 mg, 1.01 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (373 mg, 0.66 mmol, 71.7 % yield) as a yellow foam: LCMS (ES) m/e 567 (M+H)+.

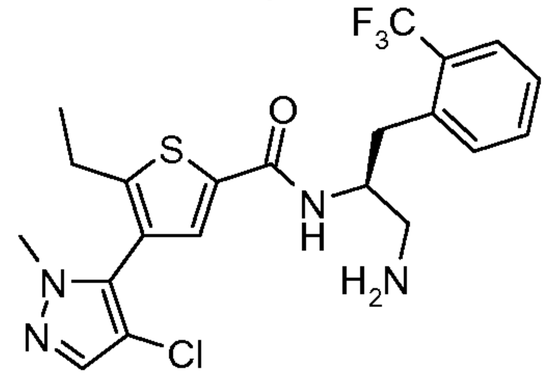
f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (373 mg, 0.66 mmol) in tetrahydrofuran (1.65 ml) and methanol (1.65 ml) at 25 °C was added hydrazine (0.21 ml, 6.58 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-

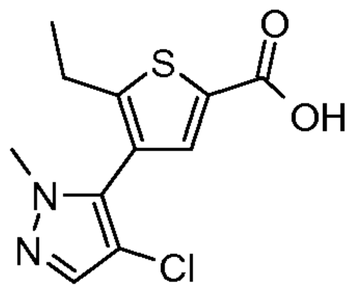
thiophenecarboxamide (253 mg, 0.497 mmol, 75 % yield) as a yellow solid: LCMS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.80 (d, J=8.59 Hz, 1 H) 8.09 (br. s., 3 H) 7.82 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.58 (t, J=8.08 Hz, 1 H) 7.43 (t, J=7.33 Hz, 1 H) 7.38 (s, 1 H) 4.47 (br. s., 1 H) 3.64 (s, 3 H) 2.99 - 3.07 (m, 4 H) 2.27 (s, 3 H) 1.89 (s, 3 H).

Example 100



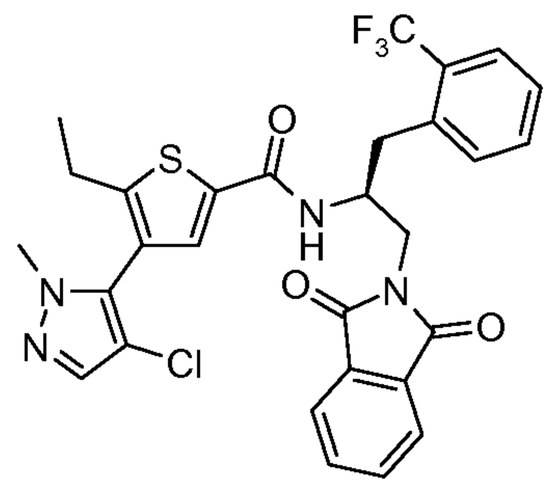
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



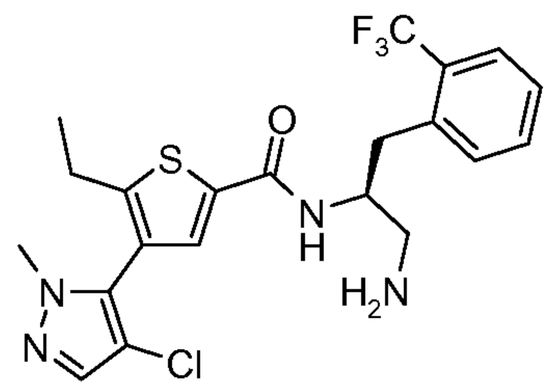
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.2 mmol)[Prepared in Example 98] and N-chlorosuccinimide (160 mg, 1.2 mmol) in tetrahydrofuran (6 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (1 ml, 5.99 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAC in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (325 mg, 1.20 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 271, 273 (M, M+2)$^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (200 mg, 0.74 mmol), N,N-diisopropylethylamine (0.64 ml, 3.69 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (284 mg, 0.74 mmol)[prepared according to Preparation 6] in DCM at 25 ºC was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (414 mg, 0.886 mmol) in one portion. The solution stirred at 25 ºC for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (316 mg, 0.526 mmol, 71 % yield) as a white foam: LCMS (ES) m/e 601, 603 (M, M+2)$^+$.

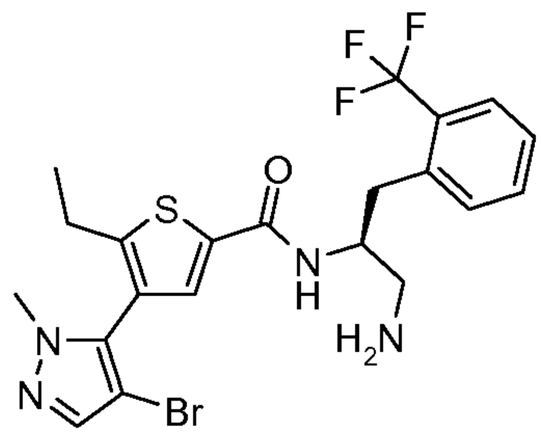
c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (316 mg, 0.53 mmol) in tetrahydrofuran (1.314 ml) and methanol (1.3 ml) at 25 ºC was added hydrazine (0.16 ml, 5.26 mmol) dropwise. After 12h, the solution was concentrated, purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) and converted to the HCl salt by adding excess 2M HCl in Et_2O (2 ml) to the residue in MeOH (5 ml) affording the HCl salt of

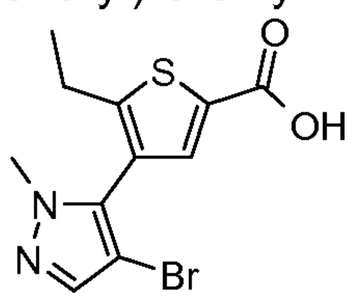
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (163 mg, 0.30 mmol, 57 % yield) as a white solid: LCMS (ES) m/z = 471, 473 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.82 (br. s., 1 H) 8.04 (bs, 3 H) 7.85 (s, 1 H) 7.65 - 7.72 (m, 2 H) 7.52-7.59 (m, 2 H) 7.39 - 7.46 (m, 1 H) 4.41-4.47 (m, 1 H) 3.71 (s, 3 H) 2.98-3.07 (m, 4H) 2.67 (q, J=7.58 Hz, 2 H) 1.16 (t, J=7.58 Hz, 3 H).

Example 101



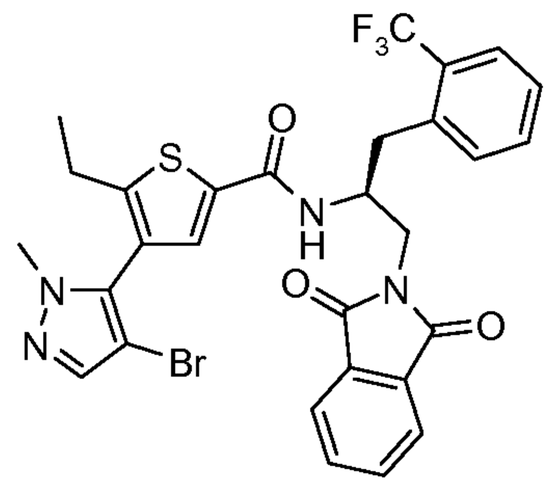
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



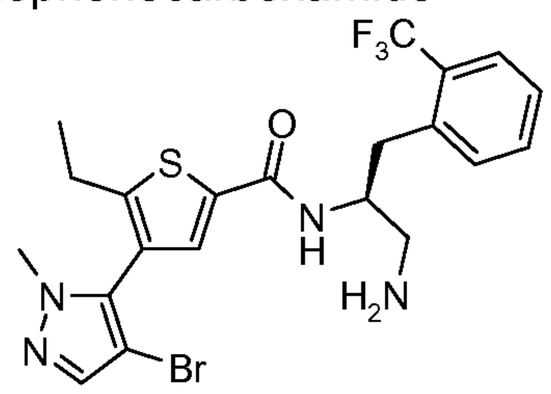
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.2 mmol)[Prepared in Example 98] and N-bromosuccinimide (213 mg, 1.2 mmol) in Tetrahydrofuran (5.99 ml) was stirred in a sealed tube for 1h at 70 °C. Aqueous sodium hydroxide (4.0 ml, 23.97 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAC in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (378 mg, 1.2 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 314, 316 (M, M+2)$^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (200 mg, 0.57 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (181 mg, 0.57 mmol)[Prepared according to Preparation 6] and N,N-diisopropylethylamine (0.50 ml, 2.87 mmol) in Dichloromethane (4.23 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (295 mg, 0.632 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (240 mg, 0.37 mmol, 64.8 % yield) as a white foam: LCMS (ES) m/e 645, 647 (M, M+2)$^+$.

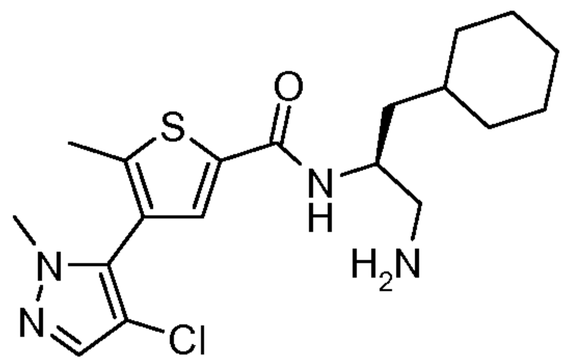
c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (240 mg, 0.37 mmol) in tetrahydrofuran (1.31 ml) and methanol (1.31 ml) at 25 °C was added hydrazine (0.12 ml, 3.72 mmol) dropwise. After 12h, the solution was concentrated, purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) and converted to the HCl salt by adding

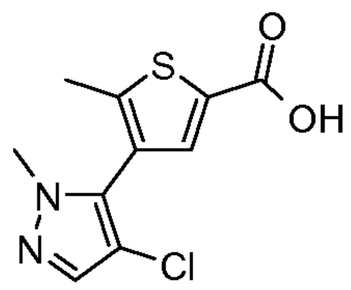
excess 4M HCl in dioxane (2 ml) to the residue in MeOH (5 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (167 mg, 0.28 mmol, 76 % yield) as a white solid: LCMS (ES) m/z = 515, 517 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.77 (dd, J=15.66, 9.09 Hz, 1 H) 8.02 (br. s., 3 H) 7.80 (s, 1 H) 7.66 - 7.72 (m, 2 H) 7.54 - 7.61 (m, 2 H) 7.41 - 7.48 (m, 1 H) 4.42 - 4.47 (m, 1 H) 3.71 (s, 3 H) 2.98 - 3.06 (m, 4 H) 2.66 (dd, J=7.45, 3.16 Hz, 2 H) 1.15 (t, J=7.45 Hz, 3 H).

Example 102



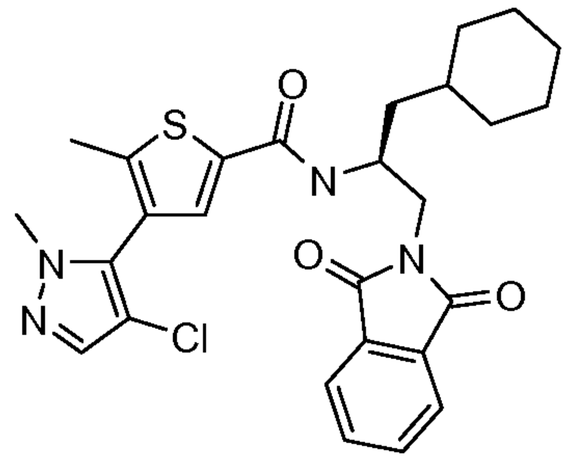
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



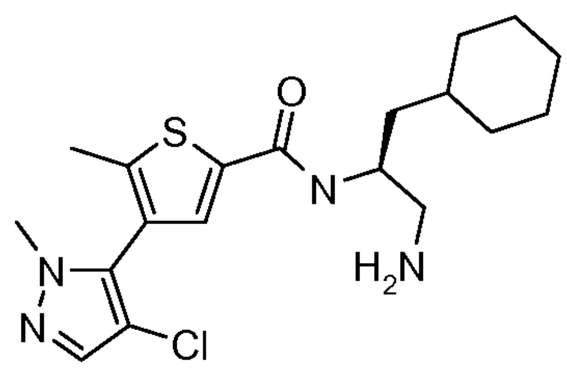
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.75 g, 11.64 mmol)[Prepared in Example 99] and N-chlorosuccinimide (1.55 g, 11.64 mmol) in tetrahydrofuran (58 ml) was stirred in a sealed tube for 1h at 70 °C. Sodium hydroxide (9.70 ml, 58 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (2.3 g, 8.96 mmol, 77 % yield) as a yellow oil: LCMS (ES) m/e 257, 259 (M, M+2)+.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (159 mg, 0.62 mmol), N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 45% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (231 mg, 0.44 mmol, 71 % yield) as a clear oil: LCMS (ES) m/e 525, 527 $(M, M+2)^+$.

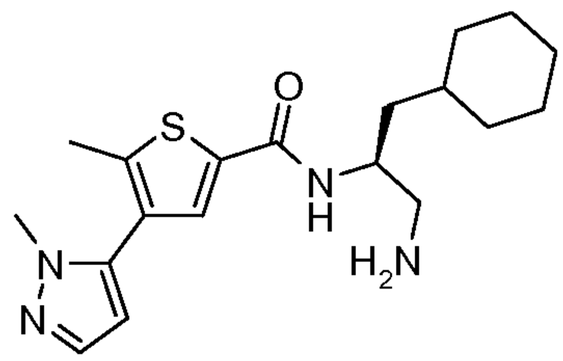
c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (231 mg, 0.44 mmol) in tetrahydrofuran (2.20 ml) and methanol (2.20 ml) at 25 °C was added hydrazine (0.14 ml, 4.40 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by

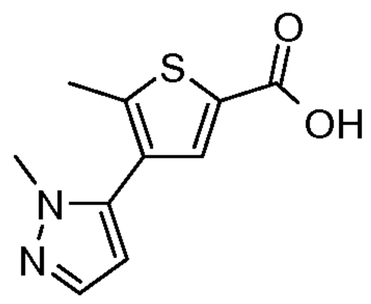
column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (124 mg, 0.27 mmol, 60 % yield) as a yellow solid: LCMS (ES) m/z = 394, 396 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 (br. s., 1 H) 7.97 (br. s., 3 H) 7.86 (s, 1 H) 7.70 (s, 1 H) 4.24 - 4.26 (m, 1 H) 3.71 (s, 3 H) 2.90 - 2.99 (m, 2 H) 2.36 (s, 3 H) 1.75 - 1.79 (m, 1 H) 1.61 1.64 (m, 4 H) 1.48 - 1.51 (m, 1 H) 1.31 - 1.36 (m, 2 H) 1.10 - 1.14 (m, 2 H) 0.91 - 0.94 (m, 2 H).

Example 103



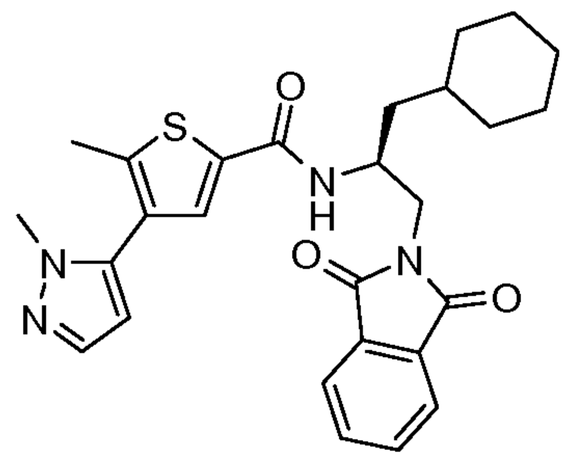
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



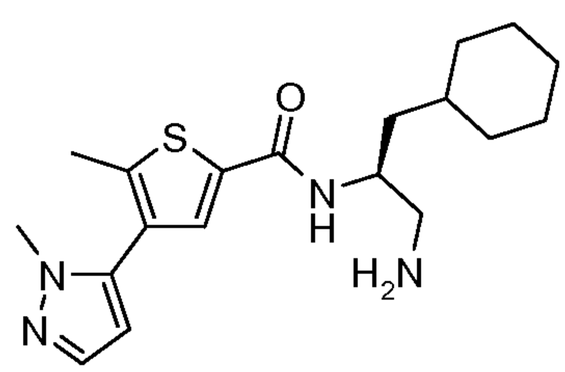
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.06 mmol)[Prepared in Example 99] in 6N sodium hydroxide (1.76 ml, 10.6 mmol) and tetrahydrofuran (5.290 ml) was stirred at 70 ºC in a sealed tube for 1h. The resulting solution was cooled and partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (151 mg, 0.68 mmol, 64 % yield) as a white solid; LCMS (ES) m/z = 223 $(M+H)^+$.

b) N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (138 mg, 0.62 mmol), N,N-diisopropylethylamine (0.541 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (285 mg, 0.581 mmol, 94 % yield) as a white foam: LCMS (ES) m/e 491, 493 (M, M+2)$^+$.

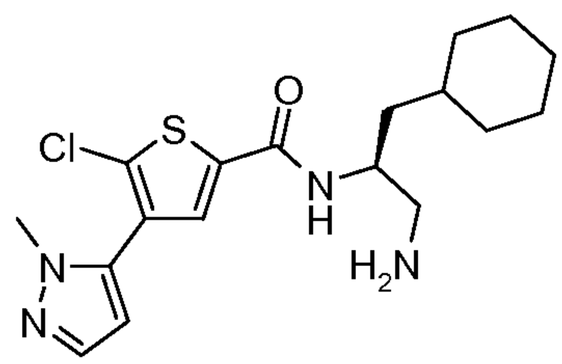
c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (285 mg, 0.581 mmol) in tetrahydrofuran (2.905 ml) and methanol (2.91 ml) at 25 °C was added hydrazine (0.18 ml, 5.81 mmol) dropwise. After 12h, the solution was

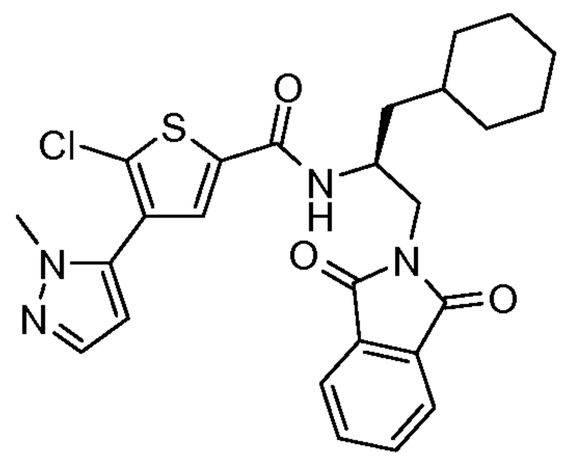
concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (173 mg, 0.40 mmol, 69 % yield) as a yellow solid: LCMS (ES) m/z = 360 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.55 (d, *J*=8.59 Hz, 1 H) 8.01 (br. s., 3) 7.94 (s, 1 H) 7.52 (d, *J*=2.02 Hz, 1 H) 6.35 (d, *J*=1.77 Hz, 1 H) 4.24 - 4.27 (m, 1 H) 3.77 (s, 3 H) 2.91 - 2.94 (m, 2 H) 2.39 (s, 3 H) 1.72 - 1.77 (m, 1 H) 1.60 - 1.64 (m, 4 H) 1.49 - 1.52 (m, 1 H) 1.21 - 1.29 (m, 2 H) 1.15 - 1.25 (m, 2 H) 0.89 - 0.94 (m, 2 H).

Example 104



Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

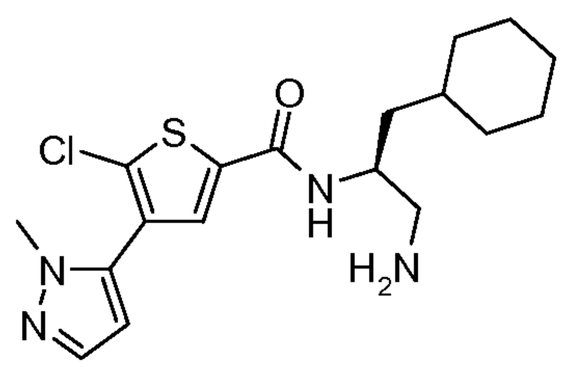
a) 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.62 mmol)[Prepared in Example 95], N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-

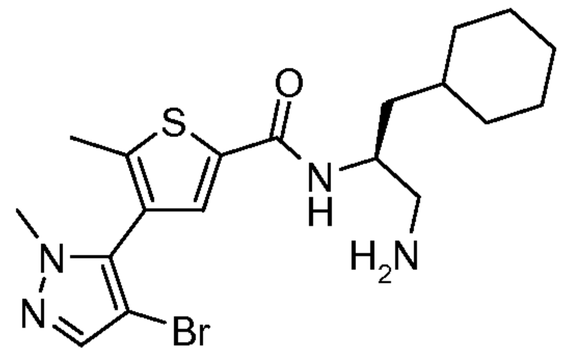
phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 45% EtOAc in hexanes) yielding 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.33 mmol, 53 % yield) as a clear oil: LCMS (ES) m/e 511, 513 (M, M+2)$^+$.

b) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



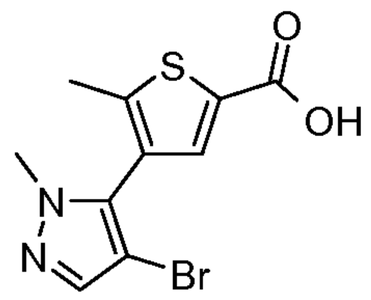
To a solution of 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.33 mmol) in tetrahydrofuran (1.644 ml) and methanol (1.644 ml) at 25 °C was added hydrazine (0.10 ml, 3.29 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 mL) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (79 mg, 0.17 mmol, 53 % yield) as a yellow solid: LCMS (ES) m/z = 380, 382 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 8.82 (d, *J*=8.59 Hz, 1 H) 8.10 (s, 1 H) 7.99 (br. s., 3 H) 7.55 (d, *J*=1.77 Hz, 1 H) 6.48 (d, *J*=2.02 Hz, 1 H) 4.22 - 4.28 (m, 1 H) 3.81 (s, 3 H) 2.90 - 2.95 (m, 2 H) 1.74 - 1.78 (m, 1 H) 1.62 - 1.65 (m, 4 H) 1.48-1.51 (m, 1 H) 1.37 - 1.39 (m, 2 H) 1.09 - 1.13 (m, 2 H) 0.92 - 0.96 (m, 2 H).

Example 105



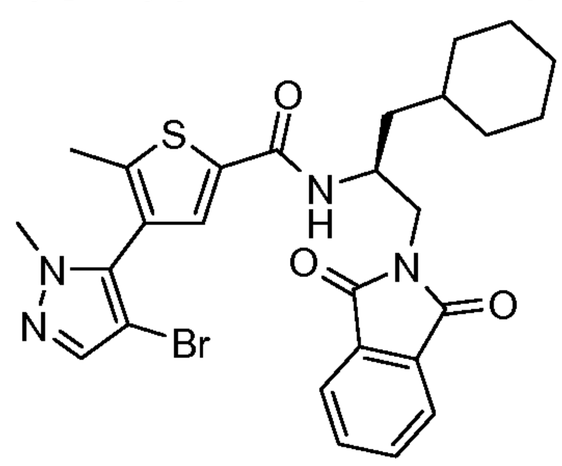
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.058 mmol)[prepared in Example 99] and N-bromosuccinimide (188 mg, 1.06 mmol) in tetrahydrofuran (5.29 ml) was stirred in a sealed tube for 1h at 70 °C. Sodium hydroxide (3.53 ml, 21.16 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (289 mg, 0.96 mmol, 91 % yield) as a yellow oil: LCMS (ES) m/e 301, 303 (M, M+2)$^+$.

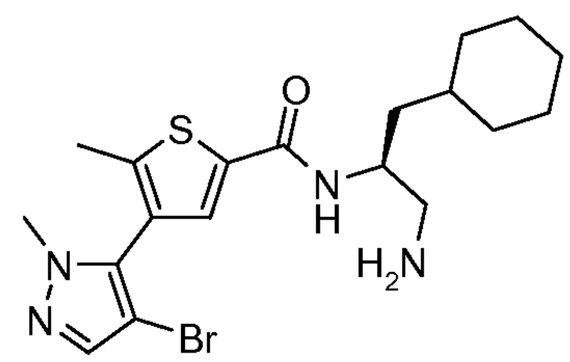
b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (187 mg, 0.62 mmol), N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione

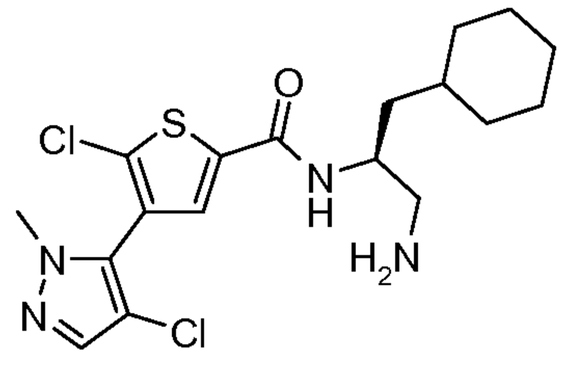
(200 mg, 0.62 mmol))[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (226 mg, 0.40 mmol, 64 % yield) as a white foam: LCMS (ES) m/e 569, 571 $(M, M+2)^+$.

c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



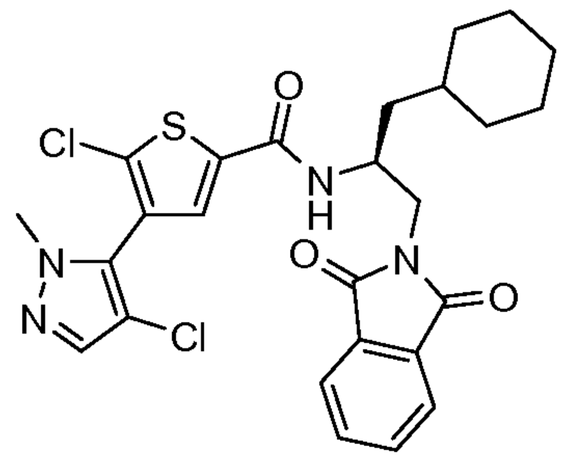
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (226 mg, 0.40 mmol) in tetrahydrofuran (1.98 ml) and methanol (1.98 ml) at 25 °C was added hydrazine (0.13 ml, 3.97 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography. The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (153 mg, 0.30 mmol, 75 % yield) as a yellow solid: LCMS (ES) m/z =439, 441 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 (br. s., 1 H) 7.96 (br. s., 3 H) 7.83 (br. s., 1 H) 7.70 (s, 1 H) 4.21 - 4.25 (m, 1 H) 3.94 (s, 3H) 2.89 - 2.92 (m, 2 H) 2.35 (s, 3 H) 1.76 - 1.79 (m, 1 H) 1.60 - 1.64 (m, 4 H) 1.48 - 1.54 (m, 1 H) 1.26 - 1.32 (m, 2 H) 1.09 - 1.16 (m, 2 H) 0.92 - 0.95 (m, 1 H) 0.82 - 0.86 (m, 1 H).

Example 106



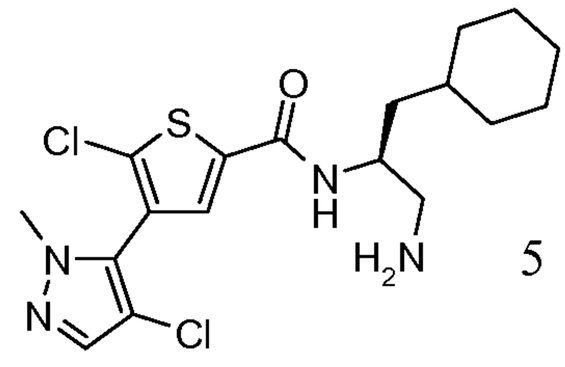
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (216 mg, 0.78 mmol)[prepared according to Example 96], N,N-diisopropylethylamine (0.68 ml, 3.90 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (252 mg, 0.78 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (401 mg, 0.86 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (303 mg, 0.55 mmol, 71 % yield) as a clear oil: LCMS (ES) m/e 545, 547 $(M, M+2)^+$.

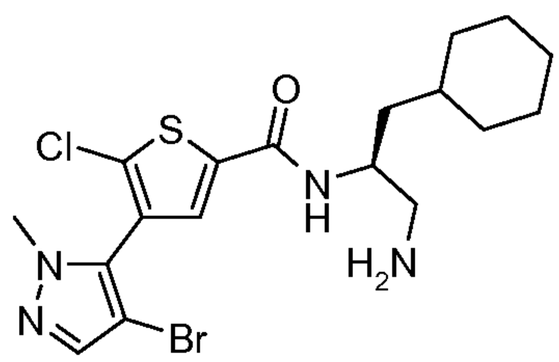
b) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



5

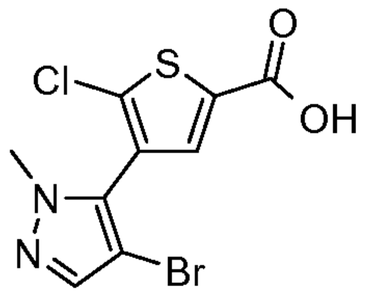
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (303 mg, 0.55 mmol) in tetrahydrofuran (2.78 ml) and methanol (2.78 ml) at 25 °C was added hydrazine (0.17 ml, 5.55 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (190 mg, 0.389 mmol, 70.0 % yield) as a yellow solid: LCMS (ES) m/z =415, 417 $(M, M+2)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (br. s., 1 H) 8.06 (s, 4 H) 7.74 (s, 1 H) 4.25 (dd, *J*=8.84, 4.29 Hz, 1 H) 3.77 (s, 3 H) 2.87 - 2.93 (m, 2 H) 1.71 - 1.79 (m, 1H) 1.64 (d, *J*=9.85 Hz, 3 H) 1.54 (br. s., 1 H) 1.48 (br. s., 1 H) 1.37 (dd, *J*=13.26, 4.93 Hz, 1 H) 1.14 (br. s., 1 H) 1.17 (d, *J*=7.33 Hz, 2 H) 0.93 (d, *J*=10.86 Hz, 1 H) 0.82 - 0.89 (m, 1 H).

Example 107



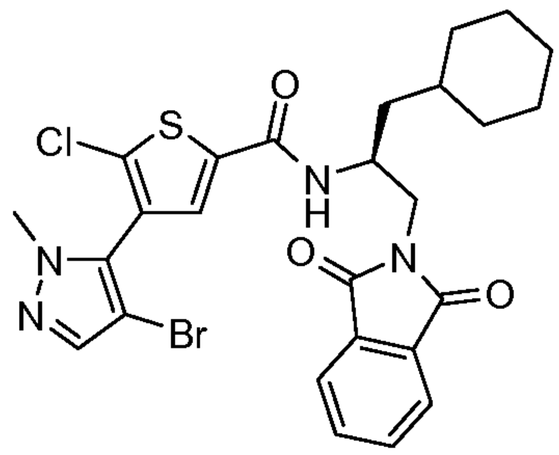
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



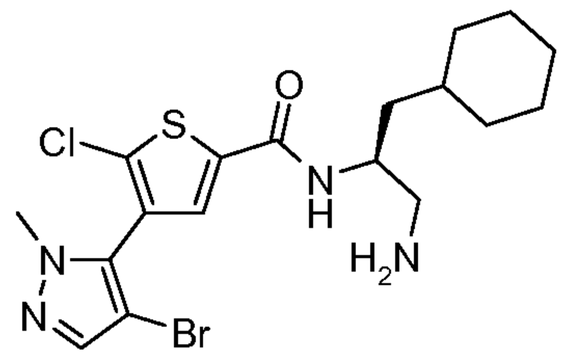
A solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (50 mg, 0.21 mmol)[prepared in Example 95] and NBS (36.7 mg, 0.21 mmol) in tetrahydrofuran (2.06 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (82 mg, 0.16 mmol, 79 % yield) as a yellow oil: LCMS (ES) m/e 257, 259 $(M, M+2)^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



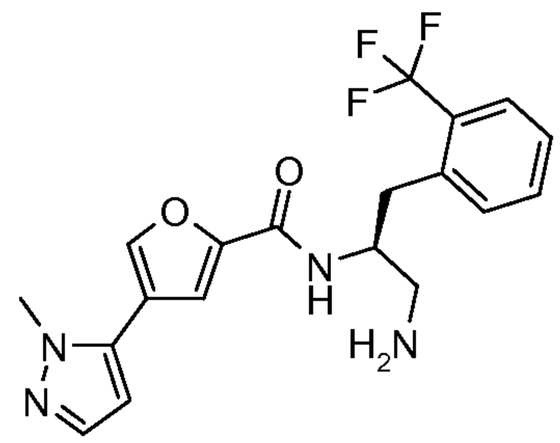
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (81 mg, 0.252 mmol), n,n-diisopropylethylamine (0.22 ml, 1.26 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (81 mg, 0.25 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (141 mg, 0.302 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (47 mg, 0.080 mmol, 31.6 % yield) as a clear oil: LCMS (ES) m/e 589, 591 $(M, M+2)^+$.

c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide



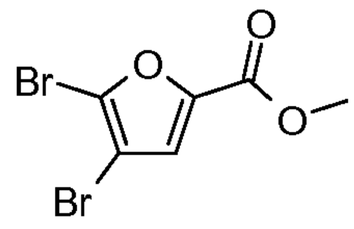
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (48 mg, 0.08 mmol) in tetrahydrofuran (0.41 ml) and methanol (0.41 ml) at 25 °C was added hydrazine (0.03 ml, 0.81 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide (11 mg, 0.02 mmol, 24 % yield) as a yellow solid: LCMS (ES) m/z =459, 461 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (br. s., 1 H) 7.96 (br. s., 4 H) 7.74 (s, 1 H) 4.21 - 4.26 (m, 1 H) 3.77 (s, 3 H) 2.92 - 2.99 (m, 2 H) 1.73 - 1.79 (m, 1 H) 1.62 - 1.67 (m, 4 H) 1.49 - 1.51 (m, 1 H) 1.25 (br. s., 2 H) 1.06 - 1.13 (m, 2 H) 0.95 (d, *J*=6.82 Hz, 1 H) 0.82 - 0.89 (m, 1 H).

Example 108



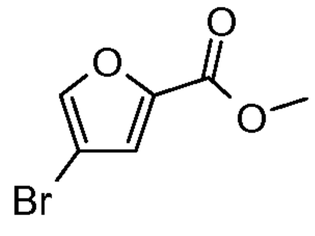
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4,5-dibromo-2-furancarboxylate



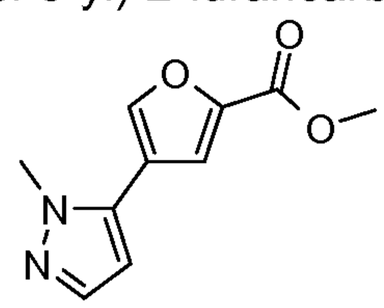
To a solution of 4,5-dibromo-2-furancarboxylic acid (5.7 g, 21.1 mmol) in methanol (106 ml) was added sulfuric acid (11.3 ml, 211 mmol). The resulting solution stirred at 50 °C over 4days. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4,5-dibromo-2-furancarboxylate (5.5 g, 19.4 mmol, 92 % yield): LCMS (ES) m/e 283 $(M+H)^+$.

b) methyl 4-bromo-2-furancarboxylate



To a solution of methyl 4,5-dibromo-2-furancarboxylate (1 g, 3.52 mmol) in tetrahydrofuran (14.1 ml) at -40 °C was added isopropylmagnesium chloride (1.85 ml, 3.70 mmol). After 2h, H_2O (3.52 ml) was added and the solution warmed to 25 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (3% EtOAc in hexanes) affording methyl 4-bromo-2-furancarboxylate (470 mg, 2.04 mmol, 58 % yield) as a white solid: LCMS (ES) m/e 204, 206 (M, M+2)$^+$.

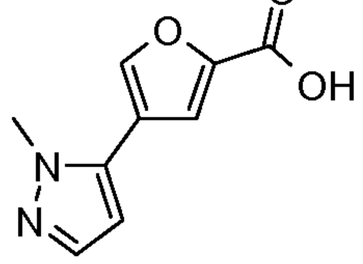
c) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-bromo-2-furancarboxylate (470 mg, 2.29 mmol), potassium carbonate (1.58 g, 11.46 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (525 mg, 2.52 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (58.6 mg, 0.115 mmol) in 1,4-Dioxane (9.5 ml) and water (1.9 ml) was stirred at 80 °C in a sealed tube for 1h. The solution was partitioned between H_2O-DCM and the aqueous phase was

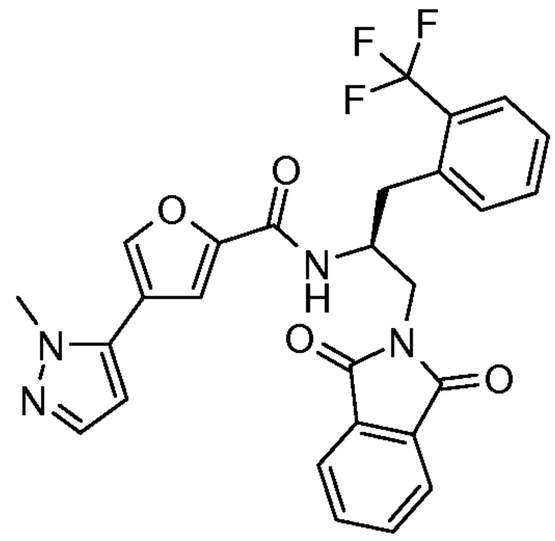
washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (30% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (124 mg, 0.60 mmol, 26 % yield) as a white powder: LCMS (ES) m/e 206 $(M+H)^+$.

d) 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (124 mg, 0.60 mmol) in 6N sodium hydroxide (2.0 ml, 12.0 mmol) and tetrahydrofuran (3.0 ml) was stirred at 70 °C in a sealed tube for 2h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (54 mg, 0.28 mmol, 47 % yield) as a white solid: LCMS (ES) m/e 192 $(M+H)^+$.

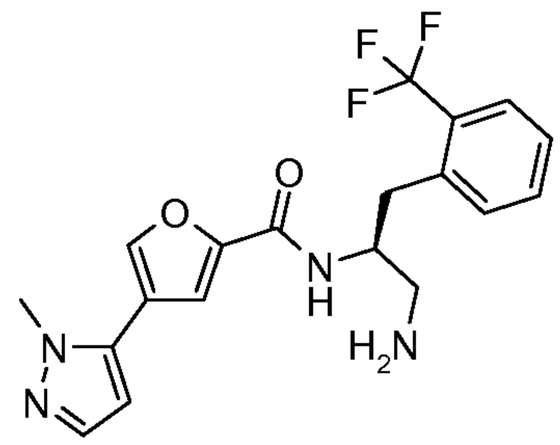
e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (54 mg, 0.28 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (108 mg, 0.28 mmol)[prepared in Preparation 6] and N,N-diisopropylethylamine (0.24 ml, 1.40 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (158 mg, 0.34 mmol) in one portion.

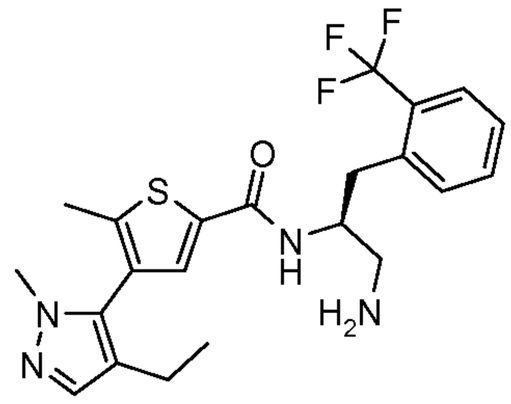
The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purfied via column chromatography (silica, 50% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (100 mg, 0.14 mmol, 50 % yield) as a white solid: LCMS (ES) m/e 523 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



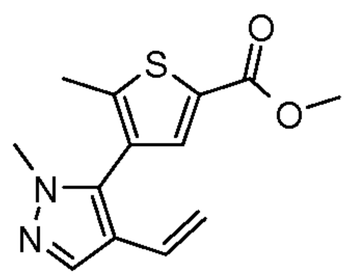
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (100 mg, 0.19 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) at 25 °C was added hydrazine (0.06 ml, 1.91 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (56 mg, 0.12 mmol, 62 % yield) as a yellow solid: LCMS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=9.09 Hz, 1 H) 8.28 (s, 1 H) 8.07 (br. s., 3 H) 7.69 (d, *J*=8.08 Hz, 1 H) 7.56 (d, *J*=8.08 Hz, 2 H) 7.50 (s, 1 H) 7.45 (d, *J*=1.77 Hz, 2 H) 6.51 (d, *J*=1.77 Hz, 1 H) 4.50 - 4.57 (m, 1 H) 3.93 (s, 3 H) 3.02 - 3.16 (m, 4 H).

Example 109



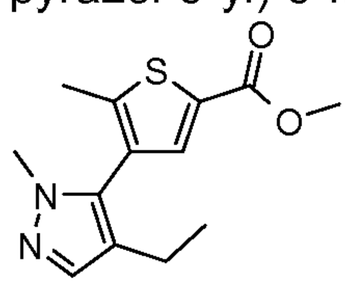
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (200 mg, 0.64 mmol)[prepared in Example 99], potassium carbonate (438 mg, 3.17 mmol), bis(tri-t-butylphosphine)palladium(0) (324 mg, 0.64 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (77 mg, 0.32 mmol) in 1,4-dioxane (5.3 ml) and H_2O (1 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (135 mg, 0.515 mmol, 81 % yield) as a yellow oil: LCMS (ES) m/z = 250 $(M+H)^+$.

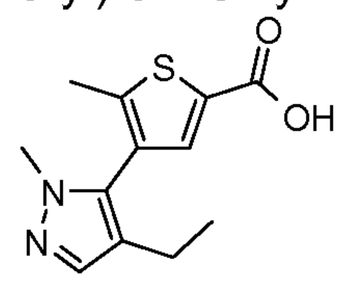
b) methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (135 mg, 0.52 mmol) in methanol (2.6 ml) was added Pd-C (21.9 mg, 0.21 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-

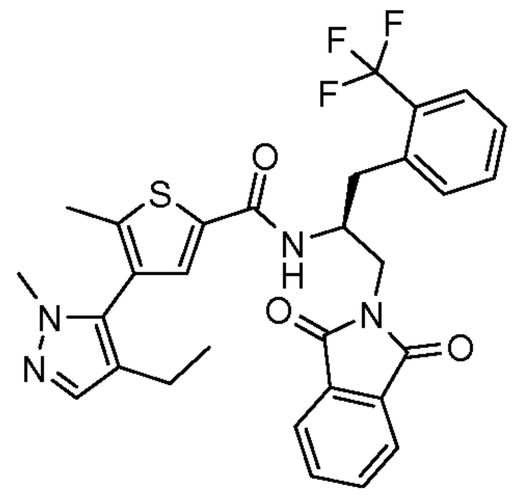
thiophenecarboxylate (145 mg, 0.51 mmol, 99 % yield) as a yellow oil which was used without further purification: LCMS (ES) m/e 265 $(M+H)^+$.

c) 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



A solution of methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (145 mg, 0.55 mmol) in 6N sodium hydroxide (1.8 ml, 10.97 mmol) and tetrahydrofuran (4.8 ml) was stirred at 60 °C in a sealed tube for 12h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (137 mg, 0.55 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 250 $(M+H)^+$.

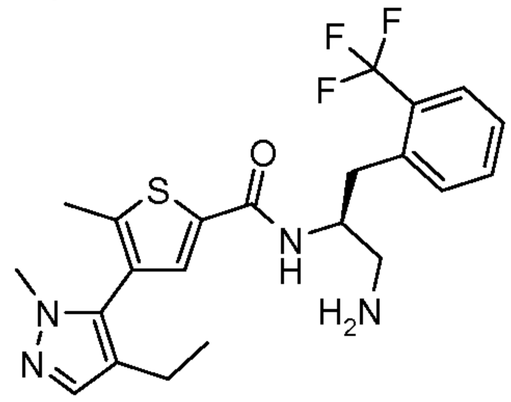
d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (137 mg, 0.55 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (211 mg, 0.55 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.48 ml, 2.74 mmol) in Dichloromethane (5.47 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (281 mg, 0.60 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-

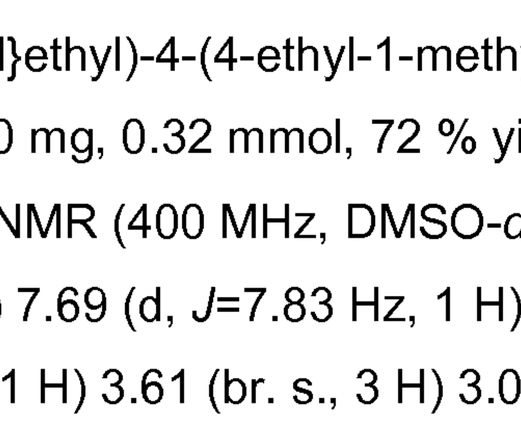
1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (262 mg, 0.45 mmol, 82 % yield) as a clear oil: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



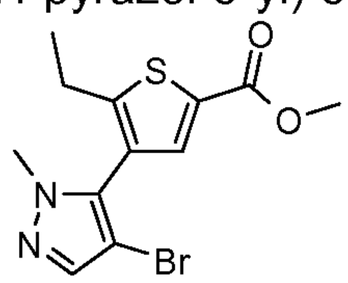
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (262 mg, 0.45 mmol) in tetrahydrofuran (2.256 ml) and methanol (2.256 ml) at 25 °C was added hydrazine (0.14 ml, 4.51 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (170 mg, 0.32 mmol, 72 % yield) as a yellow solid: LCMS (ES) m/z = 451 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (br. s., 1 H) 8.05 (br. s., 2 H) 7.76 (s, 1 H) 7.69 (d, *J*=7.83 Hz, 1 H) 7.49 - 7.52 (m, 2 H) 7.40 - 7.45 (m, 2 H) 4.42 - 4.47 (m, 1 H) 3.61 (br. s., 3 H) 3.01 - 3.07 (m, 4 H) 2.52 - 2.59 (m, 2 H) 2.26 (s, 3 H) 1.02 - 1.09 (m, 3 H).

Example 110



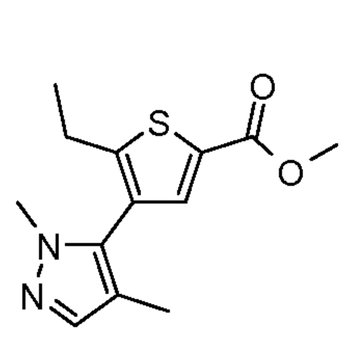
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



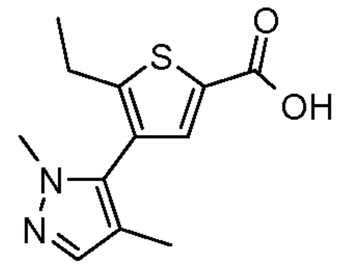
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (980 mg, 3.92 mmol)[prepared in Example 98] and N-bromosuccinimide (697 mg, 3.92 mmol) in tetrahydrofuran (19.6 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 10-40% EtOAC in hexanes) yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (1.1 g, 3.34 mmol, 85 % yield) as a yellow oil: LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



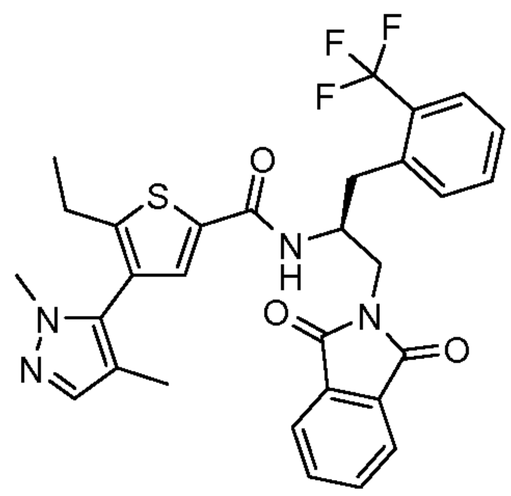
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.911 mmol), potassium carbonate (630 mg, 4.56 mmol), $PdCl_2$(dppf) (66.7 mg, 0.091 mmol) and trimethylboroxin (0.25 ml, 1.82 mmol) in N,N-dimethylformamide (9.1 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (143 mg, 0.51 mmol, 56 % yield) as a yellow oil: LCMS (ES) m/z = 265 $(M+H)^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



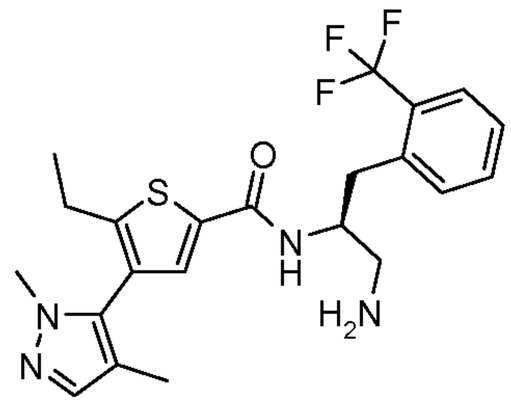
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (143 mg, 0.54 mmol) in 6N sodium hydroxide (0.90 ml, 5.41 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (136 mg, 0.54 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 251 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



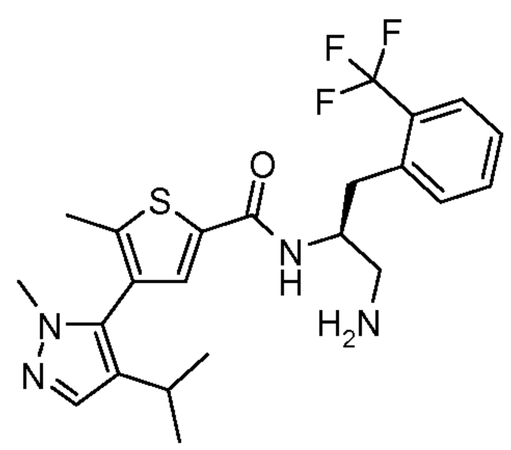
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (130 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (278 mg, 0.43 mmol, 82 % yield) as a yellow oil: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



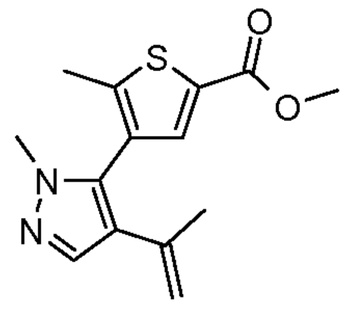
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (278 mg, 0.48 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.15 ml, 4.79 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (3-15% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 2M HCl in Et_2O (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (196 mg, 0.36 mmol, 76 % yield) as a yellow solid: LCMS (ES) m/z = 451 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.86 - 8.93 (m, 1 H) 8.15 (br. s., 3 H) 7.83 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.55 (br. s., 1 H) 7.52 (t, *J*=7.45 Hz, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 7.38 (s, 1 H) 4.22 - 4.27 (m,1 H) 3.62 (s, 3 H) 2.97 - 3.09 (m, 4 H) 2.60 (q, *J*=7.49 Hz, 2 H) 1.88 (s, 3 H) 1.13 (t, *J*=7.58 Hz, 3 H).

Example 111



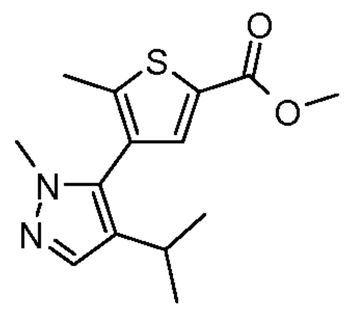
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide

a) methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate



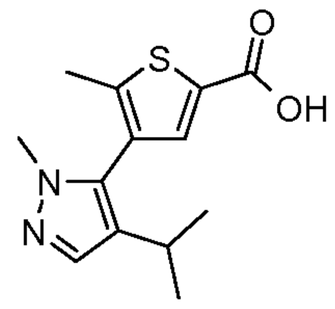
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (300 mg, 0.95 mmol), potassium carbonate (658 mg, 4.76 mmol), bis(tri-t-butylphosphine)palladium(0) (24.32 mg, 0.05 mmol) and 4,4,5,5-tetramethyl-2-(1-methylethenyl)-1,3,2-dioxaborolane (0.18 ml, 0.95 mmol) in 1,4-dioxane (5.3 ml) and H_2O (1.0 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (171 mg, 0.58 mmol, 61 % yield) as a yellow oil: LCMS (ES) m/z = 276 $(M+H)^+$.

b) methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate



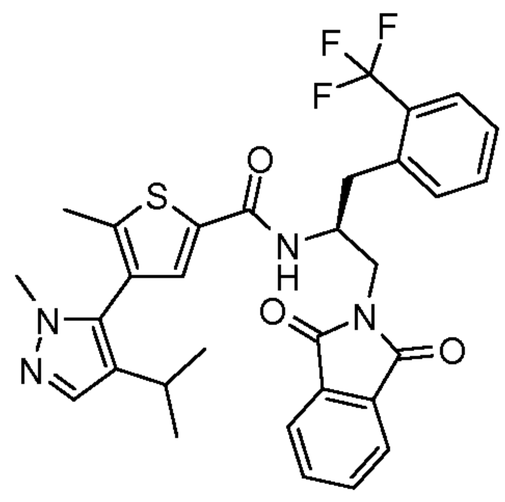
To a solution of methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (171 mg, 0.62 mmol) in methanol (3 ml) was added $PdOH_2$ (34.8 mg, 0.25 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (173 mg, 0.62 mmol, 100 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

c) 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid



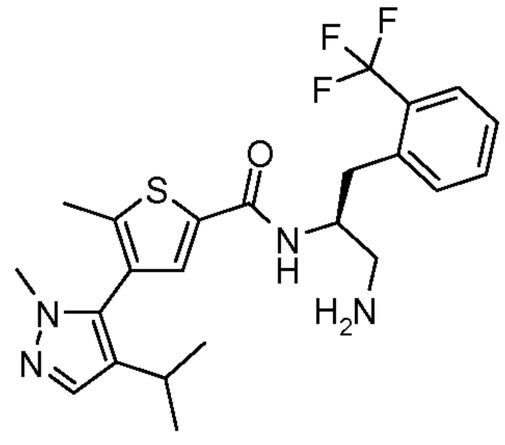
A solution of methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (173 mg, 0.62 mmol) in 6N sodium hydroxide (1 ml, 6.21 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid (148 mg, 0.49 mmol, 79 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide



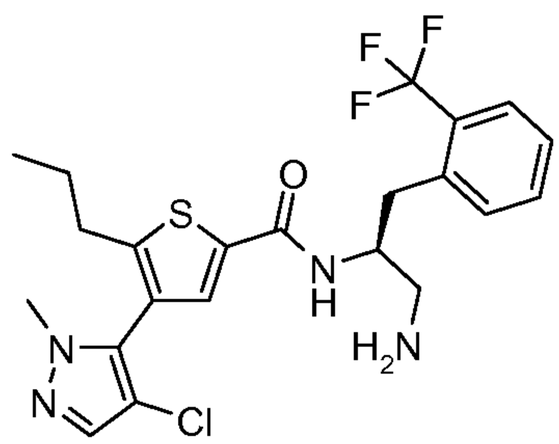
To a solution of 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid (137 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[Prepared in Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.572 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (211 mg, 0.334 mmol, 64.2 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide



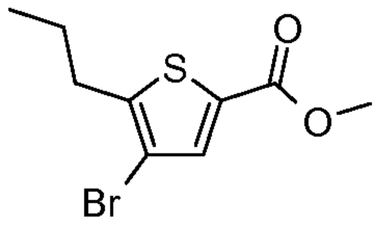
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (211 mg, 0.36 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.11 ml, 3.55 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (108 mg, 0.20 mmol, 57 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=8.59 Hz, 1 H) 8.07 (br. s., 3 H) 7.74 (s, 1 H) 7.65 - 7.68 (m, 1 H) 7.55 - 7.60 (m, 1 H) 7.46 - 7.49 (m, 1 H) 7.39 - 7.46 (m, 2 H) 4.47 (br. s., 1 H) 3.57 (s, 3 H) 2.99 - 3.05 (m, 4 H) 2.49 - 2.52 (m, 1 H) 2.25 (s, 3 H) 1.07 - 1.14 (m, 6 H).

Example 112



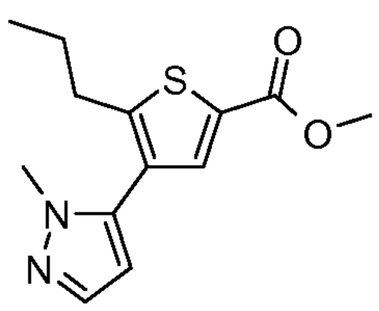
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) methyl 4-bromo-5-propyl-2-thiophenecarboxylate



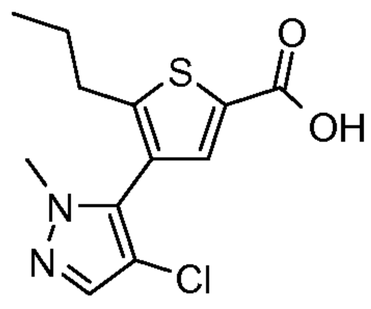
To a solution of 4-bromo-5-propyl-2-thiophenecarboxylic acid (5.0 g, 20.07 mmol) in methanol (100 ml) was added sulfuric acid (5.35 ml, 100 mmol). The resulting solution stirred at 50 °C for 36h. H_2O (50 mL) was added the aqueous phase was washed several times with DCM. The combined organic fractions were washed with saturated $NaHCO_3$, dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-5-propyl-2-thiophenecarboxylate (5.1 g, 18.61 mmol, 93 % yield) as a yellow oil: LCMS (ES) m/e 262, 264 $(M, M+2)^+$.

b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate



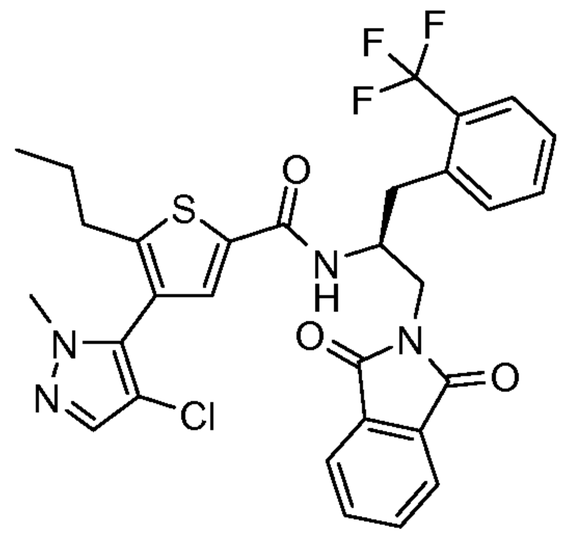
A solution of methyl 4-bromo-5-propyl-2-thiophenecarboxylate (1.0 g, 3.80 mmol), potassium carbonate (2.63 g, 19.00 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.949 g, 4.56 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.097 g, 0.19 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated and purified by column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (1.07 g, 3.76 mmol, 99 % yield) as a yellow oil: LCMS (ES) m/e 265 $(M+H)^+$.

c) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid



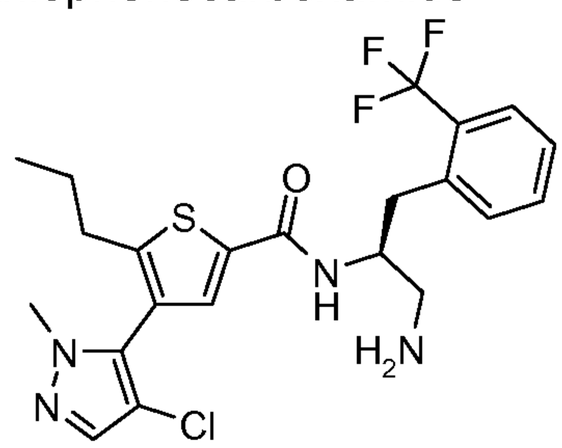
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (356 mg, 1.35 mmol) and N-chlorosuccinimide (180 mg, 1.35 mmol) in tetrahydrofuran (6.7 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (2.2 ml, 13.47 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (357 mg, 1.25 mmol, 93 % yield) as a yellow oil: LCMS (ES) m/e 271, 273 $(M, M+2)^+$.

d) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide



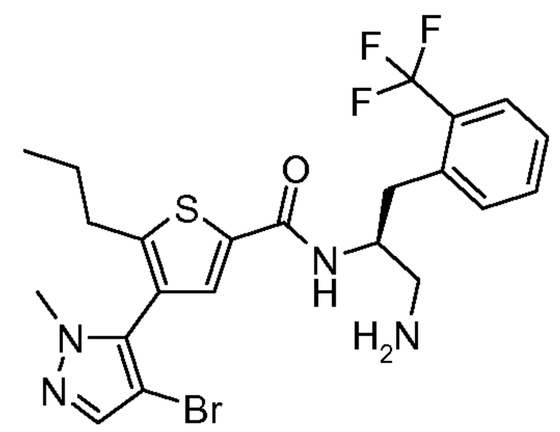
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (148 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[Prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (245 mg, 0.39 mmol, 75 % yield) as a yellow oil: LCMS (ES) m/e 615, 617 $(M, M+2)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide



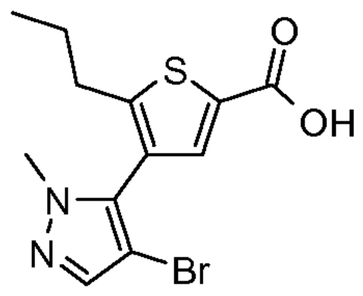
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (245 mg, 0.40 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.12 ml, 3.98 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (178 mg, 0.32 mmol, 80 % yield) as a yellow solid: LCMS (ES) m/z = 485, 487 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 (br. s., 1 H) 8.13 (br. s., 3 H) 7.93 (s, 1 H) 7.66 - 7.73 (m, 2 H) 7.62 (br. s., 1 H) 7.55 (t, *J*=7.45 Hz, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 4.48 (br. s., 1 H) 3.71 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.63 (t, *J*=7.20 Hz, 2 H) 1.53 - 1.57 (m, 2 H) 0.83 (t, *J*=7.33 Hz, 3 H).

Example 113



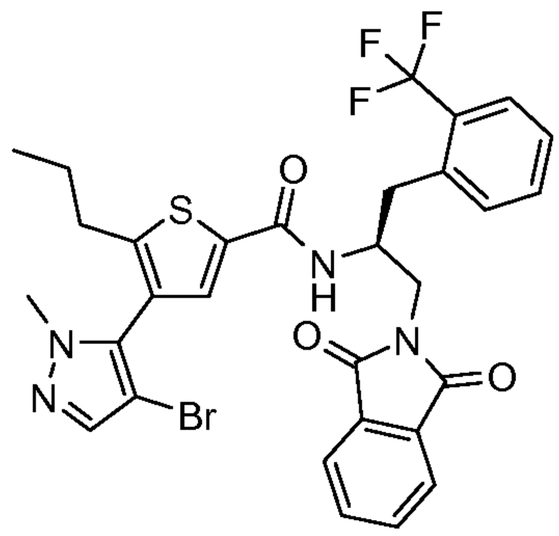
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (714 mg, 2.70 mmol)[prepared in Example 112] and N-bromosuccinimide (481 mg, 2.70 mmol) in tetrahydrofuran (12 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was treated with 6N sodium hydroxide (2.251 ml, 13.51 mmol). The reaction mixture stirred at 70 °C in a sealed tube for 12h and was partitioned between H_2O-DCM. The pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly affording 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (445 mg, 1.35 mmol, 50 % yield): LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

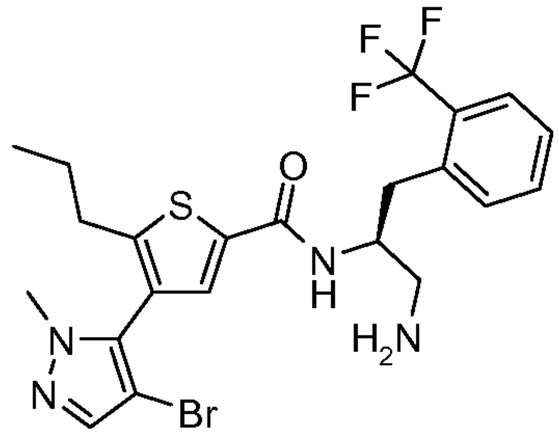
b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (171 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-

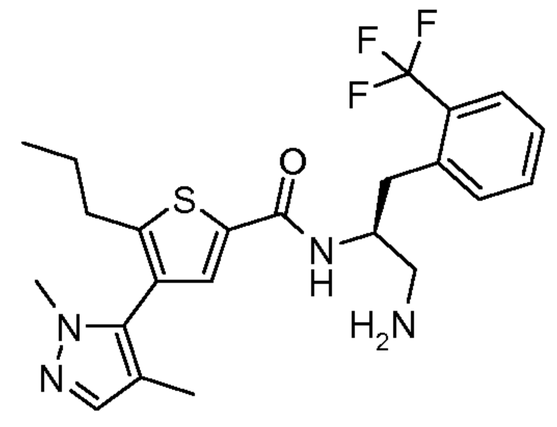
(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (251 mg, 0.37 mmol, 72 % yield) as a yellow oil: LCMS (ES) m/e 659,661 $(M, M+2)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide



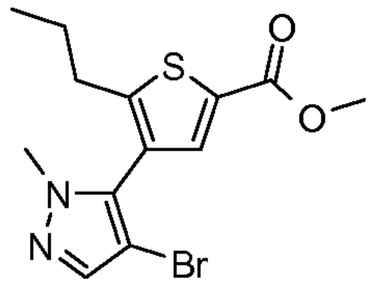
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (251 mg, 0.38 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.12 ml, 3.81 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (178 mg, 0.30 mmol, 78 % yield) as a yellow solid: LCMS (ES) m/z = 529, 531 $(M, M+2)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.94 (d, *J*=8.84 Hz, 1 H) 8.10 (br. s., 3 H) 7.87 (d, *J*=1.77 Hz, 1 H) 7.65 - 7.72 (m, 2 H) 7.58 (dd, *J*=14.78, 7.71 Hz, 2 H) 7.43 (t, *J*=7.45 Hz, 1 H) 4.48 (br. s., 1 H) 3.71 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.58 - 2.66 (m, 2 H) 1.53 (ddd, *J*=13.89, 6.82, 6.57 Hz, 2 H) 0.83 (dd, *J*=7.33, 2.02 Hz, 3 H).

Example 114



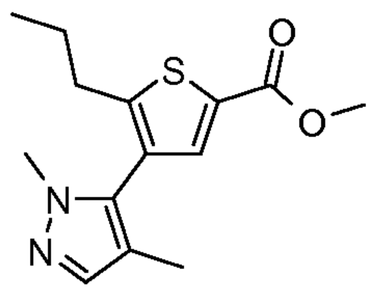
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate



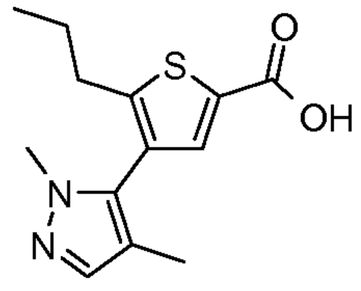
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (714 mg, 2.70 mmol) and N-bromosuccinimide (481 mg, 2.70 mmol) in tetrahydrofuran (12 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (464 mg, 1.35 mmol, 50 % yield) as an orange oil: LCMS (ES) m/e 343, 345 $(M, M+2)^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxylate



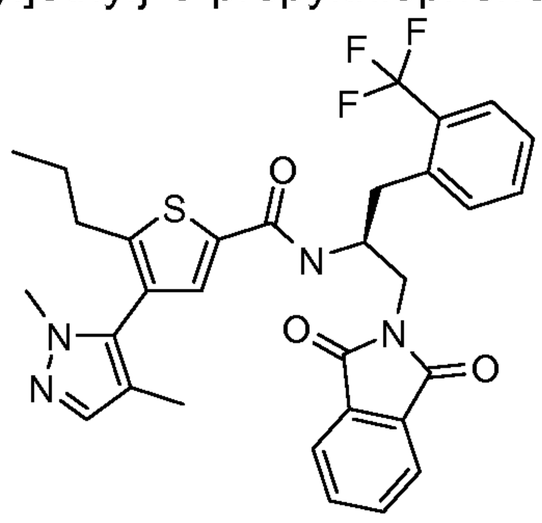
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (242 mg, 0.71 mmol), $PdCl_2$(dppf) (52 mg, 0.07 mmol), potassium carbonate (487 mg, 3.53 mmol) and trimethylboroxine (0.20 ml, 1.41 mmol) in N,N-Dimethylformamide (3.5 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (184 mg, 0.60 mmol, 84 % yield) as a yellow oil: LCMS (ES) m/z = 279 $(M+H)^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxylic acid



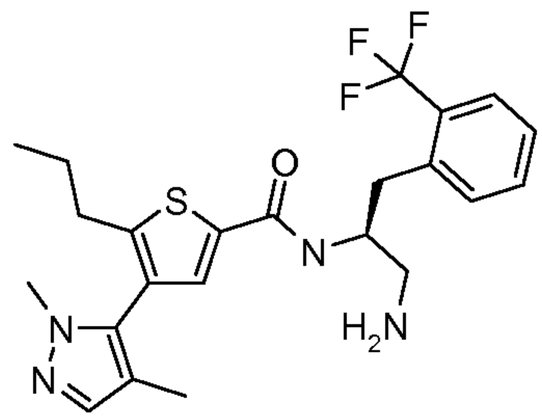
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (0.184 g, 0.66 mmol) in 6N sodium hydroxide (2.2 ml, 13.22 mmol) and tetrahydrofuran (6.6 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (180 mg, 0.66 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 265 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[2-(trifluoromethyl)benzyl]ethyl}-5-propylthiophene-2-carboxamide



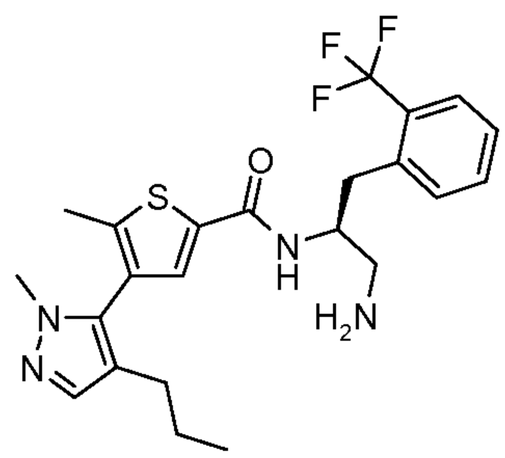
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (180 mg, 0.68 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (262 mg, 0.68 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.59 ml, 3.40 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (350 mg, 0.75 mmol) in one portion. The solution stirred at 25 °C for 2h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (243 mg, 0.41 mmol, 60 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-{(1S)-2-amino-1-[2-(trifluoromethyl)benzyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxamide



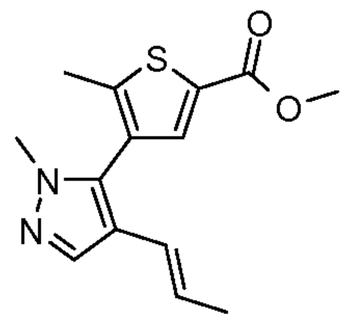
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (243 mg, 0.41 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) at 25 °C was added hydrazine (0.13 ml, 4.09 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (172 mg, 0.30 mmol, 74 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (br. s., 1 H) 8.08 (br. s., 3 H) 7.78 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.50 - 7.55 (m, 2 H) 7.43 (t, *J*=7.71 Hz, 1 H) 7.37 (s, 1 H) 4.49 (d, *J*=10.36 Hz, 1 H) 3.61 (s, 3 H) 2.99 - 3.06 (m, 4 H) 2.54 - 2.59 (m, 2 H) 1.87 (s, 3 H) 1.48 - 1.55 (m, 2 H) 0.81 (t, *J*=7.33 Hz, 3 H).

Example 115



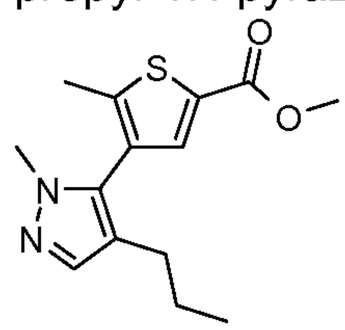
Preparation of N-{(1S)-2-amino-1-[2-(trifluoromethyl)benzyl]ethyl}-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)thiophene-2-carboxamide

a) methyl 5-methyl-4-{1-methyl-4-[(1E)-prop-1-en-1-yl]-1H-pyrazol-5-yl}thiophene-2-carboxylate



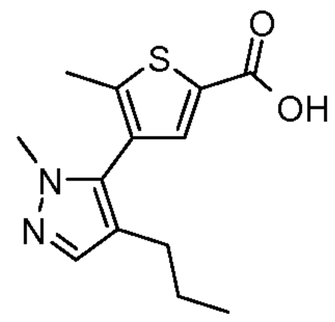
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (320 mg, 1.015 mmol)[prepared in Example 99], potassium carbonate (702 mg, 5.08 mmol), bis(tri-t-butylphosphine)palladium(0) (25.9 mg, 0.05 mmol) and(1Z)-1-propen-1-ylboronic acid (87 mg, 1.01 mmol) in 1,4-dioxane (5.3 ml) and water (1.3 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-methyl-4-{1-methyl-4-[(1Z)-1-propen-1-yl]-1H-pyrazol-5-yl}-2-thiophenecarboxylate (243 mg, 0.88 mmol, 87 % yield) as a yellow oil: LCMS (ES) m/z = 277 $(M+H)^+$.

b) methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



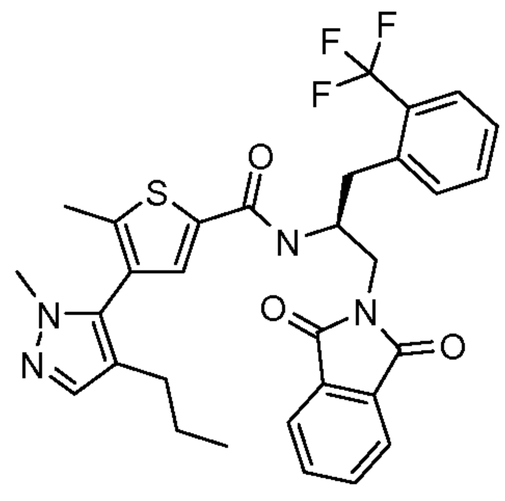
To a solution of methyl 5-methyl-4-{1-methyl-4-[(1Z)-1-propen-1-yl]-1H-pyrazol-5-yl}-2-thiophenecarboxylate (243 mg, 0.88 mmol) in methanol (6.8 ml) was added $Pd(OH)_2$ (49 mg, 0.35 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.69 mmol, 78 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

c) 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



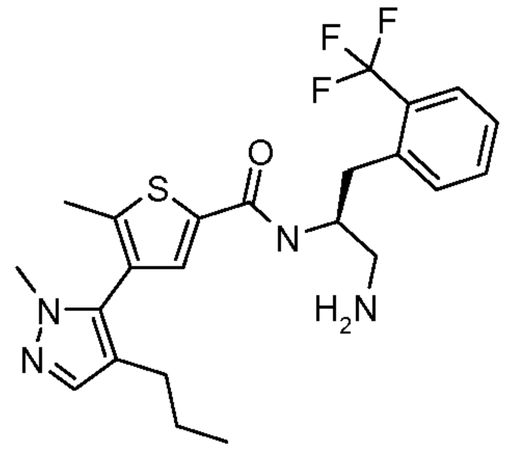
A solution of methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.78 mmol) in 6N sodium hydroxide (2.60 ml, 15.59 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (242 mg, 0.78 mmol, 100 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



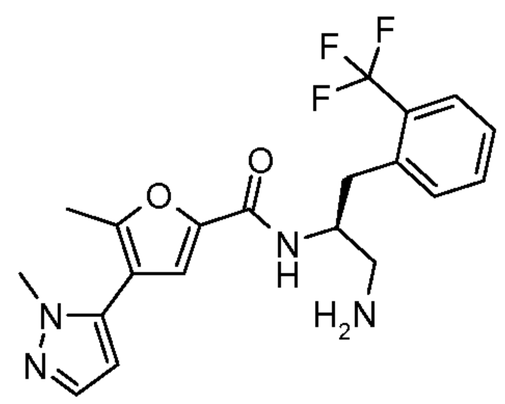
To a solution of 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (206 mg, 0.78 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (300 mg, 0.78 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.68 ml, 3.90 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (400 mg, 0.86 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (283 mg, 0.46 mmol, 60 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



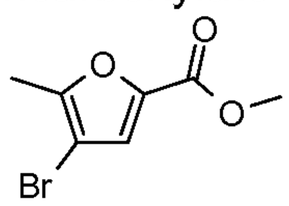
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (283 mg, 0.48 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.15 ml, 4.76 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (186 mg, 0.35 mmol, 73 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (br. s., 1 H) 8.13 (br. s., 3 H) 7.79 (s, 1 H) 7.68 (d, *J*=7.58 Hz, 1 H) 7.59 (d, *J*=7.07 Hz, 1 H) 7.42 - 7.51 (m, 1 H) 7.38 - 7.45 (m, 2 H) 4.47 (br. s., 1 H) 3.61 (d, *J*=2.78 Hz, 3 H) 2.99 - 3.08 (m, 4 H) 2.25 (s, 3 H) 2.11 - 2.21 (m, 2 H) 1.41 - 1.48 (m, 2 H) 0.83 (br. s., 3 H).

Example 116



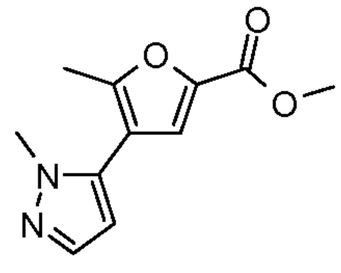
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-bromo-5-methyl-2-furancarboxylate



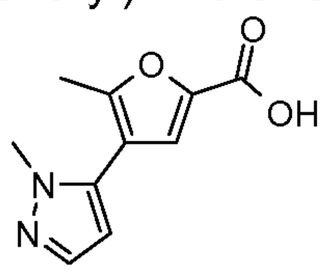
To a solution of methyl 5-methyl-2-furancarboxylate (1.5 g, 10.70 mmol) and aluminum trichloride (2.14 g, 16.06 mmol) in chloroform (21 ml) at 0 °C was added bromine (0.77 ml, 14.99 mmol). The resulting solution stirred at 0 °C and warmed to RT over 12h. This reaction was run in batches (1.5g and 1g) and the batches were combined, added to ice and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (0.5-10% EtOAc in hexanes) affording the title compound (2.1 g, 54%) as a white solid; LCMS (ES) m/z = 219, 221 $(M, M+2)^+$.

b) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



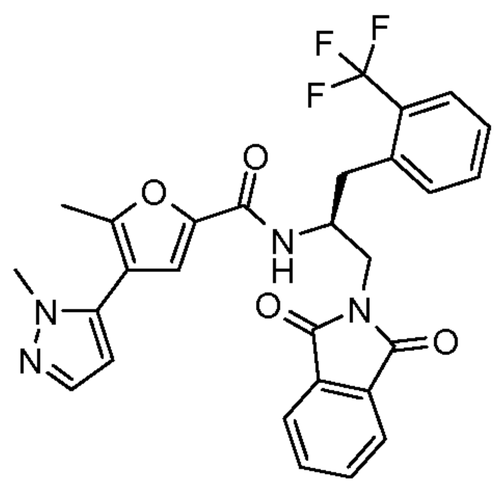
A solution of methyl 4-bromo-5-methyl-2-furancarboxylate (2.1 g, 9.59 mmol), potassium carbonate (6.63 g, 47.9 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.19 g, 10.55 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.24 g, 0.48 mmol) in 1,4-dioxane (40 ml) and water (8 ml) was stirred at 80 °C in a sealed tube for 1h. 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.19 g, 10.55 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.245 g, 0.48 mmol) were added and the reaction stirred an additional 1h and was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-40% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (1.7 g, 7.72 mmol, 81 % yield) as a yellow oil: LCMS (ES) m/e 221 $(M+H)^+$.

c) 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



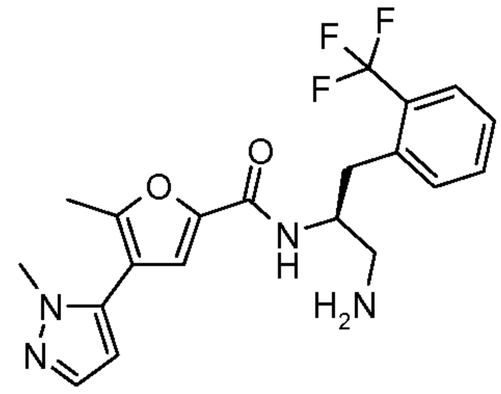
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (200 mg, 0.91 mmol) in 6N sodium hydroxide (2.3 ml, 13.62 mmol) and tetrahydrofuran (4.5 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (130 mg, 0.57 mmol, 63 % yield) as a yellow oil: LCMS (ES) m/e 207 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



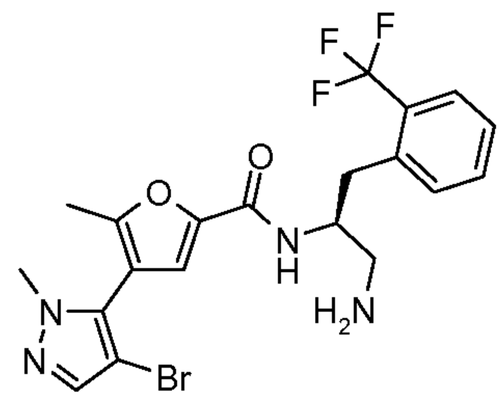
To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (130 mg, 0.63 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (243 mg, 0.63 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.55 ml, 3.15 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (324 mg, 0.69 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (190 mg, 0.23 mmol, 37 % yield) as a clear oil: LCMS (ES) m/e 537 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



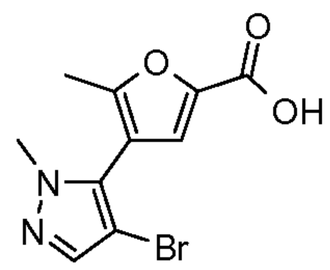
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (190 mg, 0.35 mmol) in tetrahydrofuran (1.5 ml) and methanol (1.5 ml) at 25 ºC was added hydrazine (0.11 ml, 3.54 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (71 mg, 0.15 mmol, 42 % yield) as a yellow solid: LCMS (ES) m/z 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.60 Hz, 1 H) 8.04 (br. s., 3 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.53 - 7.59 (m, 2 H) 7.49 (d, *J*=1.77 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 6.33 (br. s., 1 H) 4.52 (br. s., 1 H) 3.80 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.38 (s, 3 H).

Example 117



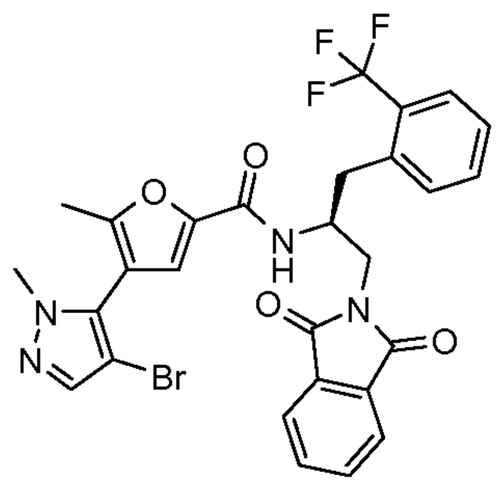
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



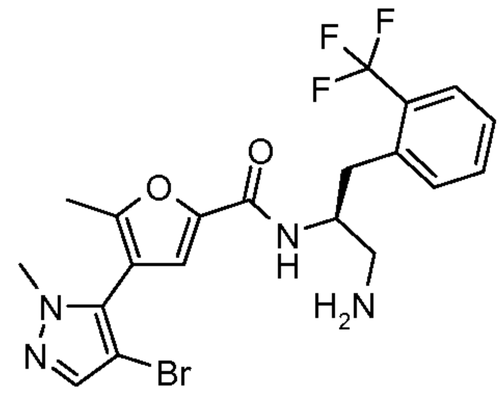
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (600 mg, 2.72 mmol)[prepared in Example 116] and n-bromosuccinimide (485 mg, 2.72 mmol) in tetrahydrofuran (13.6 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was treated with 6N sodium hydroxide (4.54 ml, 27.2 mmol) which stirred at 70 °C in a sealed tube for 4h. The solution was partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly affording 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (369 mg, 1.29 mmol, 48 % yield) as an orange oil: LCMS (ES) m/e 285, 287 $(M, M+2)^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



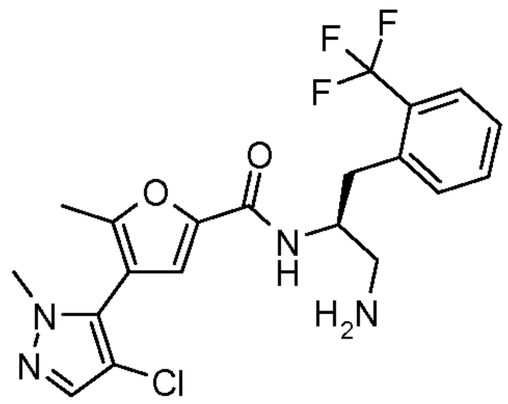
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (200 mg, 0.70 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (270 mg, 0.70 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.61 ml, 3.51 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (361 mg, 0.77 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (232 mg, 0.32 mmol, 46 % yield) as a clear oil: LCMS (ES) m/e 615, 617 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



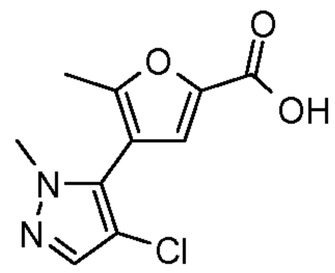
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (232 mg, 0.38 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) at 25 °C was added hydrazine (0.12 ml, 3.77 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (106 mg, 0.19 mmol, 50 % yield) as a yellow solid: LCMS (ES) m/z = 485, 487 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.60 Hz, 1 H) 7.99 (br. s., 3 H) 7.68 (s, 2 H) 7.71 (d, *J*=8.08 Hz, 1 H) 7.59 (d, *J*=7.33 Hz, 1 H) 7.44 - 7.56 (m, 1 H) 7.25 - 7.33 (m, 1 H) 4.50 - 4.57 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.07 (m, 4 H) 2.32 (s, 3 H).

Example 118



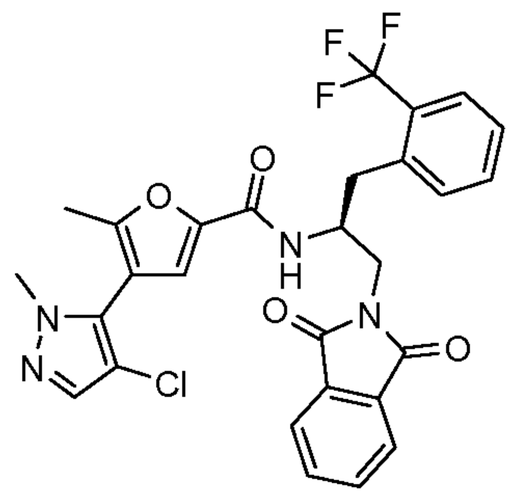
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



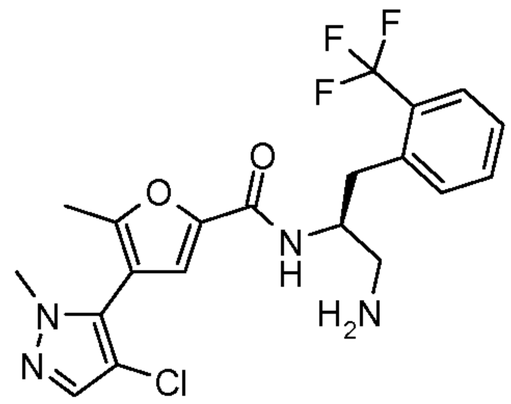
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.36 mmol) and N-chlorosuccinimide (182 mg, 1.36 mmol) in tetrahydrofuran (6.7 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (3.4 ml, 20.4 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (275 mg, 1.14 mmol, 84 % yield) as a orange oil: LCMS (ES) m/e 241, 243 (M, M+2)$^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



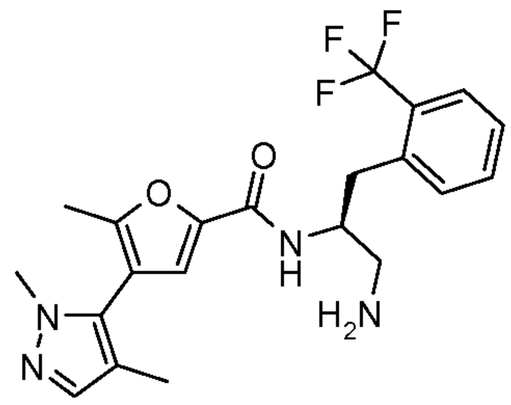
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (200 mg, 0.83 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (320 mg, 0.83 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.72 ml, 4.16 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (427 mg, 0.91 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (246 mg, 0.40 mmol, 49 % yield) as a clear oil: LCMS (ES) m/e 571, 573 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



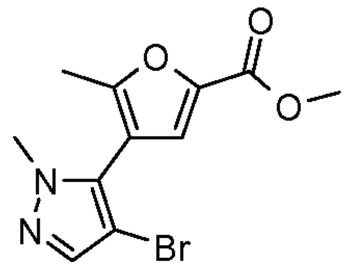
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (246 mg, 0.43 mmol) in tetrahydrofuran (2.1 ml) and methanol (2.1 ml) at 25 ºC was added hydrazine (135 µl, 4.31 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (125 mg, 0.24 mmol, 56 % yield) as a yellow solid: LCMS (ES) m/z = 441, 443 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (d, *J*=9.09 Hz, 1 H) 8.04 (br. s., 3 H) 7.65 - 7.72 (m, 2 H) 7.59 (d, *J*=7.33 Hz, 1 H) 7.57 (br. s., 1 H) 7.39 - 7.47 (m, 1 H) 7.29 - 7.37 (m, 1 H) 4.54 (br. s., 1 H) 3.73 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.33 (s, 3 H).

Example 119



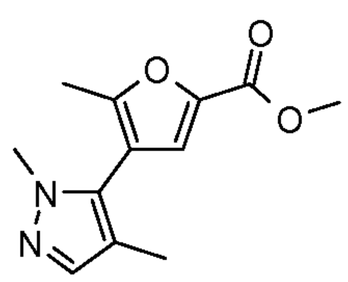
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate



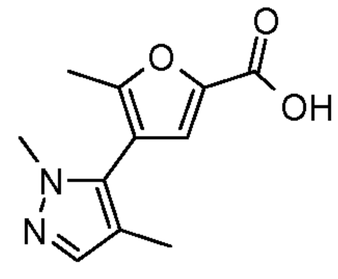
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (600 mg, 2.72 mmol)[prepared in Example 116] and N-bromosuccinimide (485 mg, 2.72 mmol) in tetrahydrofuran (13 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (5-15% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (130 mg, 0.41 mmol, 15 % yield) as an orange oil: LCMS (ES) m/e 299, 301 (M, M+2)$^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate



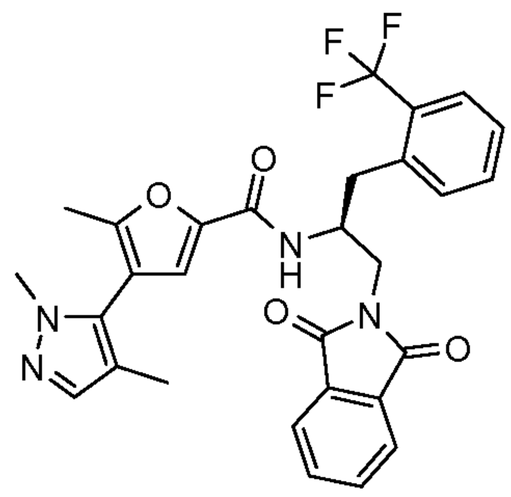
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (130 mg, 0.43 mmol) , potassium carbonate (300 mg, 2.17 mmol), $PdCl_2$(dppf) (15.9 mg, 0.02 mmol) and trimethylboroxine (0.12 ml, 0.87 mmol) in N,N-Dimethylformamide (3.5 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (60 mg, 0.26 mmol, 59 % yield) as a yellow oil: LCMS (ES) m/z = 235 (M+H)$^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



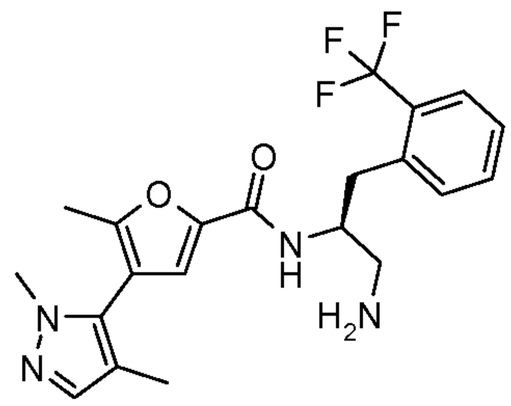
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (60 mg, 0.26 mmol) in 6N sodium hydroxide (0.8 ml, 5.1 mmol) and tetrahydrofuran (2.5 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (53 mg, 0.24 mmol, 94 % yield) as a white foam: LCMS (ES) m/e 221$(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



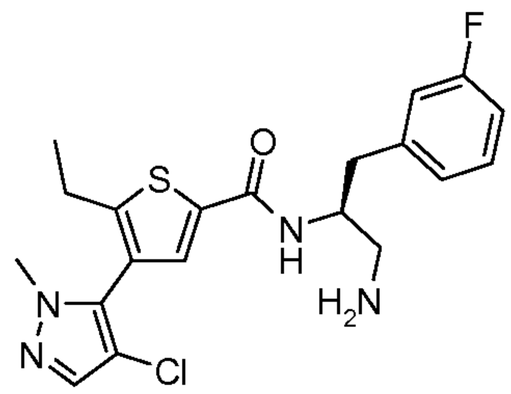
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (53 mg, 0.24 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (93 mg, 0.24 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.21 ml, 1.20 mmol) in dichloromethane (2.4 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (124 mg, 0.26 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (113 mg, 0.21 mmol, 85 % yield) as a white foam: LCMS (ES) m/e 551 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (113 mg, 0.21 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL) at 25 °C was added hydrazine (64 µl, 2.05 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (32 mg, 0.06 mmol, 32 % yield) as a yellow solid: LCMS (ES) m/z = 421 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.70 (d, *J*=7.58 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.40 - 7.47 (m, 1 H) 7.35 (s, 1 H) 7.27 (s, 1 H) 4.54 (br. s., 1 H) 3.65 (s, 3 H) 2.98 - 3.07 (m, 4 H) 2.26 (s, 3 H) 1.90 (s, 3 H).

Example 120

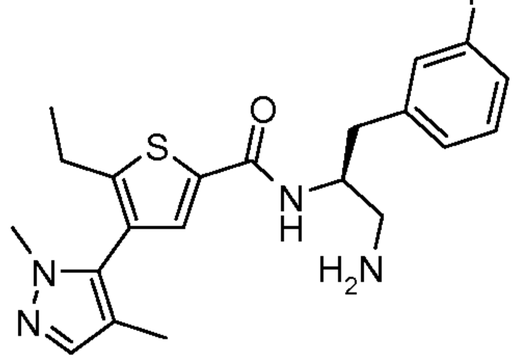


Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 100, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (155 mg, 0.46 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 421,

423 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. s., 1 H) 8.06 (br. s., 3 H) 7.85 (s, 1 H) 7.69 (s, 1 H) 7.28 - 7.36 (m, 1 H) 7.12 (d, *J*=7.07 Hz, 2 H) 7.03 (dd, *J*=17.05, 2.15 Hz, 1 H) 4.36 (br. s., 1 H) 3.69 (s, 3 H) 2.93 - 3.02 (m, 4 H) 2.67 (q, *J*=7.33 Hz, 2 H) 1.16 (t, *J*=7.45 Hz, 3 H).

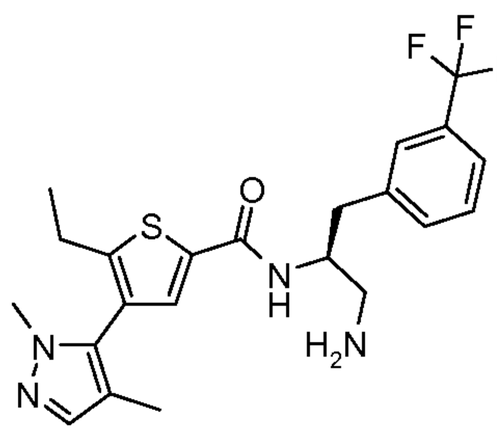
Example 121



N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 110, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (241 mg, 0.72 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 401 (M+H)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. S., 1 H) 8.11 (br. S., 3 H) 7.79 (s, 1 H) 7.37 (s, 1 H) 7.28 – 7.36 (m, 1 H) 7.12 (d, *J*=6.82 Hz, 2 H) 7.03 (td, *J*=8.65, 1.64 Hz, 1 H) 4.41 – 4.43 (m, 1 H, obscured) 3.60 (br. S., 3 H) 2.99 – 3.02 (m, 4 H) 2.60 (q, *J*=7.33 Hz, 2 H) 1.86 (s, 3 H) 1.13 (t, *J*=7.45 Hz, 3 H).

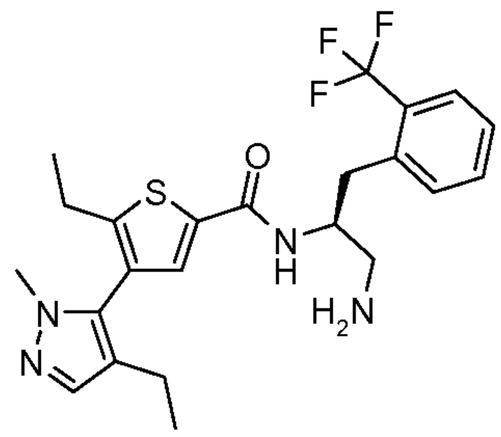
Example 122



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

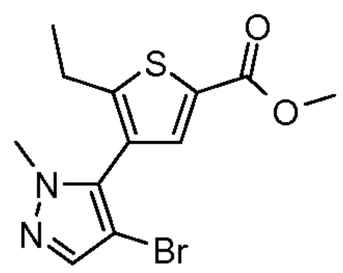
The title compound was prepared as a yellow solid according to Example 110, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (277 mg, 0.72 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 451 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (br. s., 1 H) 8.06 (br. s., 3 H) 7.68 - 7.75 (m, 1 H) 7.52 (s, 1 H) 7.50 - 7.56 (m, 3 H) 7.37 (s, 1 H) 4.36 (d, *J*=8.84 Hz, 1 H) 3.58 (br. s., 3 H) 2.98 - 3.02 (m, 4 H) 2.55 - 2.61 (m, 2 H) 1.86 (s, 3 H) 1.12 (t, *J*=7.58 Hz, 3 H).

Example 123



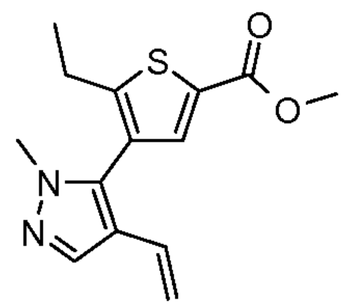
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



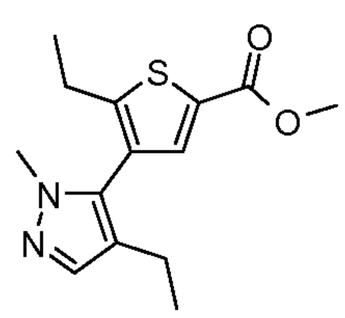
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1 g, 3.99 mmol)[prepared in Example 98] and N-bromosuccinimide (0.711 g, 3.99 mmol) in tetrahydrofuran (8 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (10-50% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (1.2 g, 3.54 mmol, 89 % yield) as an orange oil: LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

b) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



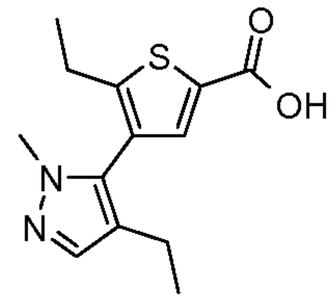
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.911 mmol), potassium carbonate (630 mg, 4.56 mmol), bis(tri-t-butylphosphine)palladium(0) (23.29 mg, 0.05 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (110 mg, 0.45 mmol) in 1,4-dioxane (5 ml) and Water (1 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.66 mmol, 73 % yield) as a clear oil: LCMS (ES) m/z = 277 $(M+H)^+$.

c) methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



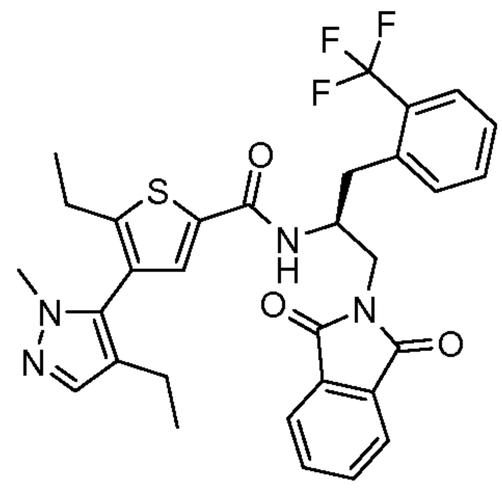
To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.68 mmol) in methanol (2.5 ml) was added Pd-C (7.20 mg, 0.07 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (187 mg, 0.64 mmol, 95 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

d) 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



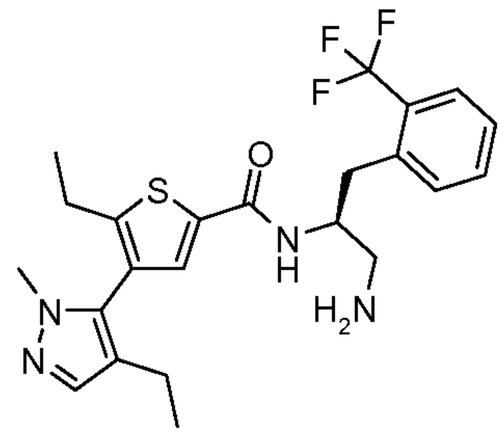
A solution of methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (181 mg, 0.65 mmol) in 6N sodium hydroxide (2.16 ml, 13.0 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (175 mg, 0.65 mmol, 100 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



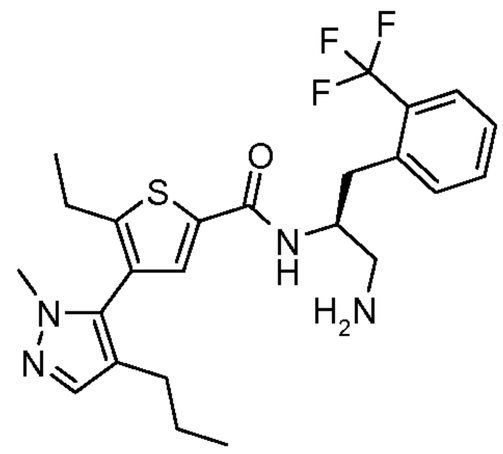
To a solution of 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (175 mg, 0.66 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (255 mg, 0.66 mmol)[prepared according to Procedure 6] and N,N-diisopropylethylamine (0.58 ml, 3.31 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (340 mg, 0.73 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (232 mg, 0.38 mmol, 57 % yield) as a clear oil: LCMS (ES) m/e 595 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (232 mg, 0.39 mmol) in tetrahydrofuran (2 mL) and methanol (2 mL) at 25 °C was added hydrazine (122 µl, 3.90 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (176 mg, 0.38 mmol, 97 % yield) as a yellow solid: LCMS (ES) m/z = 529, 531 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (br. s., 1 H) 7.97 (br. s., 3 H) 7.65 - 7.73 (m, 3 H) 7.57 (d, *J*=5.05 Hz, 2 H) 7.59 (br. s., 1 H) 7.44 (br. s., 1 H) 4.48 (br. s., 1 H) 3.69 (s, 3 H) 2.98 - 3.12 (m, 4 H) 1.24 (dd, *J*=6.82, 2.27 Hz, 3 H) 1.16 (dd, *J*=6.82, 2.53 Hz, 3 H).

Example 124

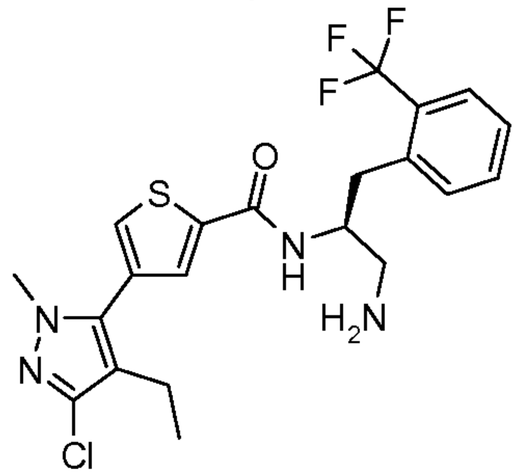


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 123, except substituting (1Z)-1-propen-1-ylboronic acid (78 mg, 0.91 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex: LCMS (ES) m/z = 479 $(M+H)^+$, ^1H

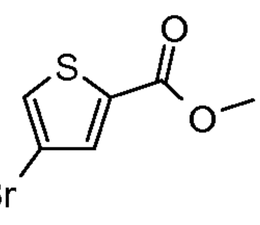
NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (s, 1 H) 8.01 (br. s., 3 H) 7.67 (s, 2 H) 7.56 (d, *J*=5.05 Hz, 2 H) 7.38 - 7.46 (m, 2 H) 4.42 - 4.47 (m, 1 H) 3.59 (s, 3 H) 2.98 - 3.02 (m, 4 H) 2.66 - 2.71 (m, 2 H) 1.40 - 1.47 (m, 2 H) 1.13 (t, *J*=7.52 Hz, 3 H) 0.83 (t, *J*=7.26 Hz, 3 H).

Example 125



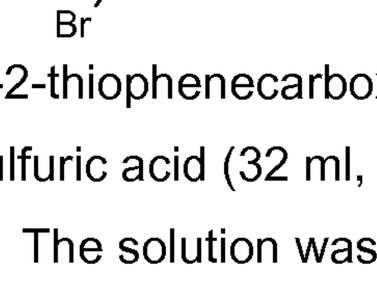
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-2-thiophenecarboxylate



To a solution of 4-bromo-2-thiophenecarboxylic acid (25 g, 121 mmol) in methanol (241 ml) was added sulfuric acid (32 ml, 604 mmol). The resulting solution stirred at 50 ºC over 4d. The solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-2-thiophenecarboxylate (26 g, 118 mmol, 97 % yield), LCMS (ES) m/e 222 $(M+H)^+$.

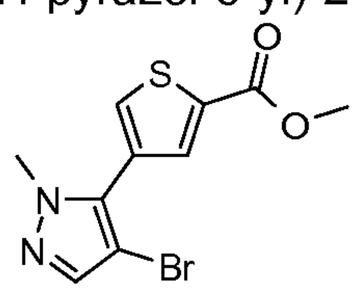
b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-bromo-2-thiophenecarboxylate (2.5 g, 11.31 mmol), potassium carbonate (7.81 g, 56.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-

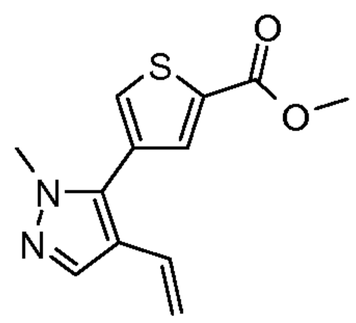
dioxaborolan-2-yl)-1H-pyrazole (2.59 g, 12.44 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.289 g, 0.56 mmol) in 1,4-dioxane (47 ml) and water (9 ml) was stirred at 80 °C in a sealed tube for 1h. 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.59 g, 12.44 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.289 g, 0.56 mmol) were added and the reaction stirred an additional 1h. The mixture was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-40% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.5 g, 11.25 mmol, 99 % yield) as a yellow solid: LCMS (ES) m/e 223 $(M+H)^+$.

c) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.5 g, 11.25 mmol) and n-bromosuccinimide (2.002 g, 11.25 mmol) in tetrahydrofuran (56.2 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (10-50% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.7 g, 8.97 mmol, 80 % yield) as a yellow solid: LCMS (ES) m/e 301, 303 (M, M+2)$^+$.

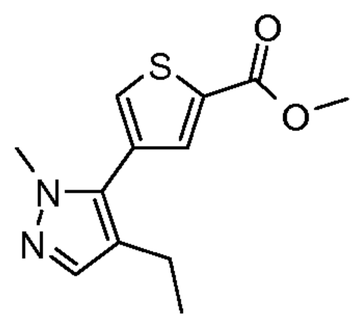
d) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.91 mmol), potassium carbonate (630 mg, 4.56 mmol), bis(tri-t-butylphosphine)palladium(0) (23 mg, 0.05 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (110 mg, 0.46 mmol) in 1,4-dioxane (5 ml)

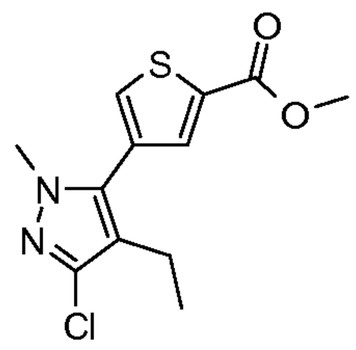
and water (1 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.66 mmol, 73 % yield) as a clear oil: LCMS (ES) m/z = 277 $(M+H)^+$.

e) methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.68 mmol) in methanol (2.5 ml) was added Pd-C (7.20 mg, 0.07 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (187 mg, 0.64 mmol, 95 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

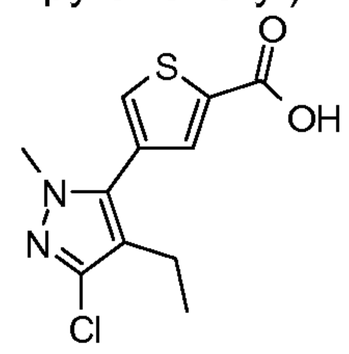
f) methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (202 mg, 0.81 mmol) and NCS (108 mg, 0.81 mmol) in N,N-dimethylformamide (4 ml) was stirred in a sealed tube for 1h at 100 °C. Additional NCS (108 mg, 0.81 mmol) was added and the solution stirred 1h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (2-30% EtOAc in hexanes) affording methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-

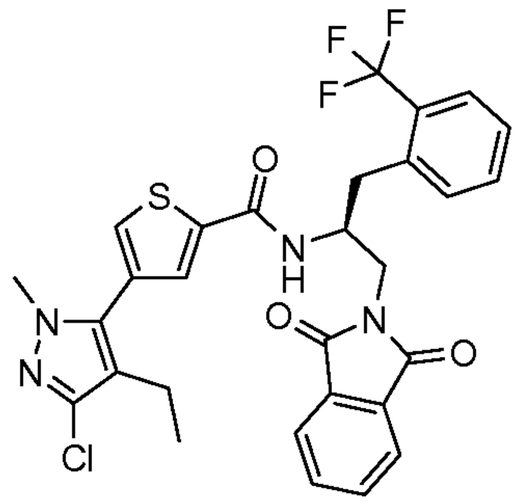
thiophenecarboxylate (135 mg, 0.45 mmol, 56 % yield) as a yellow oil: LCMS (ES) m/e 285 $(M+H)^+$.

g) 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (135 mg, 0.47 mmol) in 6N sodium hydroxide (1.6 ml, 9.48 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 12h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (120 mg, 0.41 mmol, 87 % yield) as a white foam: LCMS (ES) m/e 270, 272 (M, $M+2)^+$.

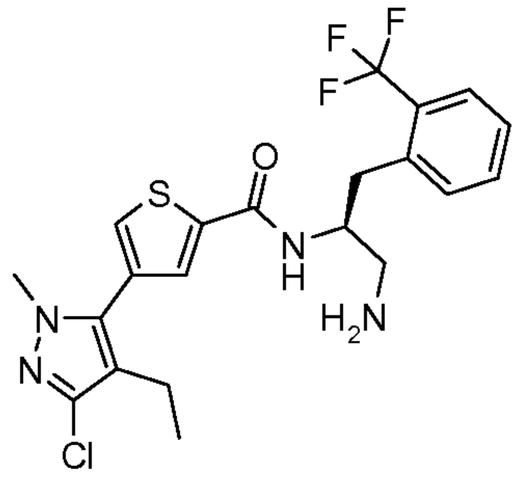
h) 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (120 mg, 0.44 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (171 mg, 0.44 mmol)[prepared according to Preparation 6] and n,n-diisopropylethylamine (0.39 ml, 2.22 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (228 mg, 0.49 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(3-chloro-4-

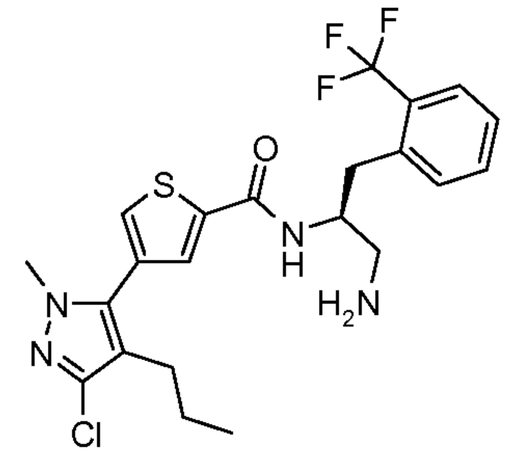
ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (190 mg, 0.30 mmol, 68 % yield) as a white solid: LCMS (ES) m/e 601, 603 $(M, M+2)^+$.

i) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (190 mg, 0.32 mmol) in tetrahydrofuran (1.58 ml) and methanol (1.58 ml) at 25 °C was added hydrazine (0.08 ml, 2.53 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (145 mg, 0.26 mmol, 83 % yield) as a yellow solid: LCMS (ES) m/z = 471, 473 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (br. s., 1 H) 7.87 - 7.99 (m, 6 H) 7.69 (d, J=7.71 Hz, 1H)) 7.57 (d, *J*=7.83 Hz, 1 H) 7.40 - 7.44 (m, 1 H) 4.43 - 4.48 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.06 (m, 4 H) 2.40 (d, *J*=7.58 Hz, 2 H) 1.04 (t, *J*=7.58 Hz, 3 H).

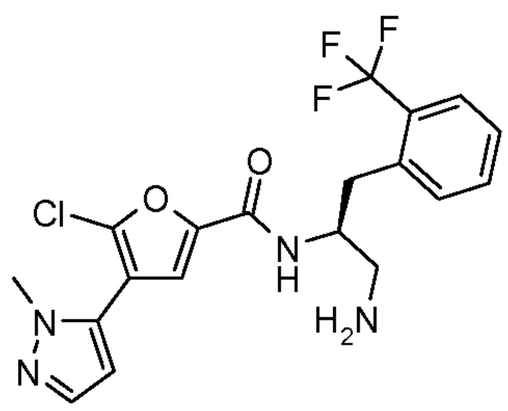
Example 126



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

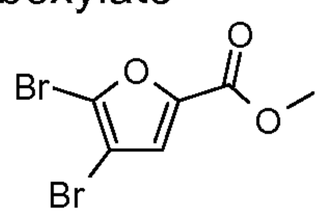
The title compound was prepared as a yellow solid according to Example 125, except substituting (1Z)-1-propen-1-ylboronic acid (125 mg, 1.46 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex: LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.94 (d, *J*=9.09 Hz, 1 H) 8.05 (s, 4 H) 7.98 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.55 - 7.63 (m, 1 H) 7.52 (t, *J*=7.58 Hz, 1 H) 7.42 (t, *J*=7.33 Hz, 1 H) 4.49 (d, *J*=4.29 Hz, 1 H) 3.74 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.37 (q, *J*=7.07 Hz, 2 H) 1.37 - 1.45 (m, 2 H) 0.80 (t, *J*=7.33 Hz, 3 H).

Example 127



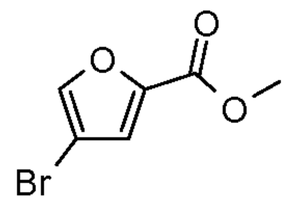
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4,5-dibromo-2-furancarboxylate



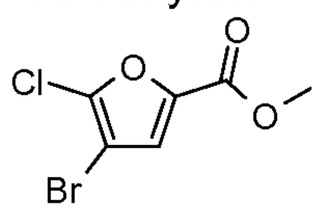
To a solution of 4,5-dibromo-2-furancarboxylic acid (25 g, 93 mmol) in methanol (185 ml) was added sulfuric acid (24.7 ml, 463 mmol). The resulting solution stirred at 50 ºC over 12h. The solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4,5-dibromo-2-furancarboxylate (23.67 g, 83 mmol, 90 % yield), LCMS (ES) m/e 283, 285, 287 (M, M+2, M+4)$^+$.

b) methyl 4-bromo-2-furancarboxylate



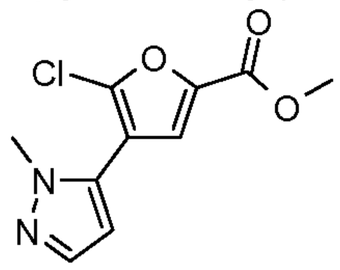
To a solution of methyl 4,5-dibromo-2-furancarboxylate (3.3 g, 11.62 mmol) in tetrahydrofuran (46 ml) at -40 °C was added isopropylmagnesium chloride (6.97 ml, 13.95 mmol). After 1h, Water (11 ml) was added and the solution warmed to 25 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (3% EtOAc in hexanes) affording methyl 4-bromo-2-furancarboxylate (1.4 g, 6.49 mmol, 56 % yield) as a yellow solid: LCMS (ES) m/e 205, 207 $(M, M+2)^+$.

c) methyl 4-bromo-5-chloro-2-furancarboxylate



A solution of methyl 4-bromo-2-furancarboxylate (1.4 g, 6.83 mmol) and NCS (0.912 g, 6.83 mmol) in N,N-dimethylformamide (13.7 ml) was stirred in a sealed tube for 1h at 100 °C. After 1h, the solution was partitioned between DCM-H_2O and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (2-10% EtOAc in hexanes) affording methyl 4-bromo-5-chloro-2-furancarboxylate (1.348 g, 5.12 mmol, 75 % yield) as a white solid: LCMS (ES) m/e 238, 240, 242 $(M, M+2, M+4)^+$.

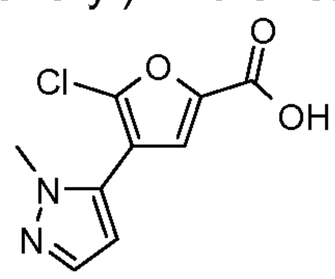
d) methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-bromo-5-chloro-2-furancarboxylate (1.1 g, 4.59 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.05 g, 5.05 mmol)[prepared according to Preparation 7], potassium carbonate (3.17 g, 22.97 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.117 g, 0.23 mmol) in 1,4-dioxane (19.14 ml) and water (3.83 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried

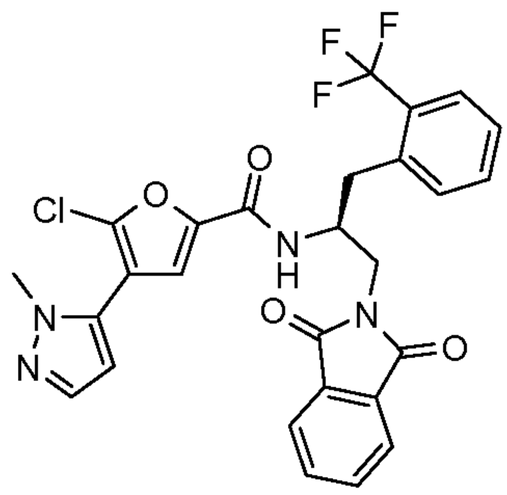
over Na_2SO_4, concentrated and purified via column chromatography (silica, 4-25% EtOAc in hexanes) yielding methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (800 mg, 2.53 mmol, 55 % yield) as a yellow oil: LCMS m/e ES 240, 242 $(M, M+2)^+$.

e) 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.25 mmol) in 6N sodium hydroxide (4.16 ml, 24.93 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (267 mg, 0.59 mmol, 47 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

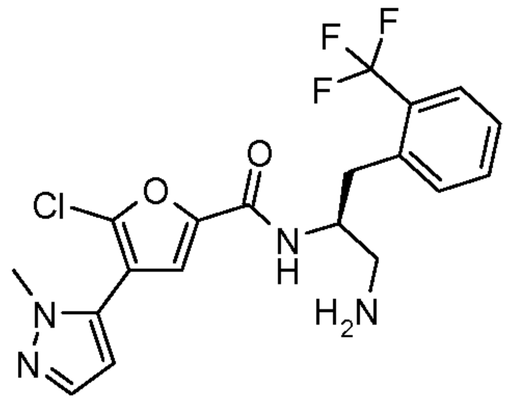
f) 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (134 mg, 0.59 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (228 mg, 0.59 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.52 ml, 2.96 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (304 mg, 0.65 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-

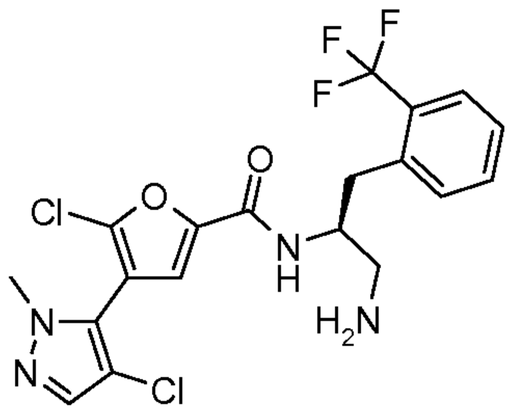
furancarboxamide (202 mg, 0.33 mmol, 55.8 % yield) as a yellow oil: LCMS (ES) m/e 557, 559 $(M, M+2)^+$.

g) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



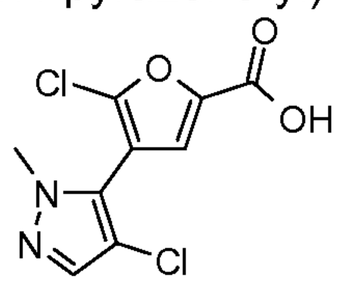
To a solution of 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (202 mg, 0.36 mmol) in tetrahydrofuran (1.8 ml) and methanol (1.8 ml) at 25 °C was added hydrazine (0.08 ml, 2.54 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in diethyl ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (120 mg, 0.24 mmol, 66 % yield) as a yellow solid: LCMS (ES) m/z = 427, 429 $(M, M+2)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, *J*=9.09 Hz, 1 H) 8.11 (br. s., 3 H) 7.66 - 7.73 (m, 2 H) 7.57 (t, *J*=7.45 Hz, 2 H) 7.53 (d, *J*=1.52 Hz, 1 H) 7.44 (d, *J*=6.82 Hz, 1 H) 6.50 (d, *J*=1.52 Hz, 1 H) 4.43 - 4.51 (m, 1 H) 3.86 (s, 3 H) 2.99 - 3.17 (m, 4H).

Example 128



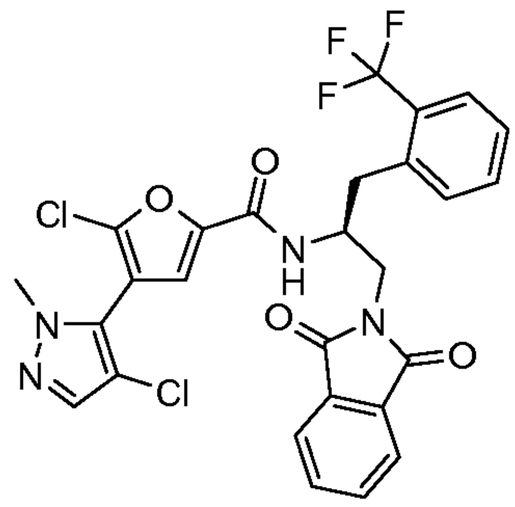
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



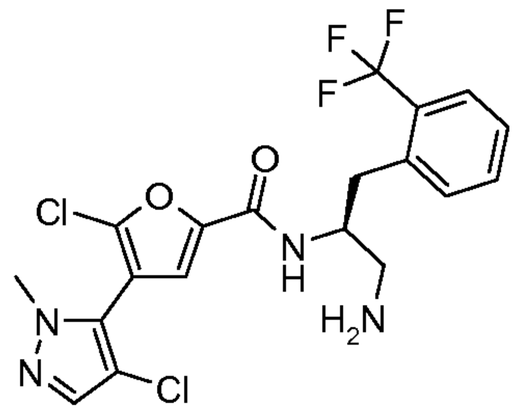
A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.25 mmol)[prepared according to Example 127] and n-chlorosuccinimide (166 mg, 1.25 mmol) in tetrahydrofuran (6 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (4.1 ml, 24.94 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (232 mg, 0.44 mmol, 36 % yield) as a yellow oil: LCMS (ES) m/e 261, 263 (M, M+2)$^+$.

b) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide



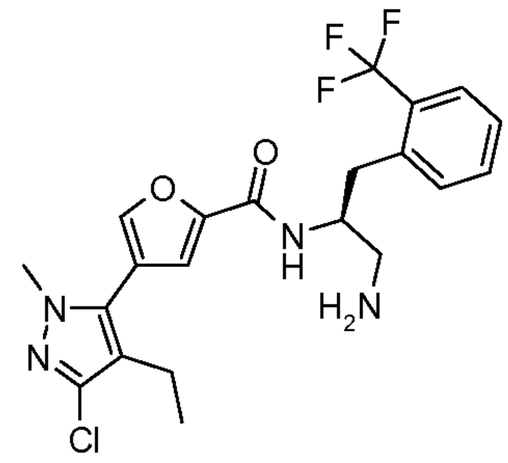
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (116 mg, 0.44 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (171 mg, 0.44 mmol)[prepared according to Preparation 6] and n,n-diisopropylethylamine (0.39 ml, 2.22 mmol) in dichloromethane (4.6 ml) at 25 ºC was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (228 mg, 0.49 mmol) in one portion. The solution stirred at 25 ºC for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide (116 mg, 0.19 mmol, 42 % yield) as a yellow oil: LCMS (ES) m/e 591, 593 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide (116 mg, 0.20 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) at 25 °C was added hydrazine (0.04 ml, 1.37 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (68 mg, 0.13 mmol, 65 % yield) as a yellow solid: LCMS (ES) m/z = 461, 463 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (d, J=9.09 Hz, 1 H) 8.03 (br. s., 3 H) 7.66 - 7.73 (m, 2 H) 7.58 - 7.61 (m, 1 H) 7.52 - 7.59 (m, 2 H) 7.40 - 7.48 (m, 1 H) 4.5 - 4.57 (m, 1 H) 3.77 (s, 3 H) 2.98 - 3.09 (m, 4 H).

Example 129

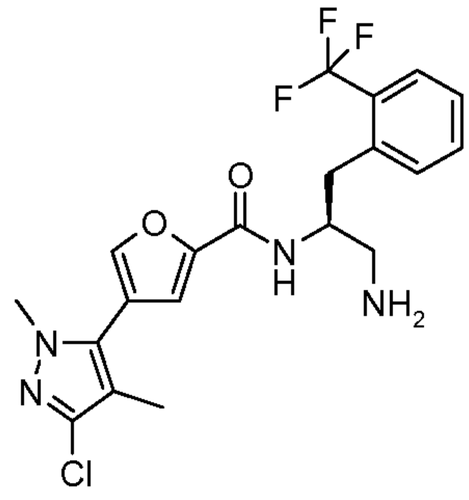


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 125, except substituting methyl 4-bromo-2-furancarboxylate (5 g, 24.39 mmol) for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z = 455, 457 $(M, M+2)^+$,

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, *J*=9.09 Hz, 1 H) 8.23 (s, 1 H) 8.05 (br. s., 3 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 7.42=0 - 7.43 (m, 2 H) 4.50 - 4.55 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.39 (q, *J*=7.33 Hz, 2 H) 1.03 (t, *J*=7.45 Hz, 3 H).

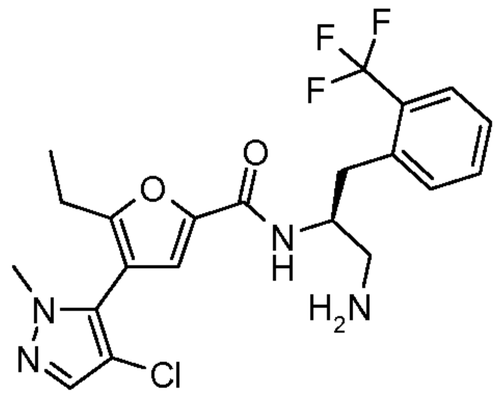
Example 130



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

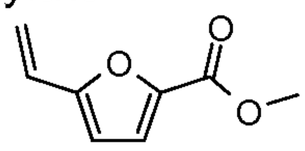
The title compound was prepared as a yellow solid according to Example 125, except substituting trimethylboroxine (0.78 ml, 5.61 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex and methyl 4-bromo-2-furancarboxylate (5 g, 24.39 mmol) for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=9.35 Hz, 1 H) 8.27 (s, 1 H) 8.01 (br. s., 3 H) 7.70 (d, *J*=7.58 Hz, 1 H) 7.55 (t, *J*=6.06 Hz, 2 H) 7.40 - 7.47 (m, 2 H) 4.50 - 4.57 (m, 1 H) 3.78 (s, 3 H) 2.99 - 3.08 (m, 4 H) 1.98 (s, 3 H).

Example 131



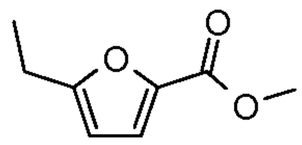
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

a) methyl 5-ethenyl-2-furancarboxylate



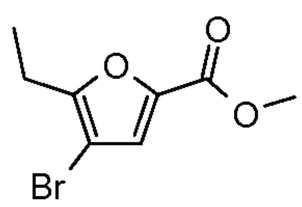
A solution of methyl 5-bromo-2-furancarboxylate (2.5 g, 12.19 mmol), potassium carbonate (8.43 g, 61.0 mmol), bis(tri-t-butylphosphine)palladium(0) (0.312 g, 0.61 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (1.47 g, 6.10 mmol) in 1,4-dioxane (50 ml) and water (10 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-ethenyl-2-furancarboxylate (1.3 g, 7.09 mmol, 58 % yield) as a yellow oil: LCMS (ES) m/z = 153 $(M+H)^+$.

b) methyl 5-ethyl-2-furancarboxylate



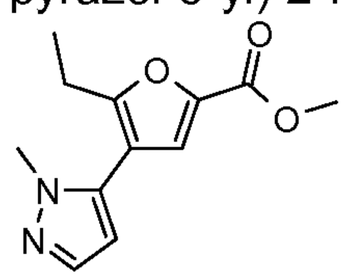
To a solution of methyl 5-ethenyl-2-furancarboxylate (1.3 g, 8.54 mmol) in methanol (15 ml) was added $PdOH_2$ (0.240 g, 1.71 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-2-furancarboxylate (1.2 g, 7.16 mmol, 84 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 155 $(M+H)^+$.

c) methyl 4-bromo-5-ethyl-2-furancarboxylate



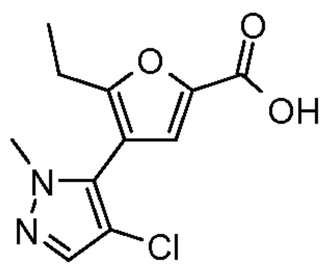
To a solution of methyl 5-ethyl-2-furancarboxylate (1.2 g, 7.78 mmol) and aluminum trichloride (1.56 g, 11.68 mmol) in chloroform (15 ml) at 25 °C was added bromine (0.56 ml, 10.90 mmol). The resulting solution stirred at 70 °C in a sealed tube for 2h and the solution was cooled, concentrated and purified via column chromatograpy (silica, 5% EtOAc in hexanes) affording methyl 4-bromo-5-ethyl-2-furancarboxylate (1.1 g, 3.26 mmol, 41.8 % yield) as a white solid; LCMS (ES) m/z = 233, 235 $(M, M+2)^+$.

d) methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



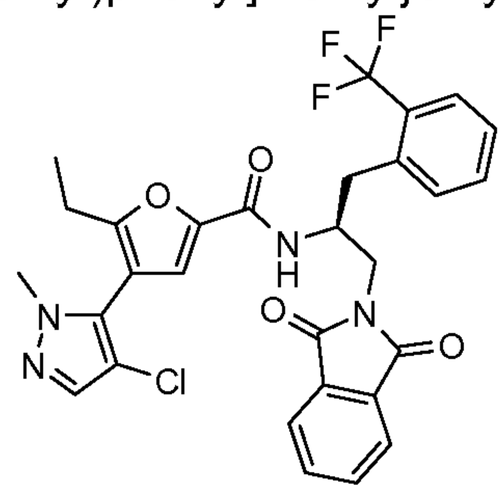
A solution of methyl 4-bromo-5-ethyl-2-furancarboxylate (1.1 g, 4.72 mmol), potassium carbonate (3.26 g, 23.60 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.178 g, 5.66 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.121 g, 0.24 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. LCMS showed 4:1 pdt/sm. Additional 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.178 g, 5.66 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.121 g, 0.24 mmol) were added and the solution stirred an additional 2h where crude LCMS showed nearly complete conversion to product. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (950 mg, 3.37 mmol, 71.3 % yield) as a yellow oil: LCMS (ES) m/e 235 $(M+H)^+$.

e) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid



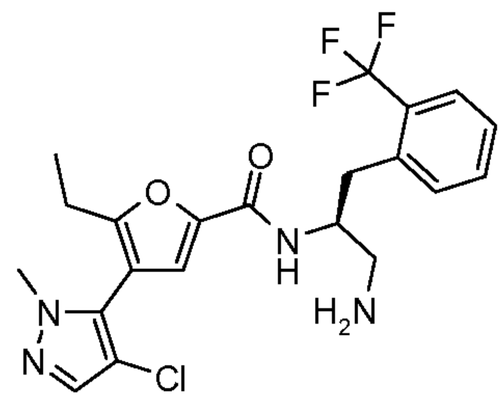
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (950 mg, 4.06 mmol) and N-chlorosuccinimide (542 mg, 4.06 mmol) in tetrahydrofuran (20 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (13.5 ml, 81 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid (683 mg, 2.55 mmol, 62.8 % yield) as a yellow oil: LCMS (ES) m/e 254, 256 (M, M+2)$^+$.

f) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid (145 mg, 0.57 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (219 mg, 0.57 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.50 ml, 2.85 mmol) in dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (292 mg, 0.63 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide (250 mg, 0.41 mmol, 71 % yield) as a white solid: LCMS (ES) m/e 585, 587 $(M, M+2)^+$.

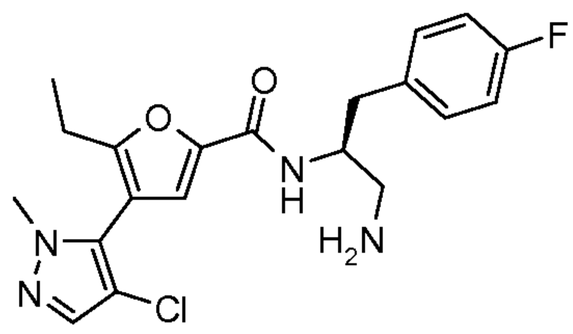
g) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide (250 mg, 0.43 mmol) in tetrahydrofuran (1.8 ml) and methanol (1.8 ml) at 25 °C was added hydrazine (0.13 ml, 4.27 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-

2-furancarboxamide (166 mg, 0.30 mmol, 70 % yield) as a yellow solid: LCMS (ES) m/z = 455, 457 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.59 (br. s., 1 H) 8.06 (br. s., 3 H) 7.67 (s, 1 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.59 (d, *J*=4.29 Hz, 2 H) 7.44 (d, *J*=4.04 Hz, 1 H) 7.31 (d, *J*=5.81 Hz, 1 H) 4.50 - 4.57 (m, 1 H) 3.72 (s, 3 H) 2.99 - 3.12 (m, 4 H) 2.63 (q, *J*=7.33 Hz, 2 H) 1.21 (t, *J*=7.45 Hz, 3 H).

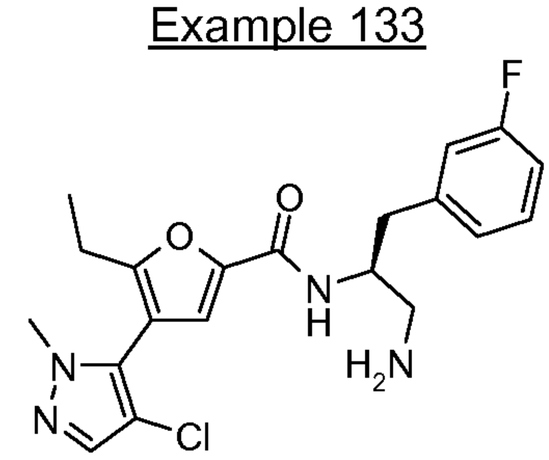
Example 132



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 131, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (170 mg, 0.57 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 405, 407(M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.56 (d, J=8.59 Hz, 1 H) 8.09 (br. s., 3 H) 7.67 (s, 1 H) 7.33 (s, 1 H) 7.31 (dd, J=8.34, 5.81 Hz, 2 H) 7.12 (t, J=8.72 Hz, 2 H) 4.36 - 4.39 (m, 1 H) 3.71 (s, 3 H) 2.91 - 3.03 (m, 4 H) 2.62 (q, J=7.58 Hz, 2 H) 1.20 (t, J=7.45 Hz, 3 H).

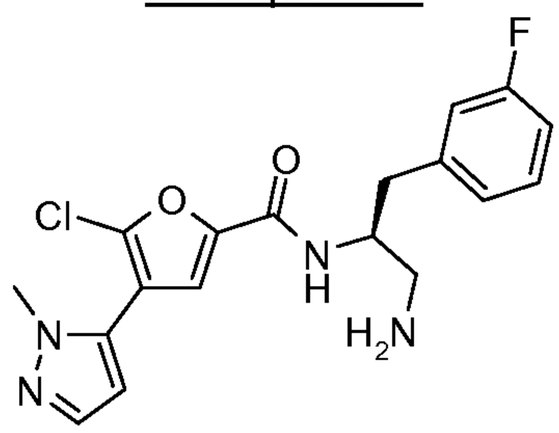
Example 133



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 131, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (170 mg, 0.57 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 405, 407 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.62 (d, *J*=8.59 Hz, 1 H) 8.13 (br. s., 3 H) 7.67 (s, 1 H) 7.30 - 7.37 (m, 2 H) 7.12 (d, *J*=6.32 Hz, 2 H) 7.04 (t, *J*=8.59 Hz, 1 H) 4.40 - 4.47 (m, 1 H) 3.71 (s, 3 H) 2.95 - 3.09 (m, 4 H) 2.62 (q, *J*=7.07 Hz, 2 H) 1.20 (t, *J*=7.33 Hz, 3 H).

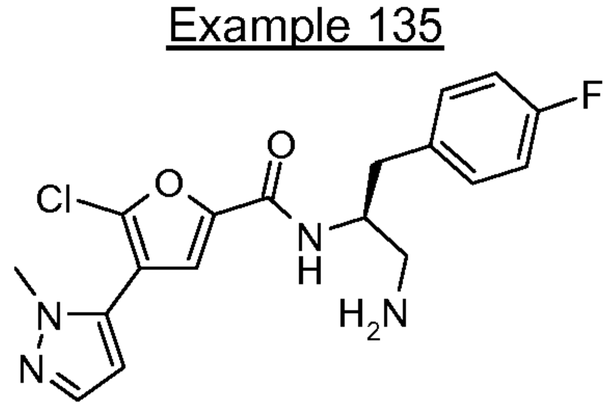
Example 134



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (295 mg, 0.88 mmol)[prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, *J*=8.84 Hz, 1 H) 8.16 (br. s., 3 H) 7.70 - 7.77 (m, 1 H) 7.53 (d, *J*=1.77 Hz, 1 H) 7.32 (t, *J*=7.20 Hz, 1 H) 7.09 - 7.14 (m, 1 H) 7.11 (d, *J*=6.57 Hz, 2 H) 7.04 (t, *J*=8.59 Hz, 1 H) 6.49 (d, *J*=1.77 Hz, 1 H) 4.41 - 4.44 (m, 1 H) 3.86 (s, 3 H) 2.95 - 3.00 (m, 4 H).

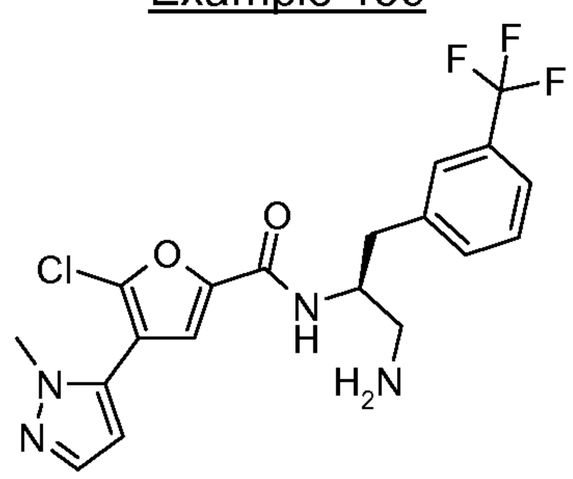
Example 135



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (295 mg, 0.88 mmol)[prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (d, *J*=8.84 Hz, 1 H) 8.11 (br. s., 3 H) 7.71 (s, 1 H) 7.53 (d, *J*=1.77 Hz, 1 H) 7.29 (dd, *J*=8.59, 5.56 Hz, 2 H) 7.12 (t, *J*=8.84 Hz, 2 H) 6.49 (d, *J*=1.77 Hz, 1 H) 4.32 - 4.38 (m, 1 H) 3.86 (s, 3 H) 2.99 - 3.01 (m, 4 H).

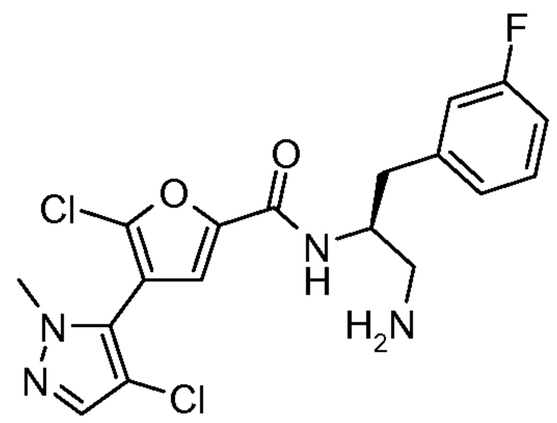
Example 136



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (340 mg, 0.88 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 427, 429 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (d, *J*=8.84 Hz, 1 H) 8.11 (br. s., 3 H) 7.62 - 7.69 (m, 2 H) 7.51 - 7.59 (m, 4 H) 6.48 (d, *J*=1.77 Hz, 1 H) 4.39 - 4.44 (m, 1 H) 3.85 (s, 3 H) 2.97 - 3.05 (m, 4 H).

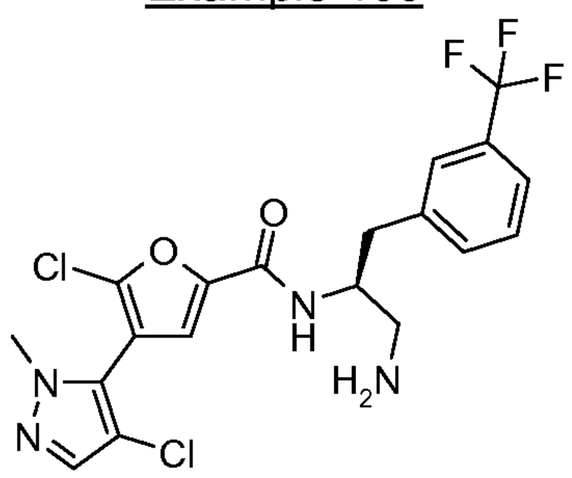
Example 137



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (321 mg, 0.96 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.77 (d, *J*=8.84 Hz, 1 H) 8.04 (br. s., 3 H) 7.72 (s, 1 H) 7.59 (s, 1 H) 7.30 - 7.38 (m, 1 H) 7.11 (d, *J*=7.58 Hz, 2 H) 7.05 (t, *J*=8.59 Hz, 1 H) 4.39 - 4.43 (m, 1 H) 3.77 (s, 3 H) 2.97 - 3.03 (m, 4 H).

Example 138

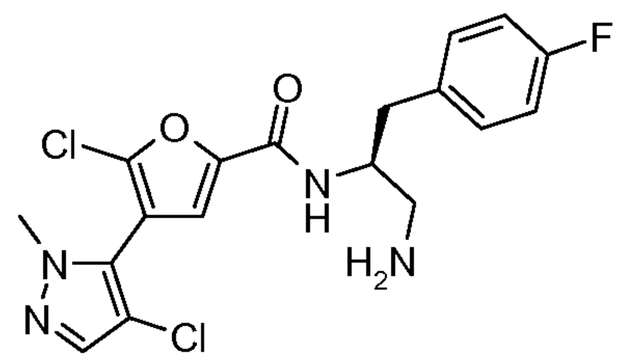


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (221 mg, 0.58 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (d, *J*=8.84 Hz, 1 H)

8.10 (br. s., 3 H) 7.72 (s, 1 H) 7.64 (s, 1 H) 7.52 - 7.60 (m, 4 H) 4.39 - 4.41 (m, 1 H) 3.76 (s, 3 H) 2.98 - 3.05 (m, 4 H).

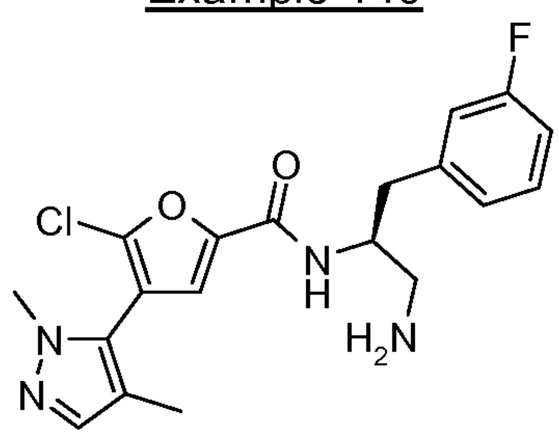
Example 139



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (256 mg, 0.77 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (d, *J*=8.59 Hz, 1 H) 8.06 (br. s., 3 H) 7.72 (s, 1 H) 7.60 (s, 1 H) 7.30 (dd, *J*=8.59, 5.56 Hz, 2 H) 7.13 (t, *J*=8.84 Hz, 2 H) 4.35 - 4.42 (m, 1 H) 3.77 (s, 3 H) 2.99 (br. s., 2 H) 2.86 - 2.93 (m, 2 H).

Example 140

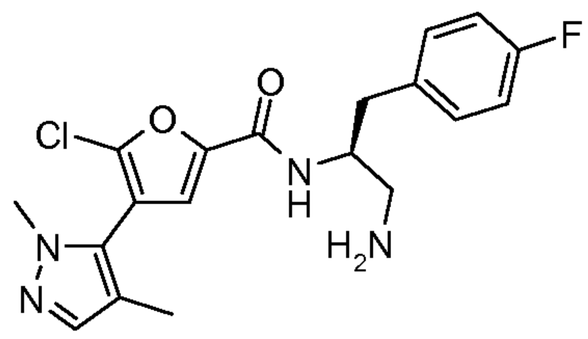


Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.02 g, 4.59 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-

pyrazole and 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (132 mg, 0.39 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 391, 393 (M, M+2)$^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, *J*=8.84 Hz, 1 H) 8.04 (br. s., 3 H) 7.55 (s, 1 H) 7.37 (s, 1 H) 7.30 - 7.36 (m, 1 H) 7.11 - 7.15 (m, 2 H) 7.05 - 7.10 (m, 1 H) 4.42 (br. s., 1 H) 3.70 (s, 3 H) 2.97 (br. s., 2 H) 2.92 - 2.96 (m, 2 H) 1.94 (s, 3 H).

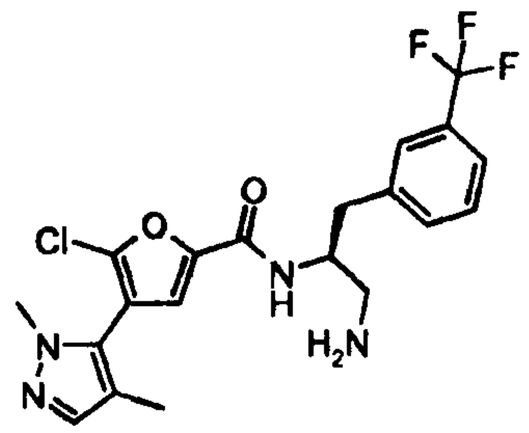
Example 141



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (174 mg, 0.52 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 391, 393 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (d, *J*=8.59 Hz, 1 H) 8.14 (br. s., 3 H) 7.59 (s, 1 H) 7.37 (s, 1 H) 7.30 (dd, *J*=8.59, 5.56 Hz, 2 H) 7.12 (t, *J*=8.84 Hz, 2 H) 4.32 - 4.38 (m, 1 H) 3.70 (s, 3 H) 2.98 (d, *J*=5.81 Hz, 2 H) 2.91 (d, *J*=6.32 Hz, 2 H) 1.94 (s, 3 H).

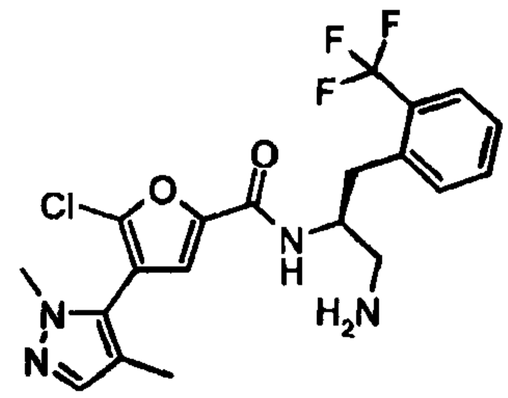
Example 142



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (br. s., 1 H) 8.15 (br. s., 2 H) 7.63 (br. s., 1 H) 7.52 - 7.58 (m, 4 H) 7.37 (s, 1 H) 4.38 - 4.42 (m, 1 H) 3.68 (s, 3 H) 2.97 - 3.08 (m, 4 H) 1.93 (s, 3 H).

Example 143

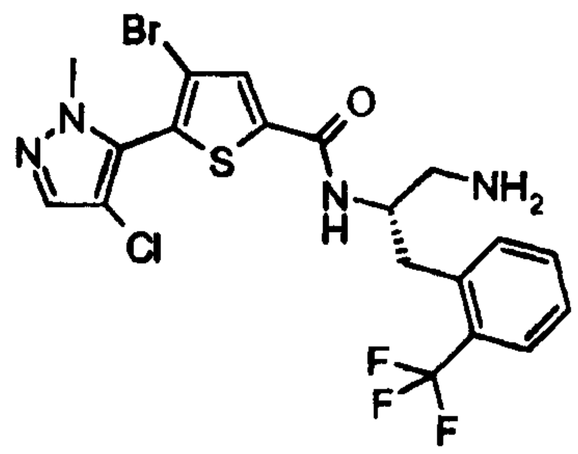


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole: LCMS (ES) m/z = 441, 443 (M,

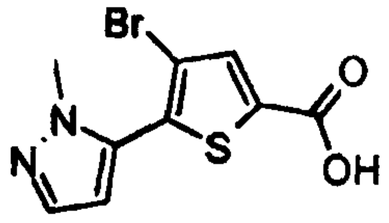
M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, J=9.35 Hz, 1 H) 8.11 (br. s., 3 H) 7.70 (d, J=7.83 Hz, 1 H) 7.52 - 7.57 (m, 3 H) 7.41 - 7.47 (m, 1 H) 7.38 (s, 1 H) 4.39 - 4.43 (m, 1 H) 3.71 (s, 3 H) 2.98 - 3.09 (m, 4 H) 1.95 (s, 3 H).

Example 144



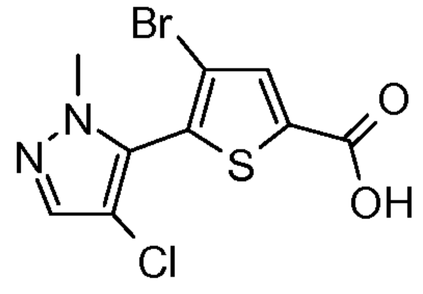
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



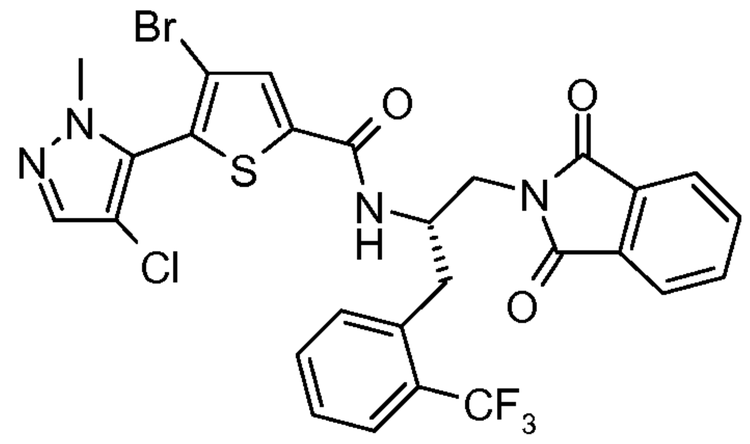
To a solution of 4,5-dibromo-2-thiophenecarboxylic acid (3.30 g, 11.54 mmol) in dioxane/H_2O (4:1, 100 mL) was added K_2CO_3 (5.5 g, 40.0 mmol), tetrakistriphenylphosphine Pd(0) (671 mg, 0.58 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (2.66 g, 13.71 mmol). The reaction mixture was heated to 80 °C in a sealed tube for 12 hours. The reaction mixture was partitioned between H_2O and $CHCl_3$. The pH of the aqueous phase was adjusted to ~3 with 6N HCl and washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (3.3 g, quant.): LC-MS (ES) m/z = 289 $(M+H)^+$.

b) 4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



N-chlorosuccinimide (NCS) (299 mg, 2.194 mmol) was added in portions to a 30 mL sealed tube reactor containing 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (503 mg, 1.23 mmol) in tetrahydrofuran (THF) (6 mL) at room temperature. The mixture was heated to 70 °C for 2 hours. Upon completion, the reaction mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, solvents removed by vacuum distillation affording the title compound (0.54 mg, quant.) which was used without further purification. LC-MS (ES) m/z = 321 $(M+H)^+$

c) 4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



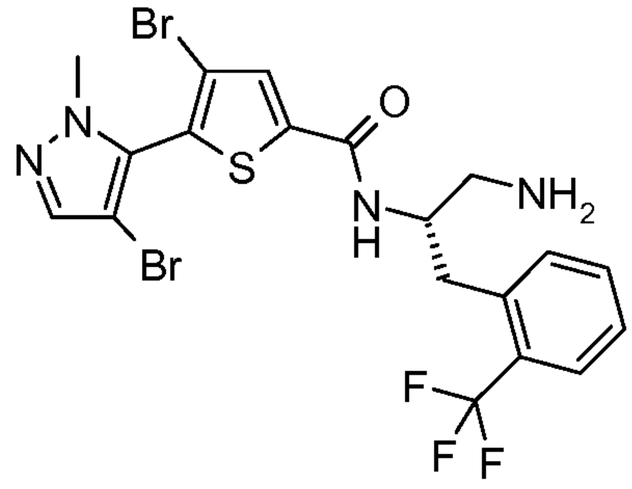
To a 50 mL round-bottomed flask was added 4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (224 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (201 mg, 0.52 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (295 mg, 0.63 mmol) in chloroform (4 mL). DIEA (0.46 mL, 2.63 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (hexanes/EtOAc) affording the title compound (153 mg, 43%): LC-MS (ES) m/z = 651 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (153 mg, 0.223 mmol) in tetrahydrofuran (THF) (2.5 mL) and Methanol (0.5 mL). Hydrazine (50 µL, 1.59 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

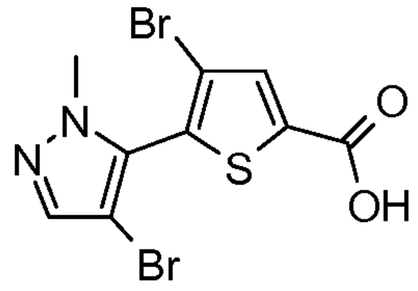
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (68 mg, 0.11 mmol, 48.7 % yield): LC-MS (ES) m/z = 523 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.02 - 3.14 (m, 4 H) 3.73 (s, 3 H) 4.50 (s, 1 H) 7.40 - 7.48 (m, 1 H) 7.56 - 7.64 (m, 2 H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.77 (s, 1 H) 8.14 (s, 3 H) 8.21 (s, 1 H) 9.24 (d, *J*=9.09 Hz, 1 H).

Example 145



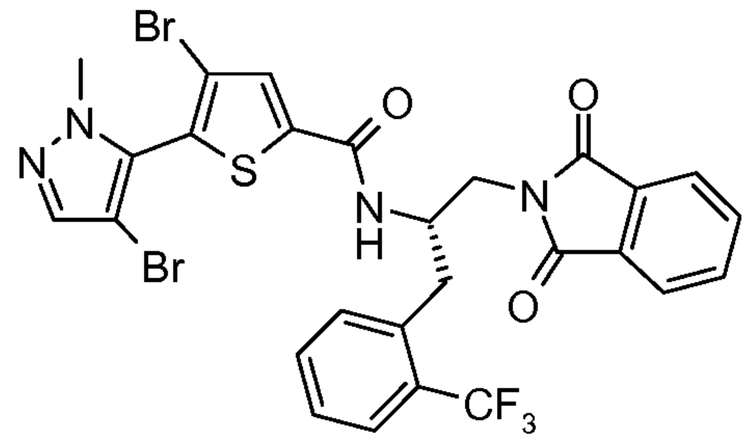
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



The title compound was prepared according to the procedure of Example 144 except substituting N-bromosuccinimide (NBS) (287 mg, 1.596 mmol) for NCS: LC-MS (ES) m/z = 364 $(M+H)^+$.

b) 4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-bromo-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (238 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (209 mg, 0.54 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (293 mg, 0.63 mmol) in chloroform (4 mL). DIEA (0.46 mL, 2.62 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica) (3:1 hex/EtOAc) affording the title compound (229 mg, 60%): LC-MS (ES) m/z = 695 $(M+H)^+$.

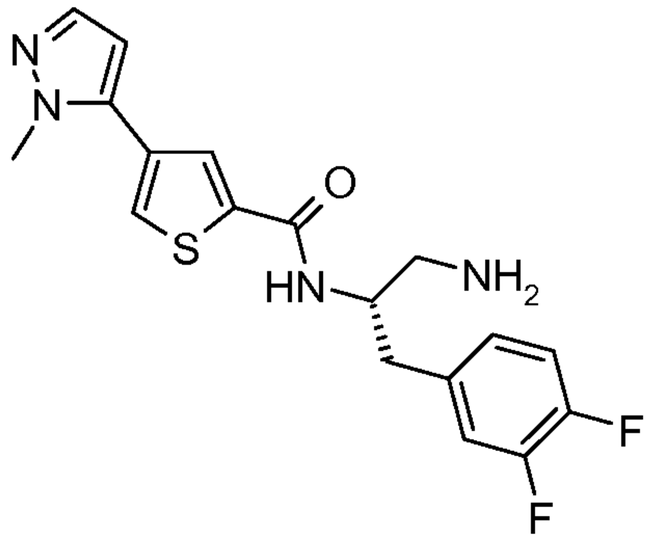
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-bromo-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (229 mg, 0.312 mmol) in Tetrahydrofuran (THF) (2.5 mL) and methanol (0.5 mL). Hydrazine (60 µL, 1.91 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica gel and purified by column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH; 12g column).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (500 mL) and concentrated affording the HCl salt of the title compound(104 mg, 0.15 mmol, 49 % yield): LC-MS (ES) m/z = 567 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.10 (s, 4 H) 3.74 (s, 3 H) 4.50 (s, 1 H) 7.45 (ddd,

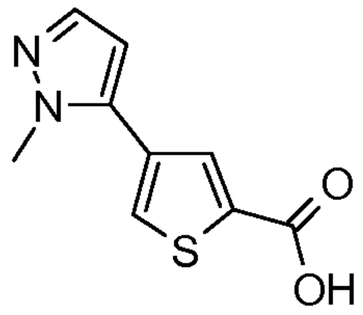
J=7.96, 4.17, 4.04 Hz, 1 H) 7.60 (d, *J*=4.04 Hz, 2 H) 7.71 (d, *J*=7.58 Hz, 1 H) 7.76 (s, 1 H) 8.11 (s, 3 H) 8.19 (s, 1 H) 9.19 (d, *J*=8.84 Hz, 1 H).

Example 146



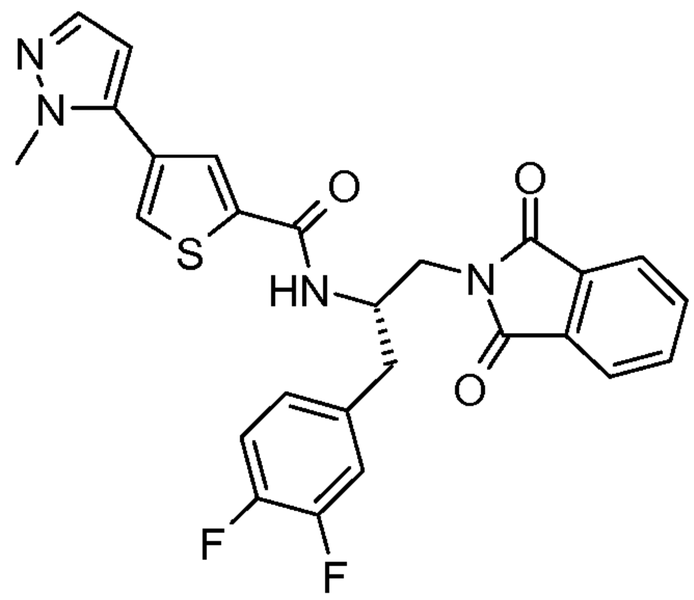
Preparation of N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (3.91 g, 18.9 mmol) in dioxane/H_2O (4:1, 100 mL) was added Cs_2CO_3 (21.7 g, 66.6 mmol), tetrakistriphenylphosphine Pd(0) (1.1 g, 0.95 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (3.94 g, 18.94 mmol) [prepared according to the procedure of Preparation 7]. The reaction mixture was heated to 85 °C in a sealed tube for 12 hours and partitioned between H_2O and $CHCl_3$. The pH of the aqueous phase was adjusted to ~3 with 6N HCl and washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (2.84 g, 13.64 mmol, 72%): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (183 mg, 0.88 mmol), 2-[(2S)-2-amino-3-(3,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (0.3 g, 0.85 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3,4-difluoro-L-phenylalanine (2.03 g, 6.74 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (528 mg, 1.13 mmol) in chloroform (5 mL). DIEA (0.77 mL, 4.41 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

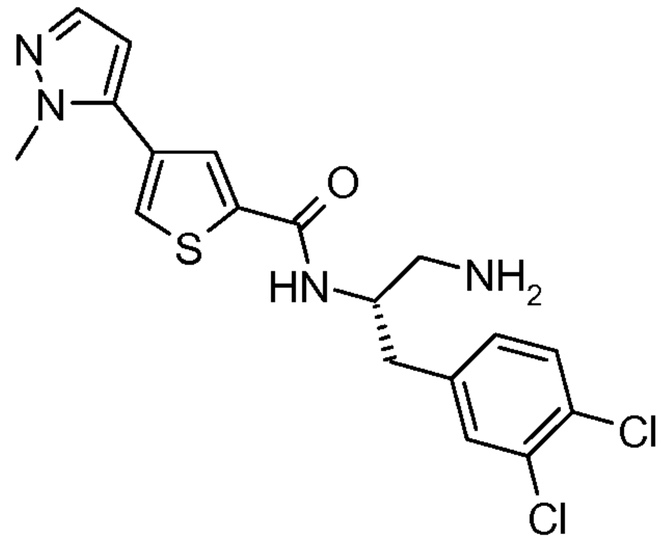
c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (149 mg, 0.265 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (71 mg, 0.15 mmol, 57 % yield): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.96 (d, *J*=6.06 Hz, 2 H) 3.00 - 3.06 (m, 2 H) 3.97 (s, 3 H) 4.33 - 4.42 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.14 (s, 1 H) 7.30 - 7.42 (m, 2 H) 7.47 (d,

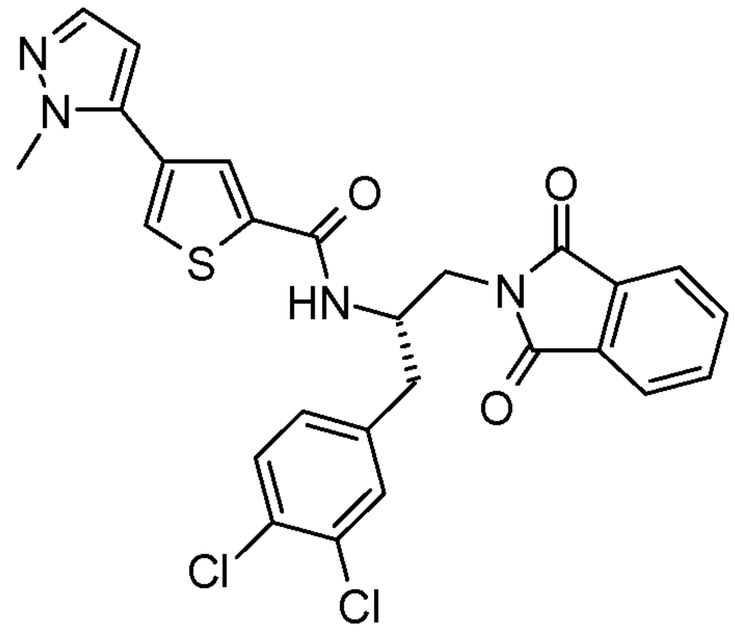
J=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.22 (s, 3 H) 8.35 (d, *J*=1.26 Hz, 1 H) 9.09 (d, *J*=8.59 Hz, 1 H).

Example 147



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(3,4-dichlorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (160 mg, 0.62 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(3,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (0.26 g, 0.67 mmol) [prepared according to the procedure of Preparation 6 except substituting 3,4-dichloro-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-phenylalanine (2.03 g, 6.07 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (376 mg, 0.80 mmol) in chloroform (4 mL). DIEA (0.55 mL, 3.15 mmol) was added and

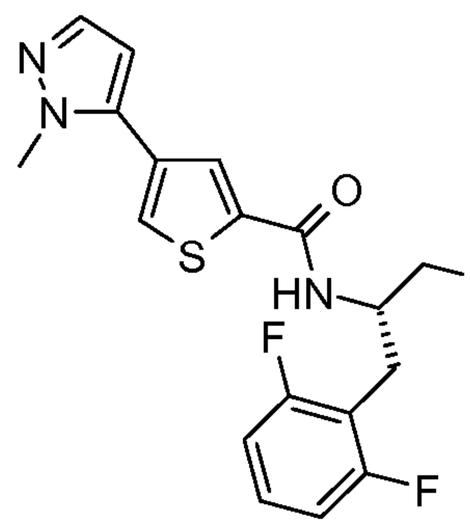
the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 30%): LC-MS (ES) m/z = 539 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(3,4-dichlorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (211 mg, 0.34 mmol) in Tetrahydrofuran (THF) (4.5 mL) and Methanol (0.45 mL). Hydrazine (75 µL, 2.390 mmol) was added and the mixture stirred overnight at room temperature. Upon completion the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

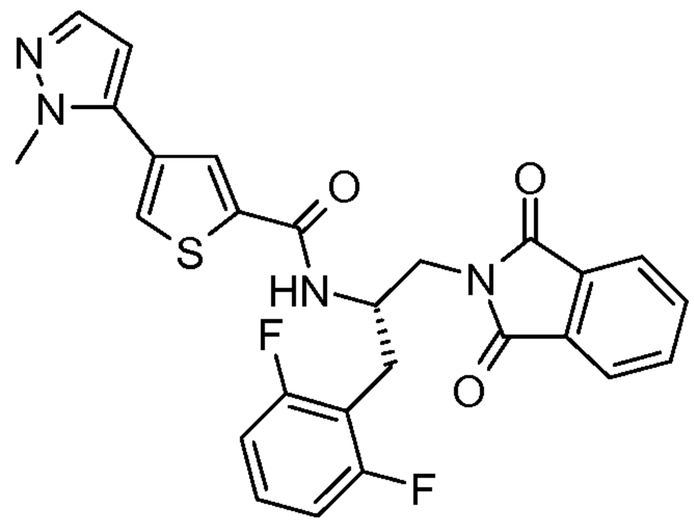
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (83 mg, 0.16 mmol, 48 % yield): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 - 3.07 (m, 4 H) 3.97 (s, 3 H) 4.32 - 4.43 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.29 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.47 (d, *J*=2.02 Hz, 1 H) 7.54 (d, *J*=8.08 Hz, 1 H) 7.60 (d, *J*=1.77 Hz, 1 H) 8.00 (d, *J*=1.26 Hz, 1 H) 8.22 (s, 3 H) 8.35 (d, *J*=1.01 Hz, 1 H) 9.11 (d, *J*=8.59 Hz, 1 H).

Example 148



Preparation of *N*-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (160 mg, 0.62 mmol) [prepared according to the procedure of Example 146], 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (231 mg, 0.69 mmol) [prepared according to the procedure of Preparation 18] and PyBrop (353 mg, 0.75 mmol) in chloroform (8 mL). DIEA (0.64 mL, 3.66 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 0.21 mmol, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

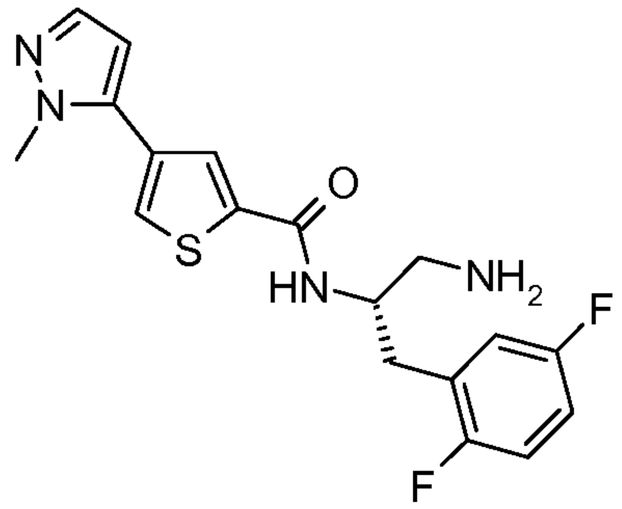
b) *N*-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.32 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (0.4 mL). Hydrazine (70 µL, 2.23 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (101 mg, 0.214 mmol, 68%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-

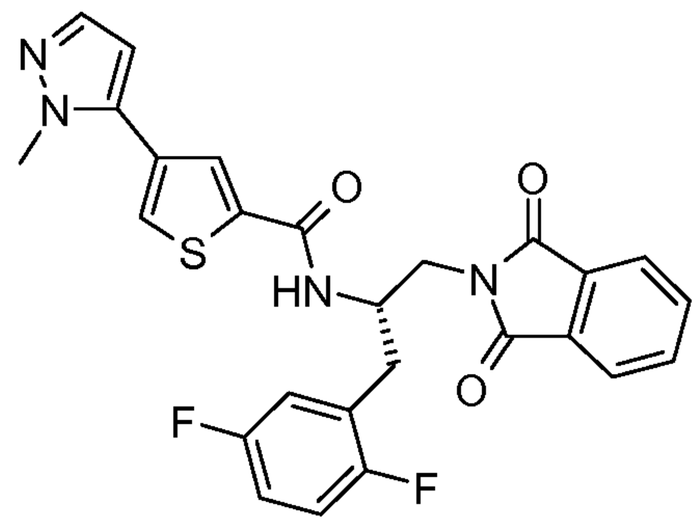
d_6) δ ppm 2.92 - 3.03 (m, 3 H) 3.17 (m, 1 H) 3.97 (s, 3 H) 4.46 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.05 (t, *J*=7.83 Hz, 2 H) 7.27 - 7.38 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.23 (d, *J*=1.26 Hz, 4 H) 8.92 (d, *J*=8.59 Hz, 1 H).

Example 149



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (257 mg, 0.93 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (476 mg, 0.81 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (535 mg, 1.14 mmol) in Chloroform (15 mL). DIEA (0.808 mL, 4.63 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and

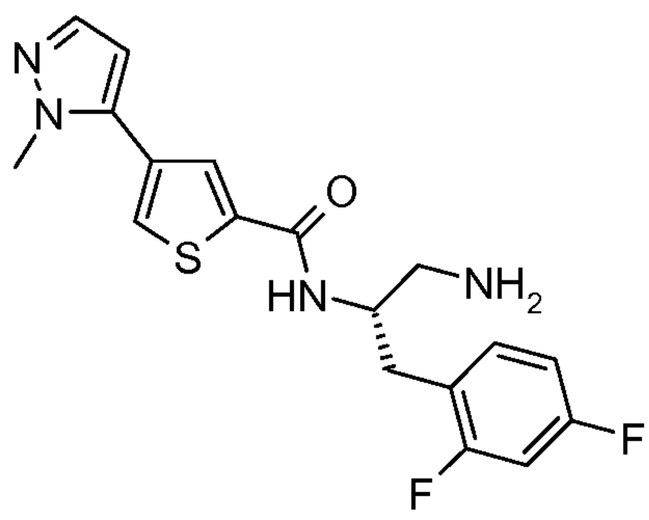
purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (225 mg, 34%): LC-MS (ES) m/z = 507 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (225 mg, 0.31 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (0.8 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

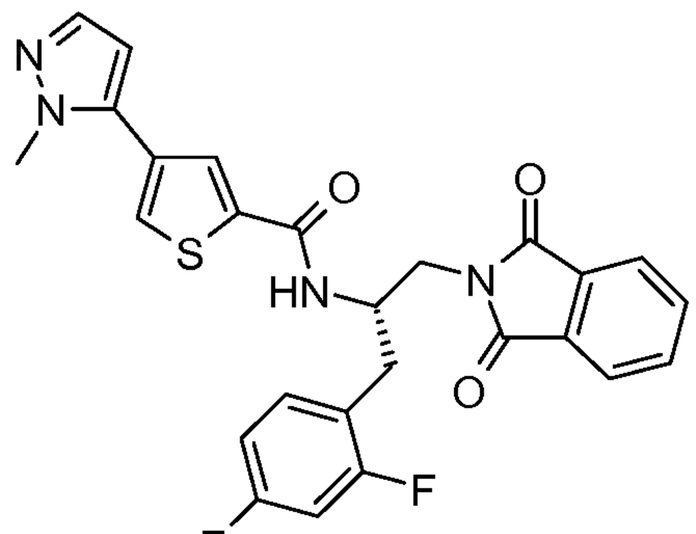
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (90.5 mg, 0.19 mmol, 63%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 - 3.01 (m, 2 H) 3.03 - 3.10 (m, 2 H) 3.92 - 3.98 (m, 3 H) 4.41 - 4.51 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.05 - 7.13 (m, 1 H) 7.20 (td, *J*=9.09, 4.55 Hz, 1 H) 7.27 (ddd, *J*=9.09, 5.81, 3.28 Hz, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.52 Hz, 1 H) 8.18 (s, 3 H) 8.29 (d, *J*=1.26 Hz, 1 H) 9.03 (d, *J*=8.84 Hz, 1 H).

Example 150



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



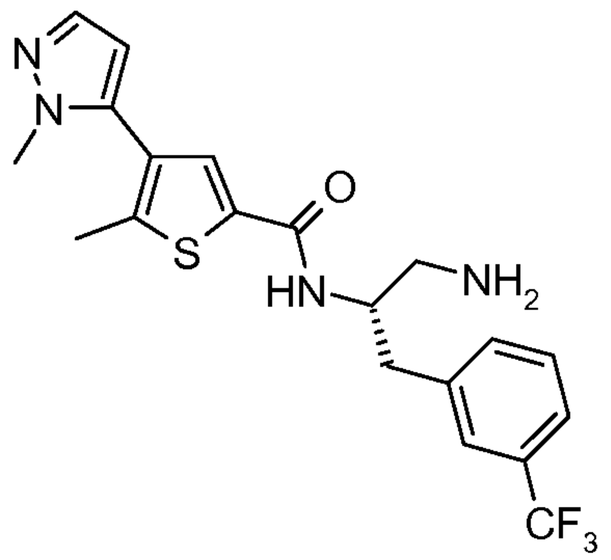
To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (222 mg, 0.80 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (331 mg, 0.78 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (1.0 g, 4.97 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (448 mg, 0.96 mmol) in chloroform (10 mL). DIEA (700 µL, 4.01 mmol) was added and the reaction stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (249 mg, 0.36 mmol, 46%): LC-MS (ES) m/z = 507 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (249 mg, 0.36 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL). Hydrazine (80 µL, 2.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

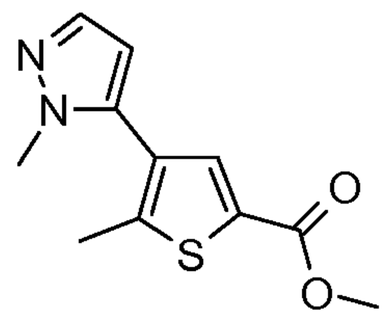
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (81 mg, 0.18 mmol, 50%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 2.98 (m, 2 H) 2.98 - 3.09 (m, 2 H) 3.93 - 3.98 (m, 3 H) 4.38 - 4.47 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.00 (td, *J*=8.46, 2.27 Hz, 1 H) 7.19 (td, *J*=9.85, 2.53 Hz, 1 H) 7.38 - 7.45 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.18 (br. s, 3 H) 8.27 (d, *J*=1.26 Hz, 1 H) 8.99 (d, *J*=8.59 Hz, 1 H).

Example 151



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

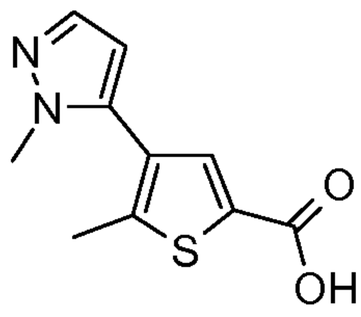
a) methyl 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 125 mL sealed flask was added methyl 4-bromo-5-methyl-2-thiophenecarboxylate (1.56 g, 6.64 mmol) [Prepared according to the procedure of Preparation 10], 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.67 g, 8.03 mmol) [prepared according to the procedure of Preparation 7], K_2CO_3 (2.76 g, 19.97 mmol) and $Pd(PtBu_3)_2$ (170 mg, 0.33 mmol) in 1,4-Dioxane (27 ml) and water (7 ml). The reaction mixture was heated to 85 °C in a sealed tube for 3 hours, cooled to room temperature and partitioned between H_2O and $CHCl_3$. The organic fraction was dried (Na_2SO_4), adsorbed onto silica and purified via

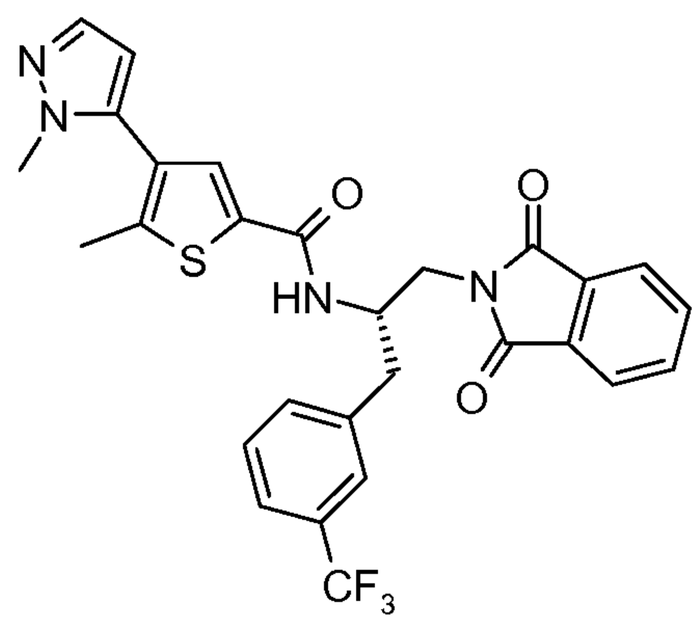
column chromatography (0-15%EtOAc/Hexane). (385 mg, 1.4 mmol, 30%): LC-MS (ES) m/z = 237 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.34 g, 5.67 mmol) in Tetrahydrofuran (THF) (31 ml). 6N NaOH (31 ml, 186 mmol) was added and the reaction mixture stirred at 70 °C overnight. The reaction mixture was neutralized by slow addition of 6N HCl and partitioned between $CHCl_3$ and H_2O. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed. The resulting solid was used without further purification (0.71 g, 2.81 mmol, 96%): LC-MS (ES) m/z = 223 $(M+H)^+$.

c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (201 mg, 0.91 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (301 mg, 0.87 mmol) [Prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 14.95 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (519 mg, 1.11 mmol) in chloroform (9 mL). DIEA (790 µL, 4.52 mmol)

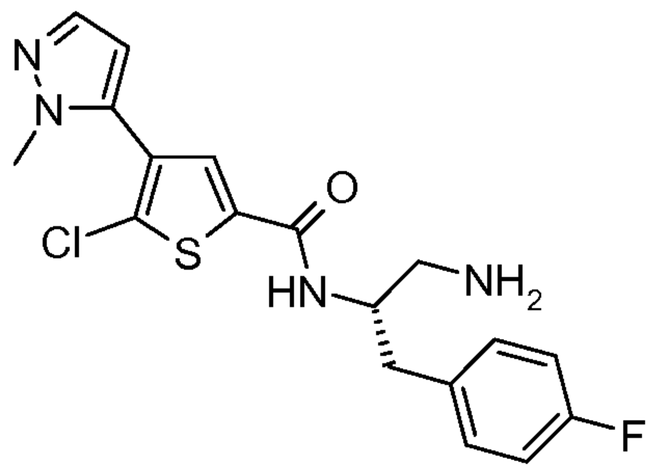
was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 45%): LC-MS (ES) m/z = 553 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (374 mg, 0.64 mmol) in Tetrahydrofuran (THF) (6 mL) and Methanol (600 µL). Hydrazine (125 µL, 3.98 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

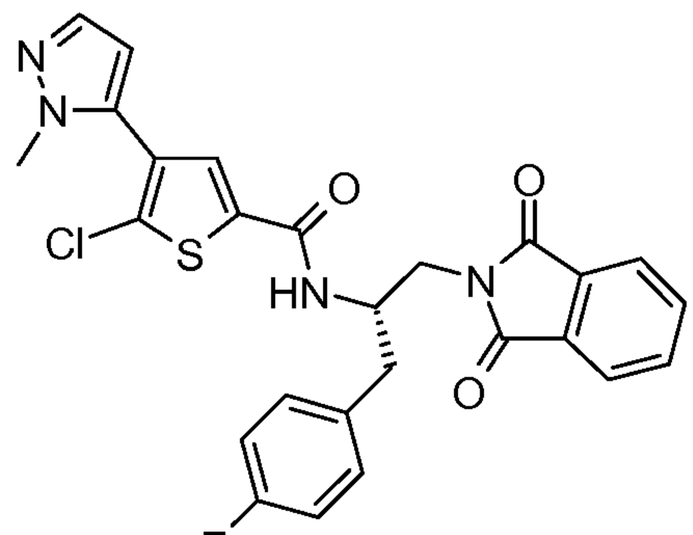
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (135 mg, 0.27 mmol, 42 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (s, 3 H) 2.95 - 3.11 (m, 4 H) 3.78 (s, 3 H) 4.32 - 4.42 (m, 1 H) 6.34 (d, *J*=1.77 Hz, 1 H) 7.48 - 7.56 (m, 3 H) 7.58 - 7.61 (m, 1 H) 7.67 (s, 1 H) 8.04 (s, 1 H) 8.21 (s, 3 H) 8.98 (d, *J*=8.59 Hz, 1 H).

Example 152



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



F

To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (201 mg, 0.91 mmol) [prepared according to the procedure of Example 95], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (301 mg, 0.87 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (519 mg, 1.11 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (186 mg, 32%): LC-MS (ES) m/z = 553 $(M+H)^+$.

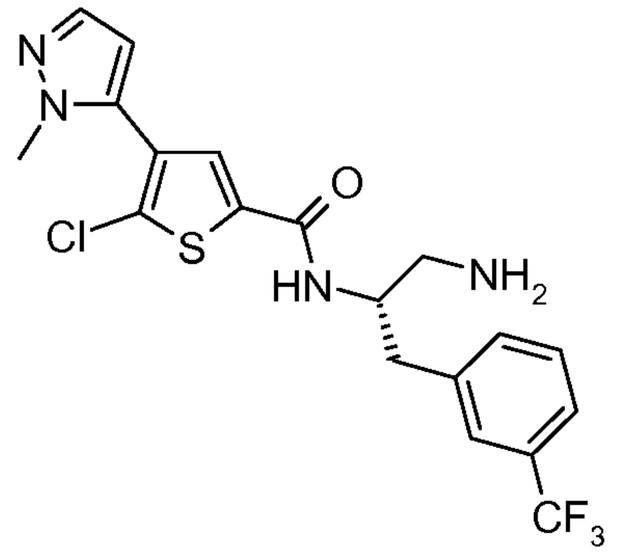
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (185 mg, 0.34 mmol) in Tetrahydrofuran (THF) (10 mL) and Methanol (1 mL). Hydrazine (63 µL, 2.0 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (101 mg, 0.24 mmol, 72%): LC-MS (ES) m/z = 393 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-

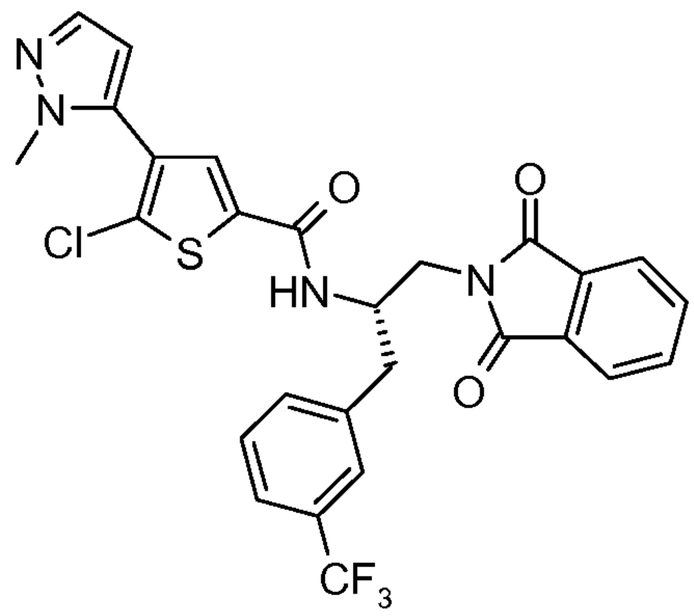
d_6) δ ppm 2.90 - 3.1 (m, 4 H) 3.85 (s, 3 H) 4.33 (s, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.32 (dd, *J*=8.46, 5.68 Hz, 2 H) 7.55 (d, *J*=2.02 Hz, 1 H) 8.19 (s, 3 H) 8.23 - 8.28 (m, 1 H) 9.25 (d, *J*=8.59 Hz, 1 H).

Example 153



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (226 mg, 0.93 mmol) [prepared according to the procedure of Example 95], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (519 mg, 1.349 mmol) [prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop

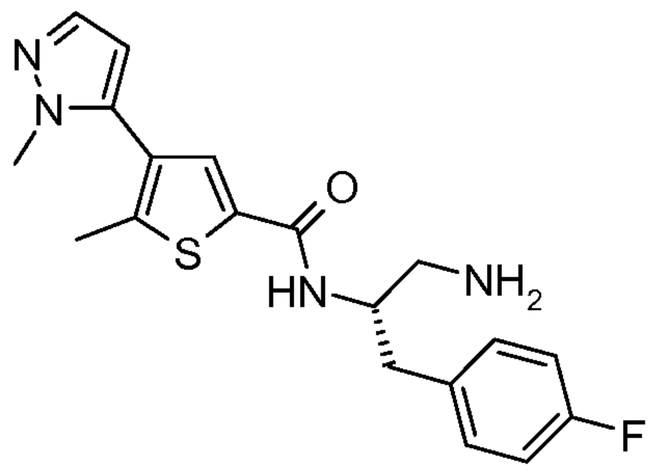
(515 mg, 1.1 mmol) in chloroform (10 mL). DIEA (820 µL, 4.70 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (379 mg, 69%): LC-MS (ES) m/z = 573 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (378 mg, 0.64 mmol) in Tetrahydrofuran (THF) (10 mL) and Methanol (1 mL). Hydrazine (122 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

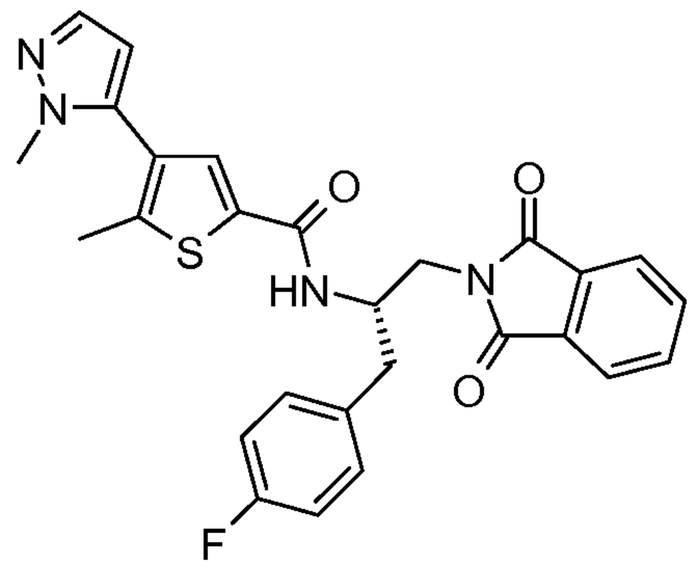
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (222 mg, 0.41 mmol, 64%): LC-MS (ES) m/z = 443 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.05 (d, *J*=6.82 Hz, 4 H) 3.84 (s, 3 H) 4.37 (d, *J*=5.05 Hz, 1 H) 6.46 (d, *J*=1.77 Hz, 1 H) 7.49 - 7.57 (m, 3 H) 7.58 - 7.61 (m, 1 H) 7.67 (s, 1 H) 8.20 (s, 3 H) 8.24 (s, 1 H) 9.31 (d, *J*=8.84 Hz, 1 H).

Example 154



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



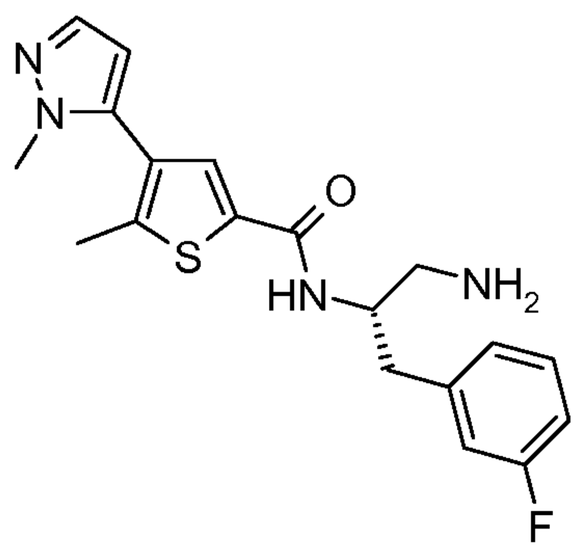
To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (200 mg, 0.90 mmol) [Prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (288 mg, 0.86 mmol) [Prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (512 mg, 1.09 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (162 mg, 32%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (162 mg, 0.29 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (300 µL). Hydrazine (58 µL, 1.85 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

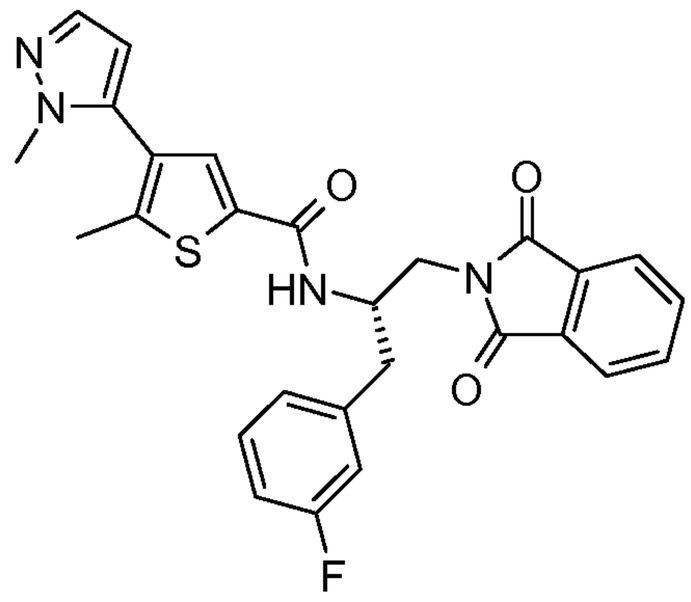
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (222 mg, 0.41 mmol, 64%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.89 - 3.02 (m, 4 H) 3.79 (s, 3 H) 4.26 - 4.48 (m, 1 H) 6.36 (d, *J*=1.77 Hz, 1 H) 7.10 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.52 (d, *J*=1.77 Hz, 1 H) 8.02 (s, 1 H) 8.17 (s, 3 H) 8.88 (d, *J*=8.59 Hz, 1 H).

Example 155



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (200 mg, 0.90 mmol) [Prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-

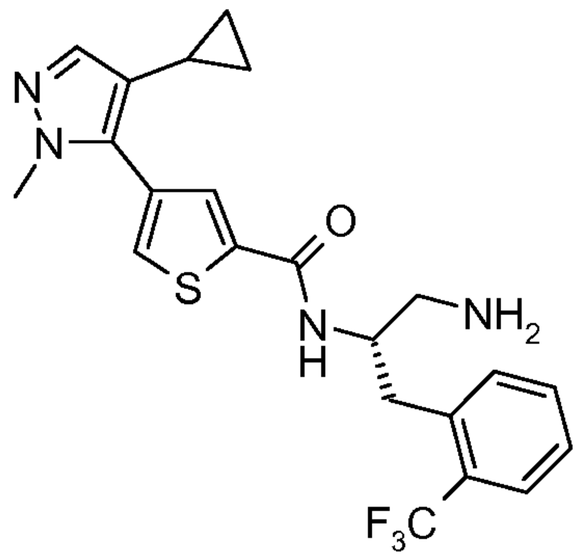
isoindole-1,3(2H)-dione (291 mg, 0.87 mmol) [Prepared according to the procedure of preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (512 mg, 1.09 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (250 mg, 50%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (250 mg, 0.45 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (400 µL). Hydrazine (66 µL, 2.10 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

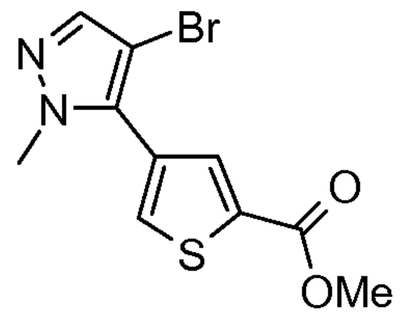
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (142 mg, 0.31 mmol, 70%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.92 - 3.04 (m, 4 H) 3.79 (s, 3 H) 4.30 -4.43 (m, 1 H) 6.36 (d, *J*=1.77 Hz, 1 H) 7.02 (td, *J*=8.53, 2.15 Hz, 1 H) 7.13 (t, *J*=7.83 Hz, 2 H) 7.26 - 7.35 (m, 1 H) 7.52 (d, *J*=2.02 Hz, 1 H) 8.04 (s, 1 H) 8.19 (s, 3 H) 8.93 (d, *J*=8.34 Hz, 1 H).

Example 156



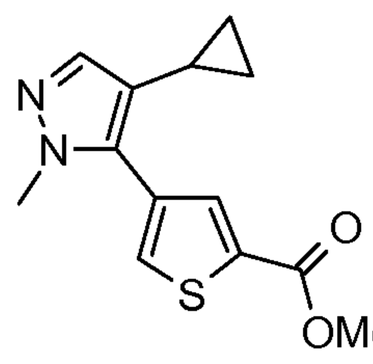
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



NBS (747 mg, 4.20 mmol) was added in portions to a 50 mL sealed tube reactor containing methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (860 mg, 3.48 mmol) [prepared according to the procedure of Example 37] in Tetrahydrofuran (THF) (17 mL) at room temperature. The mixture was heated to 70 °C for 1.5 hours, cooled to room temperature and partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (20 - 40% EtOAc / hexanes) affording the title compound (867 mg, 83%): LC-MS (ES) m/z = 303 $(M+H)^+$.

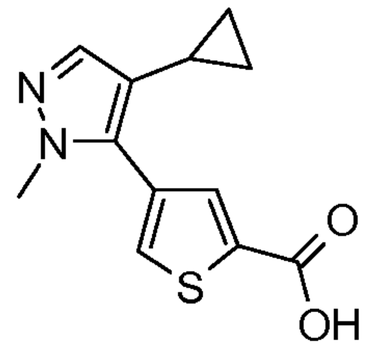
b) methyl 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 20 mL sealed tube reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (505 mg, 1.68 mmol), cyclopropylboronic acid (447 mg, 5.20 mmol), Cesium Carbonate (1.90 g, 5.84 mmol) and $PdCl_2$(dppf)-CH_2Cl_2Adduct (43.6 mg, 0.05 mmol) in Tetrahydrofuran (THF) (8.5 mL). The

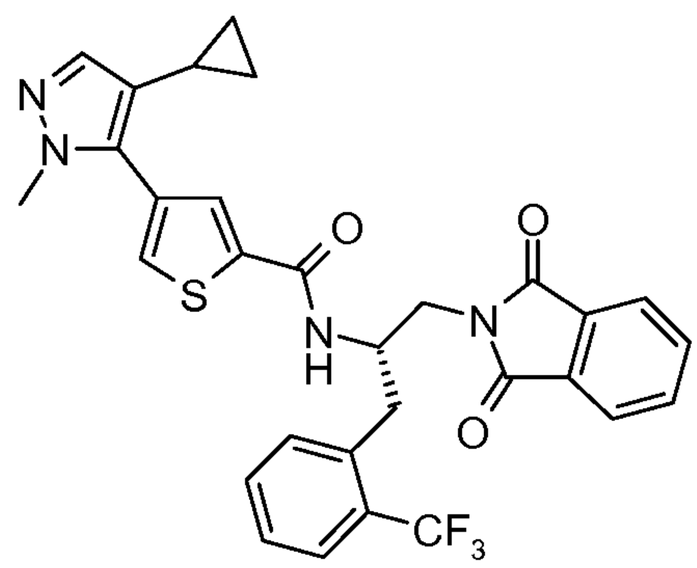
reaction was heated to 70 °C for 1.5 hours, cooled and partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (20 - 40% EtOAc / Hexane) affording the title compound (0.42 g, 1.60 mmol, 95%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (0.42 g, 1.60 mmol) in Tetrahydrofuran (THF) (8 ml). 6N NaOH (8 ml, 48.0 mmol) was added slowly and the reaction stirred at 70 °C overnight. The reaction was cooled and partitioned between $CHCl_3$ and H_2O. The pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (0.42 g, 1.60 mmol, 95%) which was used without further purification: LC-MS (ES) m/z = 249 $(M+H)^+$.

d) 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (105 mg, 0.42 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (152 mg, 0.39 mmol) [prepared according to Preparation 6] and PyBrop (246 mg, 0.52 mmol) in Chloroform (6 mL). DIEA (370 µL, 2.19 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica and purified

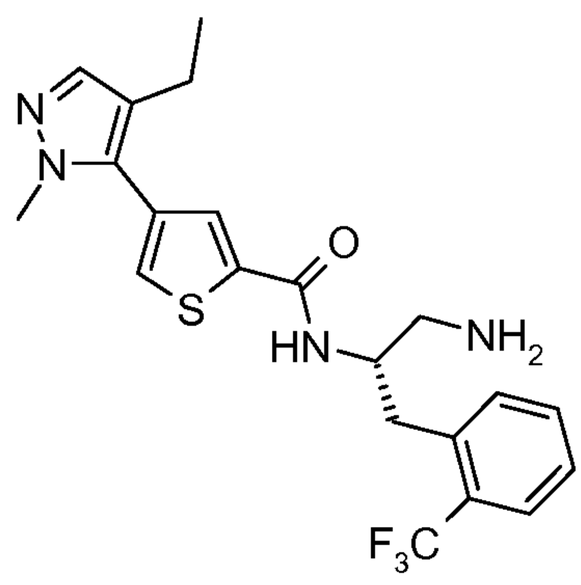
via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (171 mg, 66%): LC-MS (ES) m/z = 579 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (102 mg, 0.18 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (2 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

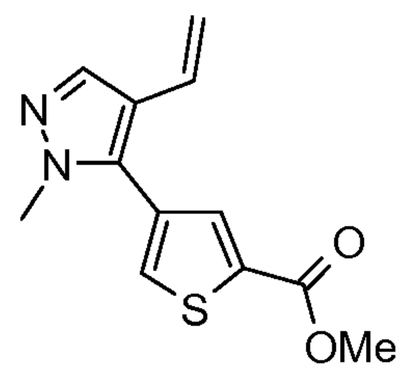
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 66 % yield): LC-MS (ES) m/z = 449 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.45 - 0.54 (m, 2 H) 0.76 - 0.83 (m, 2 H) 1.62 - 1.71 (m, 1 H) 3.03 - 3.21 (m, 4 H) 3.82 (s, 3 H) 4.46 - 4.56 (m, 1 H) 7.21 (s, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 7.53 (t, *J*=7.45 Hz, 1 H) 7.66 (dd, *J*=19.96, 7.58 Hz, 2 H) 7.95 (d, *J*=1.26 Hz, 1 H) 8.18 (s, 3 H) 8.24 (d, *J*=1.26 Hz, 1 H) 9.11 (d, *J*=9.09 Hz, 1 H).

Example 157



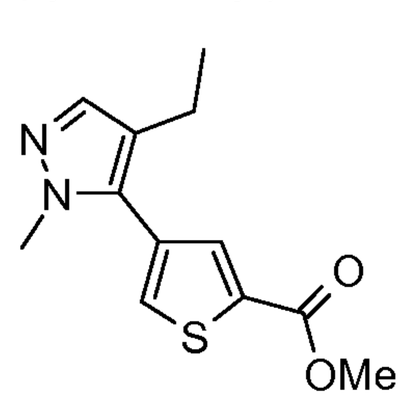
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-ethenyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 5 mL sealed tube reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (473 mg, 1.57 mmol) [prepared according to the procedure of Example 156], pyridine - triethenylboroxine (1:1) (666 mg, 2.77 mmol), $Pd(PtBu_3)_2$ (16.8 mg, 0.03 mmol) and Cs_2CO_3 (1.72 g, 5.28 mmol) in 1,4-Dioxane (6.3 mL) and water (1.6 mL). The reaction was heated at 70 °C for 2 hours and partitioned between $CHCl_3$ (75 mL) / H_2O (75 mL). The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (25-70% EtOAc/Hexane) affording the desired product: LC-MS (ES) m/z = 249 $(M+H)^+$.

b) methyl 4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate

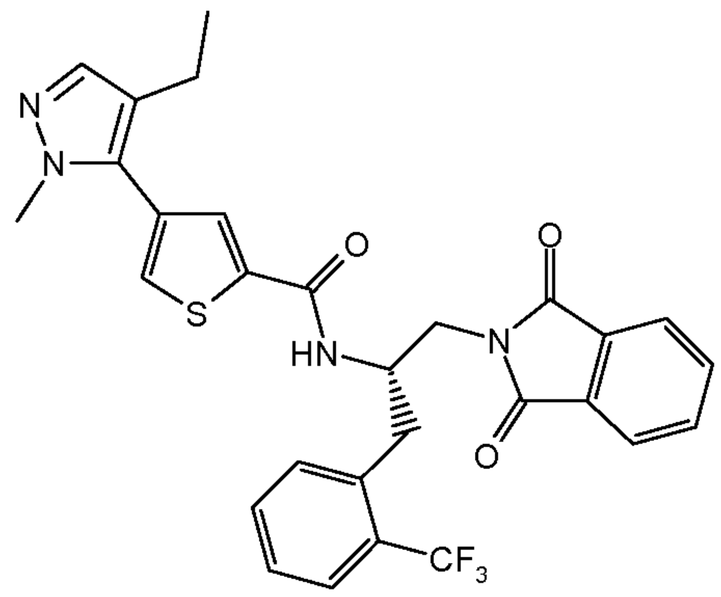


To a 100 mL round-bottomed flask was added methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate and 10% Pd/C in ethyl acetate (15 mL). The mixture was evacuated slightly, refilled with H_2 from a balloon and stirred vigorously under an atmosphere of H_2 for 1 hour. The reaction was filtered through a 0.2 µm PTFE membrane filter and used without further purification (153 mg, 0.60 mmol, 87%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid

To a 100 mL round-bottomed flask was added methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (192 mg, 0.77 mmol) in Tetrahydrofuran (THF) (4 mL). 6N NaOH (4 mL, 24.0 mmol) was added slowly, the reaction stirred at 70 °C overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer adjusted to pH 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (181 mg, quant.) used without further purification: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (106 mg, 0.45 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (164 mg, 0.43 mmol) [prepared according to Preparation 6] and PyBrop (254 mg, 0.54 mmol) in Chloroform (6 mL). DIEA (400 µL, 2.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (182 mg, 0.32 mmol, 71%): LC-MS (ES) m/z = 567 $(M+H)^+$.

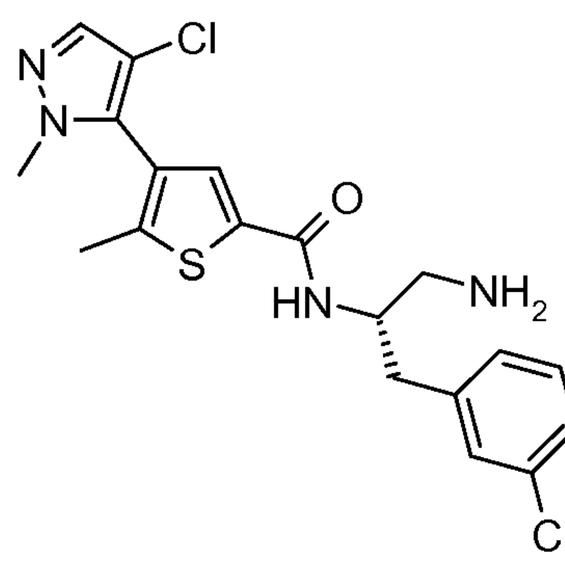
e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (101 mg, 0.18 mmol) in

Tetrahydrofuran (THF) (5 mL) and Methanol (2 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

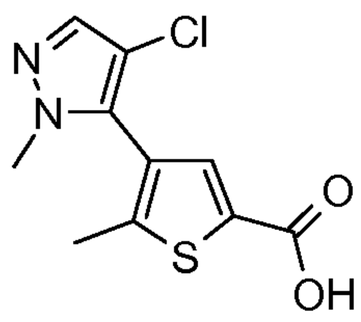
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 68%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.45 Hz, 3 H) 2.44 (q, *J*=7.41 Hz, 2 H) 2.94 - 3.17 (m, 4 H) 3.80 (s, 3 H) 4.41 - 4.57 (m, 1 H) 7.37 - 7.45 (m, 2 H) 7.53 (t, *J*=7.45 Hz, 1 H) 7.66 (dd, *J*=19.96, 7.58 Hz, 2 H) 7.88 (d, *J*=1.01 Hz, 1 H) 8.16 (s, 4 H) 9.10 (d, *J*=8.84 Hz, 1 H).

Example 158



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

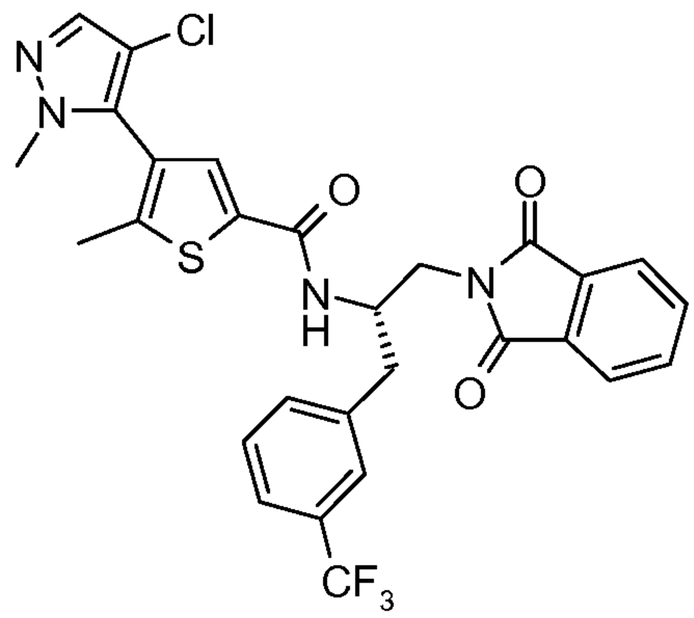
a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



NCS (1.355 g, 10.15 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.0 g, 8.46 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture

was heated to 70 °C for 2h. 6N NaOH (28 ml, 168 mmol) was added and the mixture stirred at 70 °C for an additional 2h. The mixture was cooled to room temperature and partitioned between $CHCl_3$ and H_2O. The pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The aqueous phase was washed several times with DCM and the combined organic fractions were dried with Na_2SO_4 and concentrated affording the title compound (2.36 g, 9.19 mmol, quant.): LC-MS (ES) m/z = 257 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



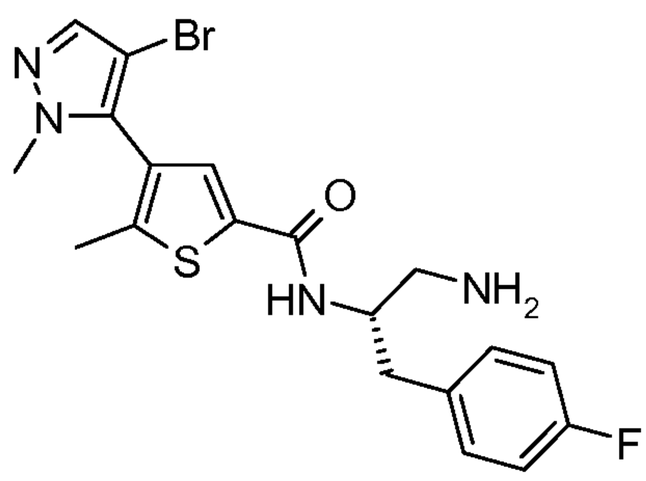
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (181 mg, 0.70 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (250 mg, 0.65 mmol) [Prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (399 mg, 0.85 mmol) in chloroform (8 mL). DIEA (620 µL, 3.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 587 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (319 mg, 0.50 mmol) in Tetrahydrofuran (THF) (4.9 mL) and Methanol (0.5 mL). Hydrazine (119 µL, 3.79 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

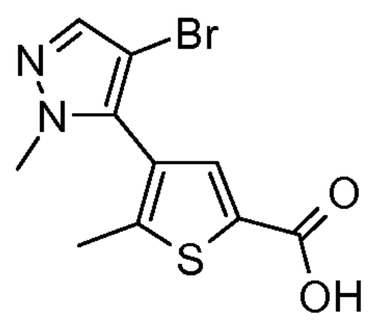
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (204 mg, 0.39 mmol, 79%): LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.95 - 3.10 (m, 4 H) 3.71 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.49 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.69 (s, 1 H) 7.94 (s, 1 H) 8.16 (s, 3 H) 8.90 (s, 1 H).

Example 159



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

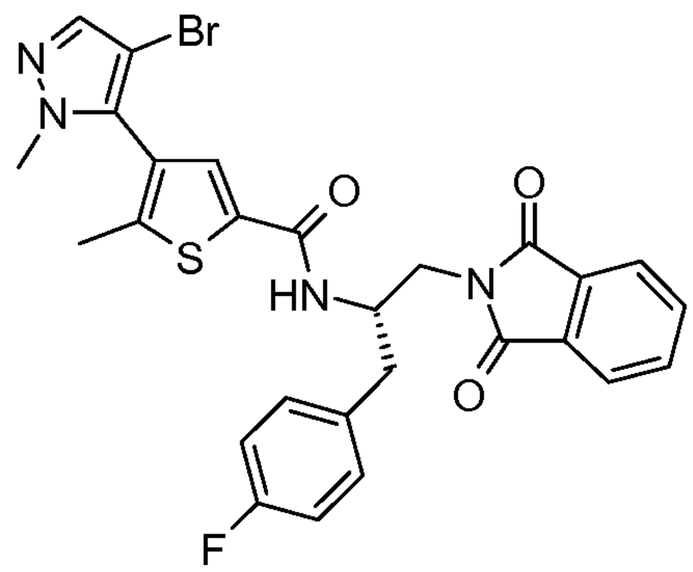
a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



NBS (1.84 g, 10.33 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2 g, 8.46 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture

was heated to 70 °C for 1h. 6N NaOH (28 ml, 168 mmol) was then added and the mixture stirred at 70 °C for 2h. The mixture was partitioned between $CHCl_3$ and H_2O and the aqueous layer was made acidic with 6N HCl. The aqueous phase was washed several times with $CHCl_3$ and the organic fractions were combined, dried over Na_2SO_4 and concentrated affording the title compound (2.68 g, 8.9mmol, quant.): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (256 mg, 0.85 mmol), 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (1272 mg, 3.80 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (485 mg, 1.03 mmol) in Chloroform (8.5 mL). DIEA (750 µL, 4.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 583 $(M+H)^+$.

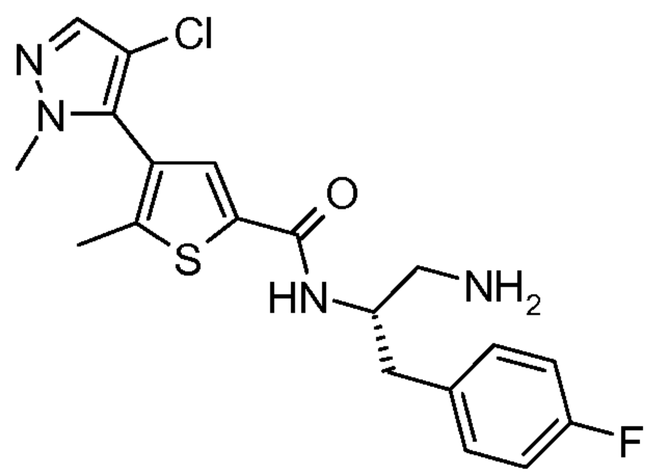
c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (133 mg, 0.21 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (50 µL, 1.59

mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

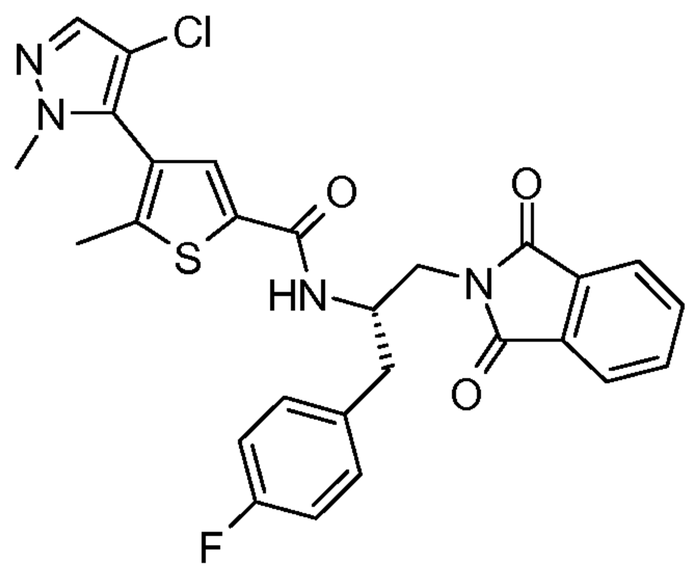
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (90 mg, 0.17 mmole, 83%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.82 - 3.08 (m, 4 H) 3.72 (s, 3 H) 4.24 - 4.39 (m, 1 H) 7.11 (t, *J*=8.84 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.69 (s, 1 H) 7.89 (s, 1 H) 8.03 - 8.25 (m, 3 H) 8.73 - 8.90 (m, 1 H).

Example 160



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (276 mg, 1.08 mmol) [Prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(4-

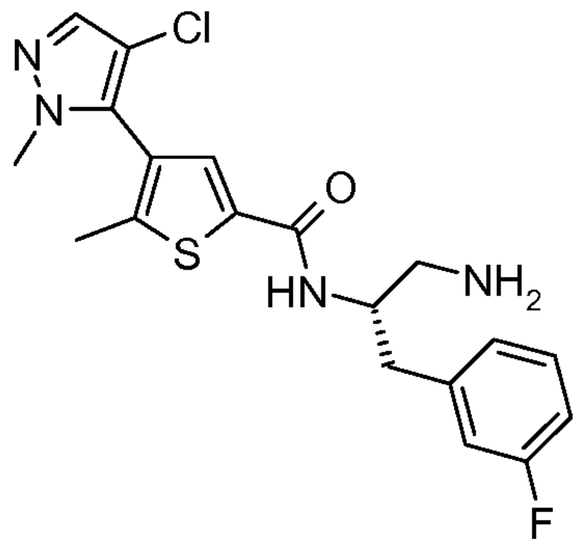
fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (317 mg, 0.95 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (612 mg, 1.31 mmol) in Chloroform (14 mL). DIEA (940 µL, 5.38 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 537 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (145 mg, 0.25 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

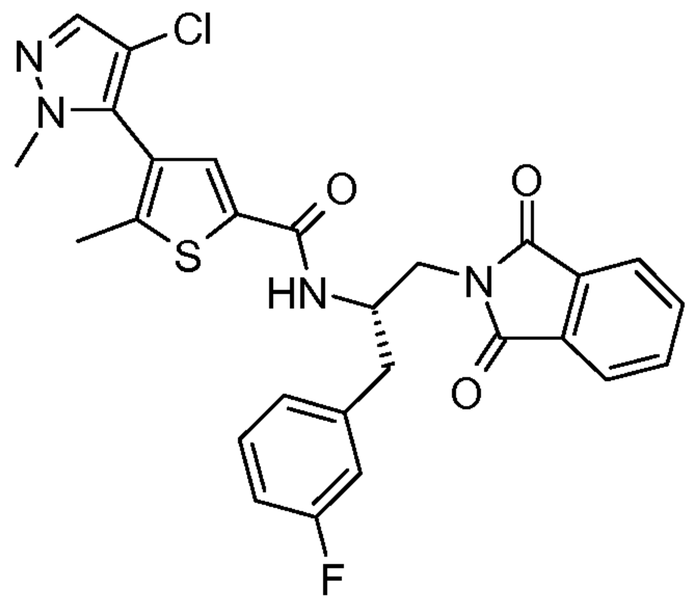
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (88 mg, 0.19 mmol, 77%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.81 - 3.10 (m, 4 H) 3.72 (s, 3 H) 4.25 - 4.40 (m, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.31 (dd, *J*=8.21, 5.68 Hz, 2 H) 7.69 (s, 1 H) 7.94 (s, 1 H) 8.15 (s, 3 H) 8.85 (s, 1 H).

Example 161



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



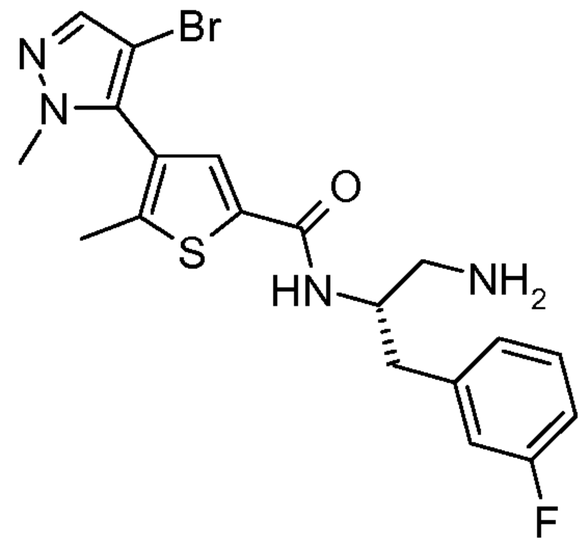
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (187 mg, 0.73 mmol) [prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (233 mg, 0.70 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (412 mg, 0.88 mmol) in Chloroform (9 mL). DIEA (640 µL, 3.66 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (180 mg, 0.30 mmol, 42%): LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (186 mg, 0.31 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (76 µL, 2.42 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

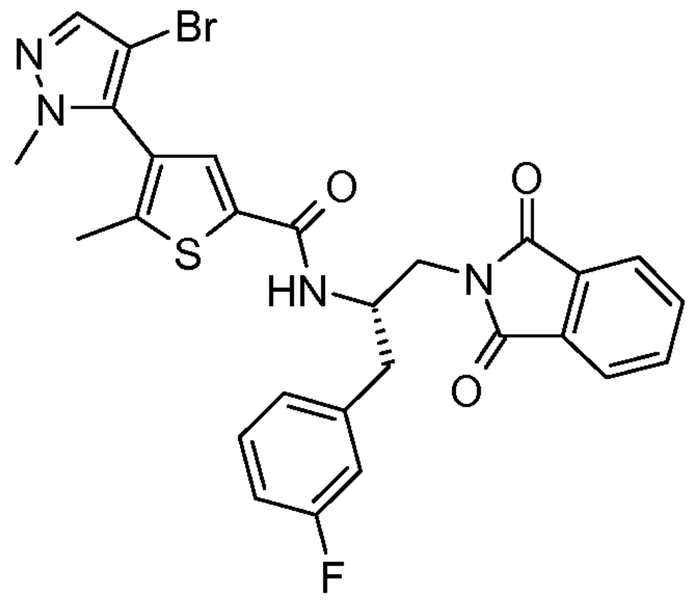
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (108 mg, 0.231, 74%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.71 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.02 (td, *J*=8.59, 2.02 Hz, 1 H) 7.13 (t, *J*=7.07 Hz, 2 H) 7.26 - 7.36 (m, 1 H) 7.69 (s, 1 H) 7.95 (s, 1 H) 8.15 (s, 3 H) 8.88 (d, *J*=6.32 Hz, 1 H).

Example 162



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (191 mg, 0.63 mmol) [prepared according to the procedure of Example 159], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (209 mg, 0.62 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (359 mg, 0.77 mmol) in chloroform (7 mL). DIEA (560 µL, 3.21 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (171 mg, 0.29 mmol, 46%): LC-MS (ES) m/z = 583 $(M+H)^+$.

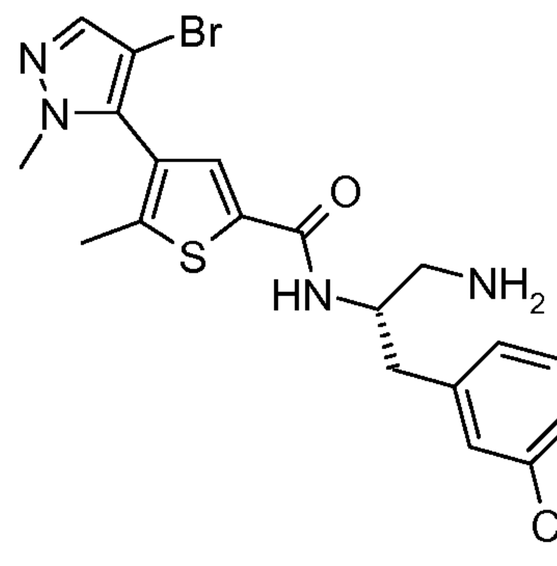
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (171 mg, 0.29 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (66 µL, 2.10 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (123 mg, 0.26 mmol, 88%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.72 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.02

(td, *J*=8.46, 2.02 Hz, 1 H) 7.12 (d, *J*=7.33 Hz, 2 H) 7.27 - 7.35 (m, 1 H) 7.64 - 7.71 (m, 1 H) 7.92 (s, 1 H) 8.14 (s, 3 H) 8.79 - 8.93 (m, 1 H).

Example 163



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (180 mg, 0.60 mmol) [prepared according to the procedure of Example 159], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (203 mg, 0.58 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (340 mg, 0.72 mmol) in Chloroform (6 mL). DIEA (530 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was

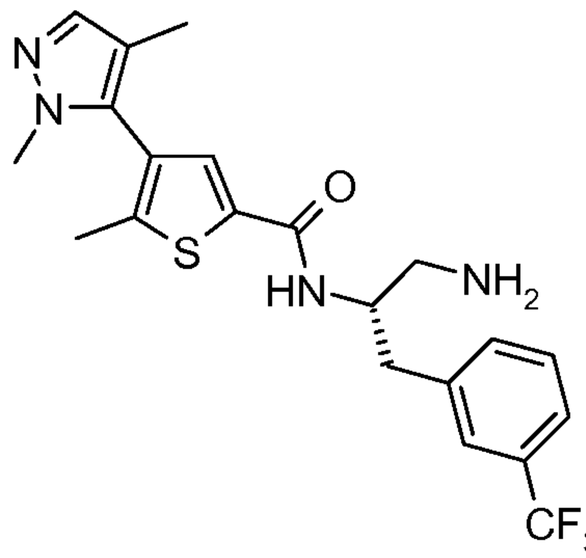
adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (259 mg, 0.41 mmol, 69%): LC-MS (ES) m/z = 633 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (259 mg, 0.41 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (90 µL, 2.87 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

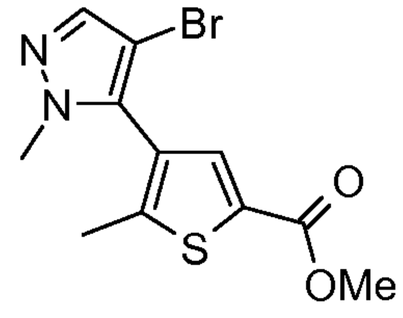
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (172 mg, 0.33 mmol, 80%): LC-MS (ES) m/z = 503 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H) 3.03 (d, *J*=6.06 Hz, 4 H) 3.71 (d, *J*=5.81 Hz, 3 H) 4.31 - 4.41 (m, 1 H) 7.49 - 7.56 (m, 2 H) 7.60 (d, *J*=6.82 Hz, 1 H) 7.64 - 7.71 (m, 2 H) 7.93 (d, *J*=12.88 Hz, 1 H) 8.18 (s, 3 H) 8.88 - 8.99 (m, 1 H).

Example 164



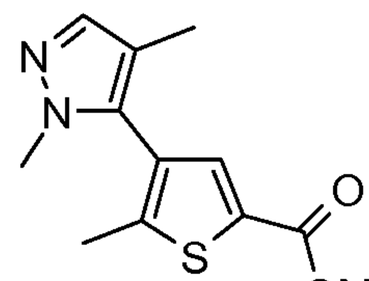
Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



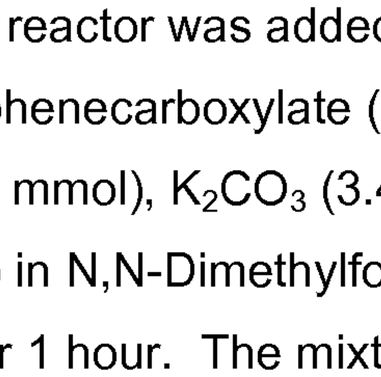
NBS (2.03 g, 11.41 mmol) was added in portions to a 75 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.1 g, 8.89 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 70 °C for 1 hour. The reaction mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, the reaction mixture adsorbed onto silica and purified via column chromatography (15 - 40% EtOAc/Hex) affording the title compound (2.57 g, 8.15 mmol, 92%): LC-MS (ES) m/z = 316 $(M+H)^+$.

b) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



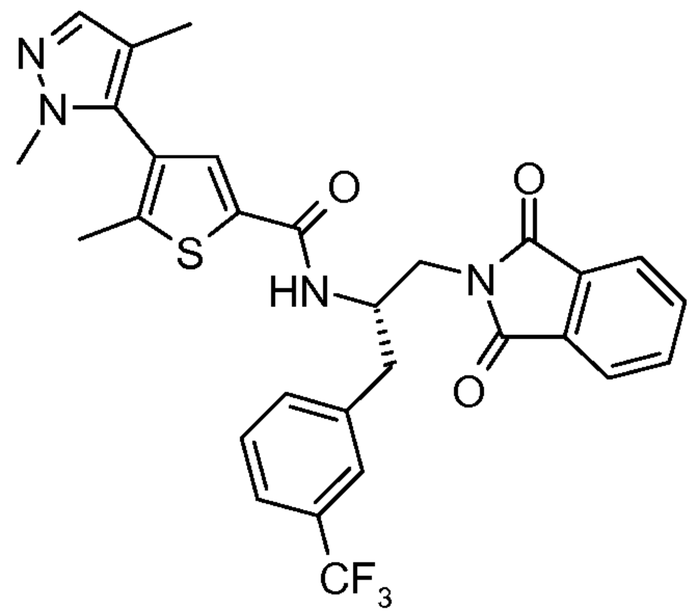
To a 350 mL sealed flask reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (2.57 g, 8.15 mmol), trimethylboroxine (2.27 ml, 16.31 mmol), K_2CO_3 (3.47 g, 25.1 mmol) and $Pd(dppf)Cl_2$ (426 mg, 0.83 mmol) in N,N-Dimethylformamide (DMF) (41 ml). The reaction was heated at 110 °C for 1 hour. The mixture was partitioned between $CHCl_3$ / H_2O, organic layer separated and dried with Na_2SO_4. The resulting material was adsorbed onto silica and purified via column chromatography (0-15% EtOAc/Hexane) affording the title compound (1.3 g, 4.76 mmol, 58%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (1.31 g, 5.23 mmol) in Tetrahydrofuran (THF) (25 mL). 6N NaOH (30 mL, 180 mmol) was added slowly and the reaction stirred at 70 °C overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer adjusted to pH 3 by the addition of 6N HCl . The layers were separated, the organic layer was dried with Na_2SO_4 and the solvent was removed affording the title compound (1.3 g, 5.5 mmol, quant.) which was used without further purification: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



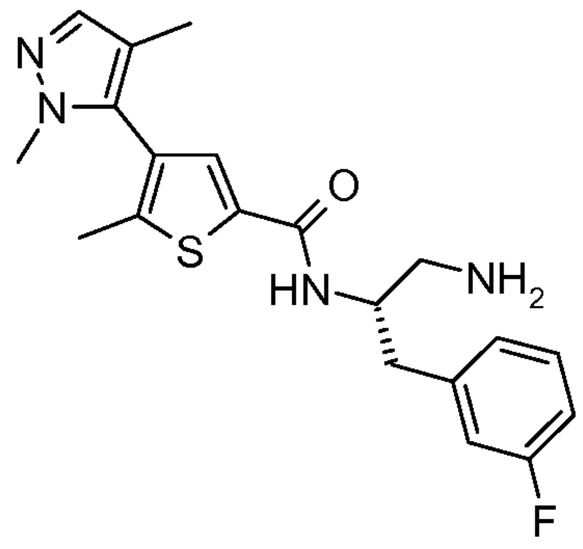
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (170 mg, 0.68 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (256 mg, 0.67 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (387 mg, 0.83 mmol) in chloroform (7 mL). DIEA (600 µL, 3.44 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (311 mg, 0.55 mmol, 80%): LC-MS (ES) m/z = 567 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (311 mg, 0.55 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.4 mL). Hydrazine (122 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

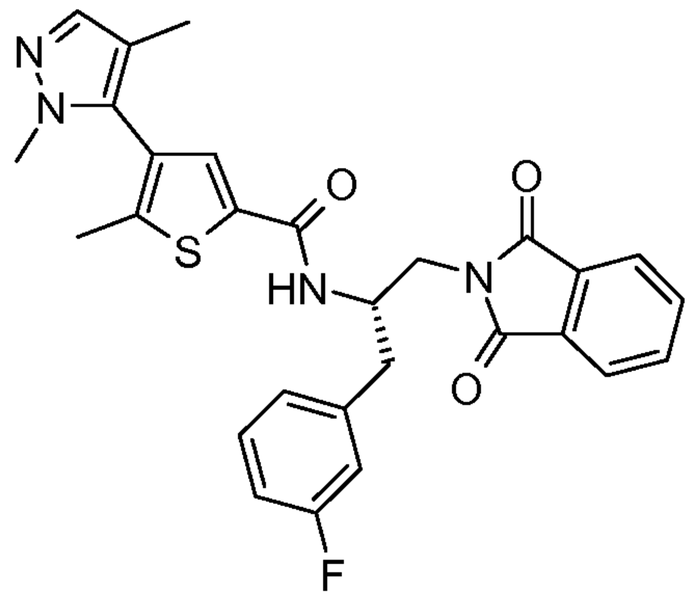
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (234 mg, 0.44 mmol, 79%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.26 (s, 3 H) 3.03 (d, *J*=6.82 Hz, 4 H) 3.62 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.38 (s, 1 H) 7.49 - 7.56 (m, 2 H) 7.58 - 7.61 (m, 1 H) 7.65 (s, 1 H) 7.87 (s, 1 H) 8.20 (s, 3 H) 8.89 (d, *J*=8.59 Hz, 1 H).

Example 165



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (207 mg, 0.83 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (279 mg, 0.83 mmol) [Prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (469 mg, 1.00 mmol) in chloroform (8 mL). DIEA (730 µL, 4.18 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (209 mg, 0.36 mmol, 43%): LC-MS (ES) m/z = 517 $(M+H)^+$.

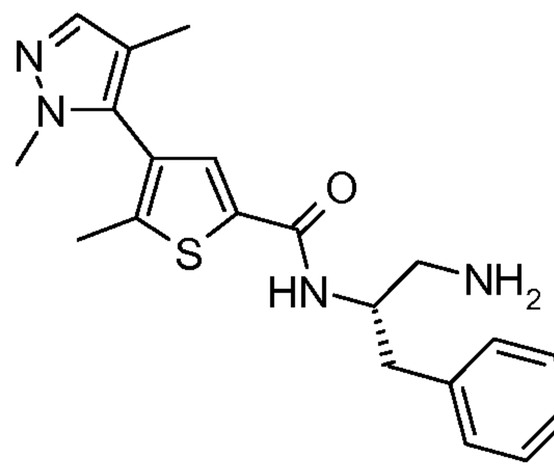
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (201 mg, 0.39 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (86 µL, 2.74 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (163 mg, 0.34 mmol, 87%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.87 - 3.09 (m, 4 H) 3.17 3.63 (s, 3 H) 4.28 -

4.45 (m, 1 H) 6.97 - 7.06 (m, 1 H) 7.13 (t, *J*=7.20 Hz, 2 H) 7.27 - 7.35 (m, 1 H) 7.38 (s, 1 H) 7.89 (s, 1 H) 8.20 (s, 3 H) 8.88 (d, *J*=7.58 Hz, 1 H).

Example 166



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide

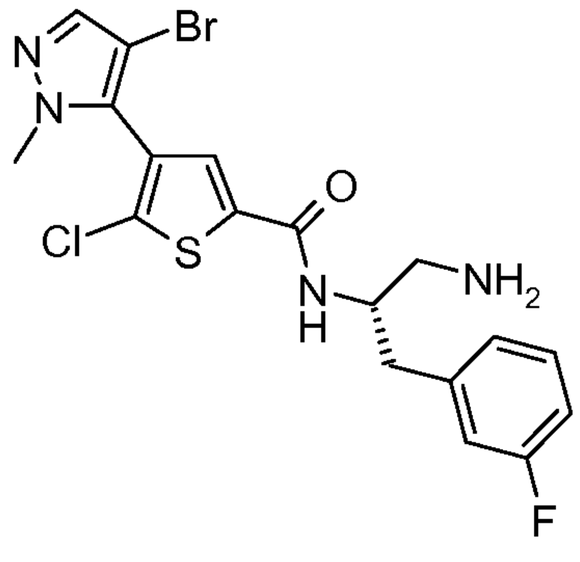
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (253 mg, 1.02 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (335 mg, 1.00 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (574 mg, 1.23 mmol) in chloroform (10 mL). DIEA (930 µL, 5.32 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (132 mg, 0.25 mmol, 24%): LC-MS (ES) m/z = 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (132 mg, 0.26 mmol) in Tetrahydrofuran (THF) (2 mL) and Methanol (1 mL). Hydrazine (57 µL, 1.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

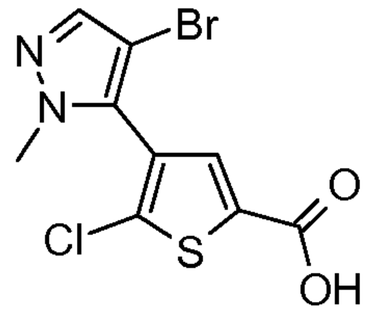
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (104 mg, 0.22 mmol, 84%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.84 - 3.11 (m, 4 H) 3.63 (s, 3 H) 4.24 - 4.39 (m, 1 H) 7.10 (t, *J*=8.72 Hz, 2 H) 7.31 (dd, *J*=8.21, 5.68 Hz, 2 H) 7.38 (s, 1 H) 7.87 (s, 1 H) 8.18 (s, 3 H) 8.83 (s, 1 H).

Example 167



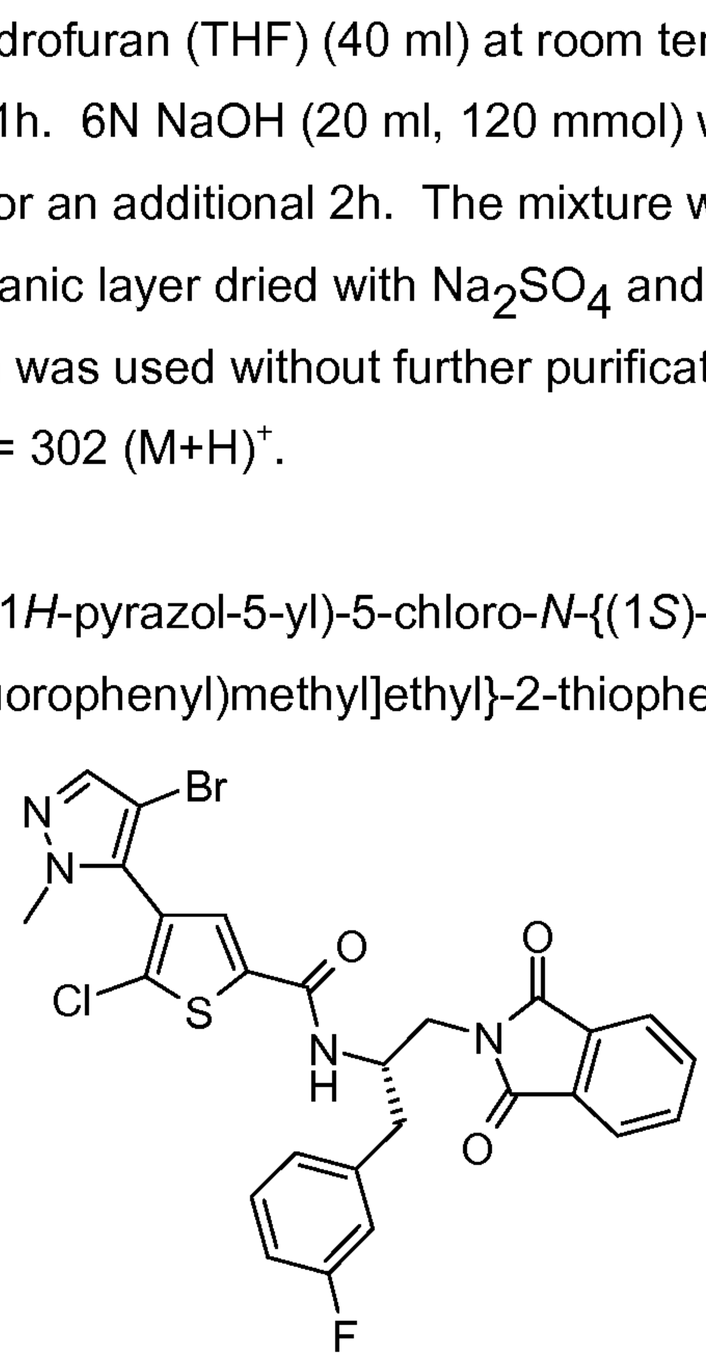
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



NBS (1.243 g, 6.98 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.47 g, 5.73 mmol) [Prepared according to the procedure of Example 151] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 70 °C for 1h. 6N NaOH (20 ml, 120 mmol) was then added and the mixture stirred at 70 °C for an additional 2h. The mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4 and concentrated affording the title compound which was used without further purification (385 mg, 1.4 mmol, 30%): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



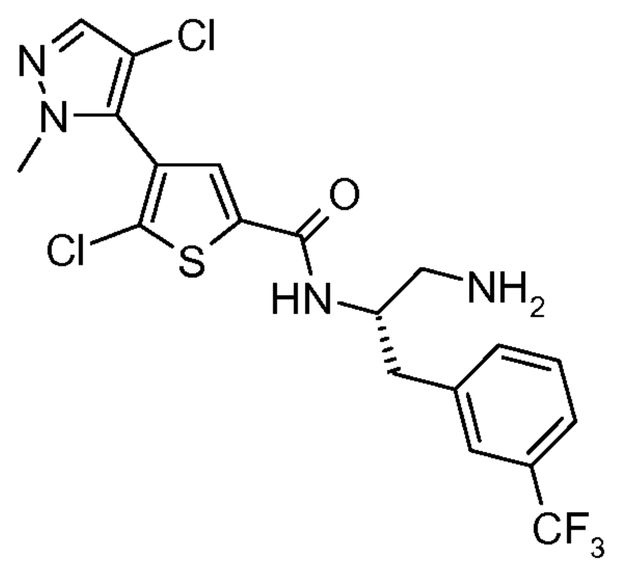
To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (204 mg, 0.60 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (215 mg, 0.64 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.7 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (380 mg, 0.81 mmol) in chloroform (6 mL). DIEA (570 µL, 3.26 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (133 mg, 0.22 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1.2 mL). Hydrazine (50 µL, 1.59 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

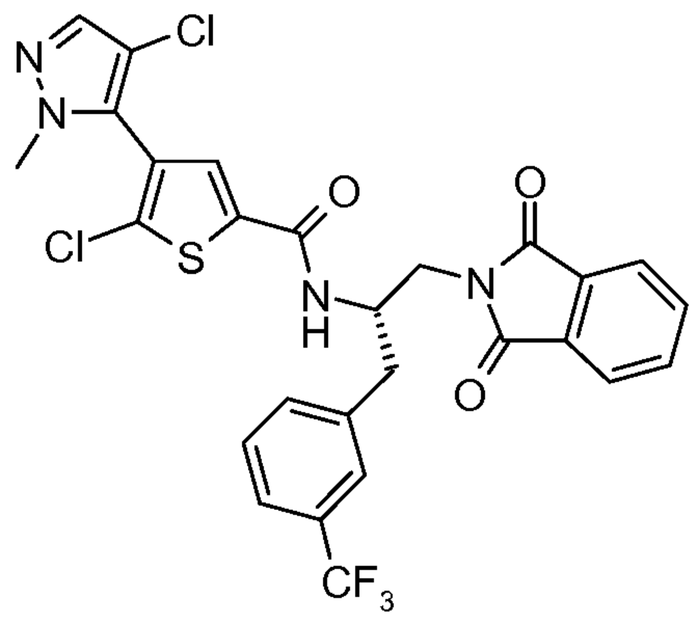
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (145 mg, 0.30 mmol, 66 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 - 3.03 (m, 4 H) 3.77 (s, 3 H) 4.30 - 4.41 (m, 1 H) 7.04 (td, *J*=8.53, 2.15 Hz, 1 H) 7.12 (d, *J*=7.07 Hz, 2 H) 7.28 - 7.36 (m, 1 H) 7.74 (s, 1 H) 8.02 - 8.14 (m, 4 H) 9.06 (s, 1 H).

Example 168



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (264 mg, 0.95 mmol) [prepared according to the procedure of Example 96], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (306 mg, 0.80 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (450 mg, 0.96 mmol) in chloroform (7 mL). DIEA (660 µl, 3.78 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (303 mg, 0.44 mmol, 56%): LC-MS (ES) m/z = 607 $(M+H)^+$.

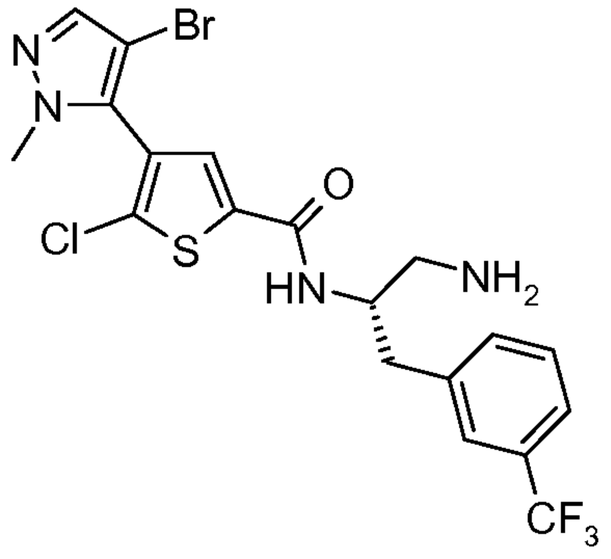
b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (303 mg, 0.50 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.5 mL). Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (177 mg, 0.31 mmol, 61 % yield): LC-MS (ES) m/z = 479 $(M+H)^+$, ^1H NMR (400 MHz,

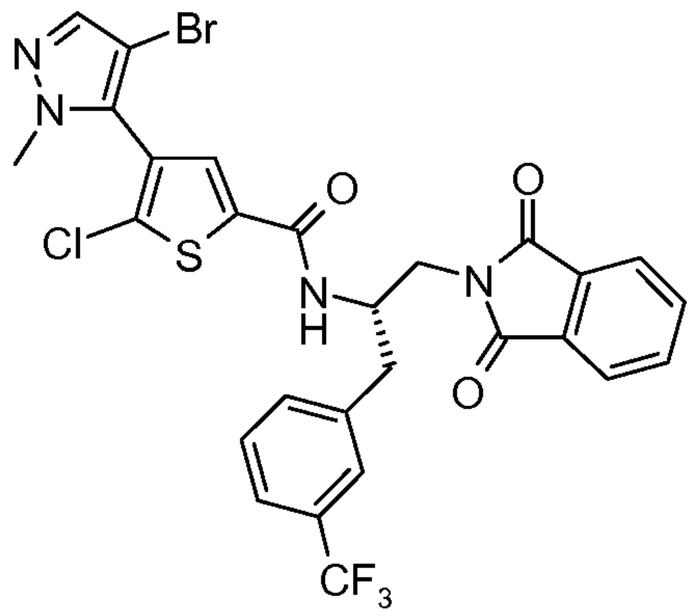
DMSO-d_6) δ ppm 2.97 - 3.08 (m, 4 H) 3.76 (s, 3 H) 4.28 - 4.44 (m, 1 H) 7.50 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.71 - 7.75 (m, 1 H) 8.10 (s, 4 H) 9.16 (d, *J*=8.59 Hz, 1 H).

Example 169



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (183 mg, 0.54 mmol) [prepared according to the procedure of Example 167], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (201 mg, 0.52 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (298 mg, 0.64 mmol) in chloroform (5 mL). DIEA (470 µL, 2.69 mmol) was

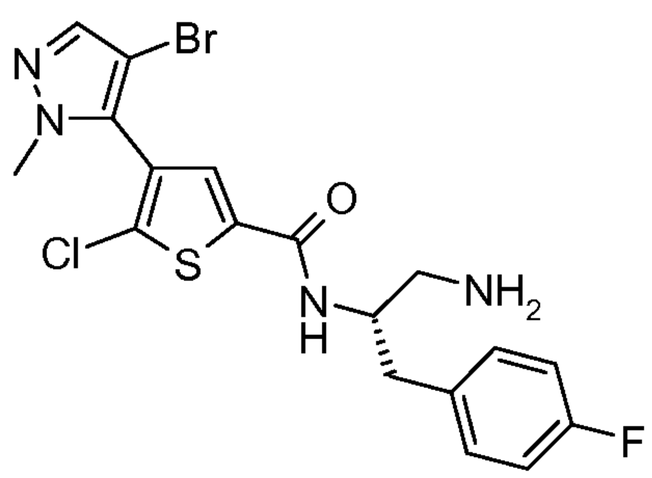
added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.36 mmol, 69%): LC-MS (ES) m/z = 653 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (246 mg, 0.38 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (0.083 mL, 2.64 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

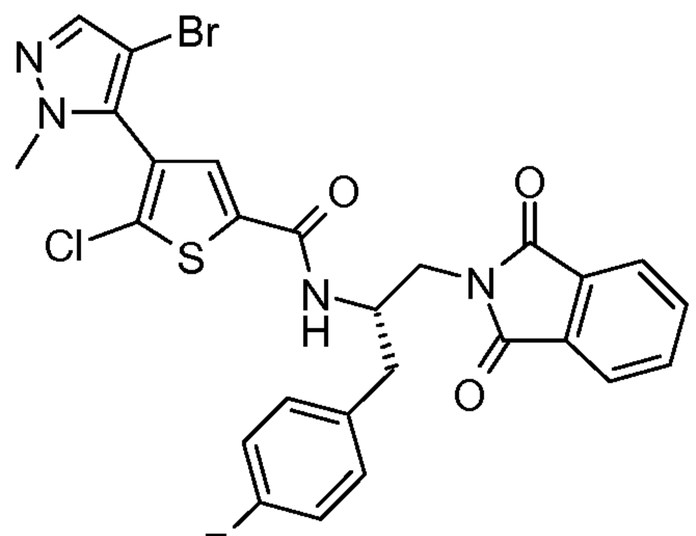
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (134 mg, 0.22 mmol, 57 % yield): LC-MS (ES) m/z = 523 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.04 (d, *J*=4.55 Hz, 4 H) 3.76 (s, 3 H) 4.29 - 443 (m, 1 H) 7.50 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.70 - 7.75 (m, 1 H) 8.06 - 8.18 (m, 4 H) 9.17 (s, 1 H).

Example 170



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



F

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (340 mg, 1.00 mmol) [prepared according to the procedure of Example 167], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (374 mg, 1.12 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (626 mg, 1.34 mmol) in chloroform (10 mL). DIEA (980 µL, 5.61 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (229 mg, 0.35 mmol, 31%): LC-MS (ES) m/z = 603 $(M+H)^+$.

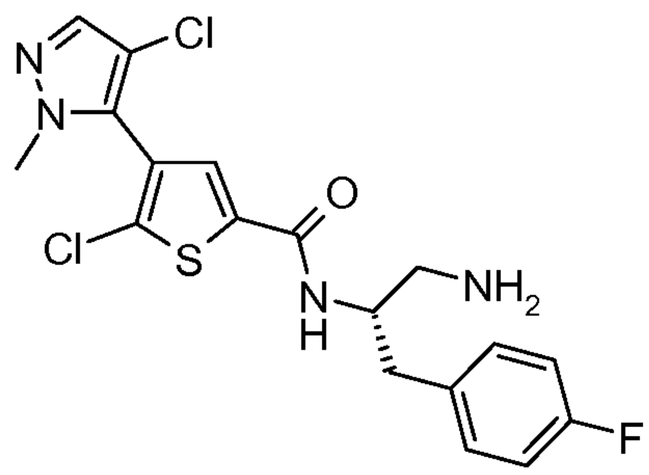
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (229 mg, 0.38 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.2 mL). Hydrazine (90 µL, 2.87 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (99

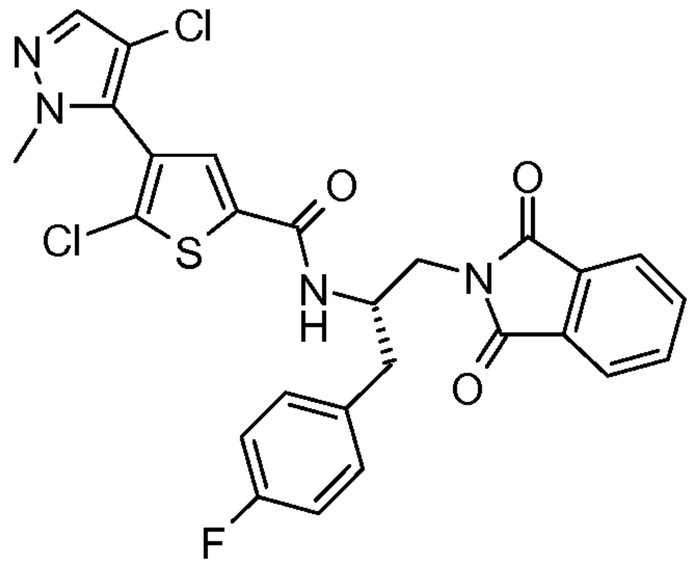
mg, 0.17 mmol, 45 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.90 (d, *J*=6.82 Hz, 2 H) 2.95 - 3.06 (m, 2 H) 3.77 (s, 3 H) 4.27 - 4.39 (m, 1 H) 7.11 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.74 (s, 1 H) 8.01 - 8.21 (m, 4 H) 9.06 (s, 1 H).

Example 171



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (320 mg, 1.16 mmol) [prepared according to the procedure of Example 168], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (318 mg, 0.95 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (535 mg, 1.14 mmol) in Chloroform (9.5 mL). DIEA (840 µl, 4.81 mmol) was added

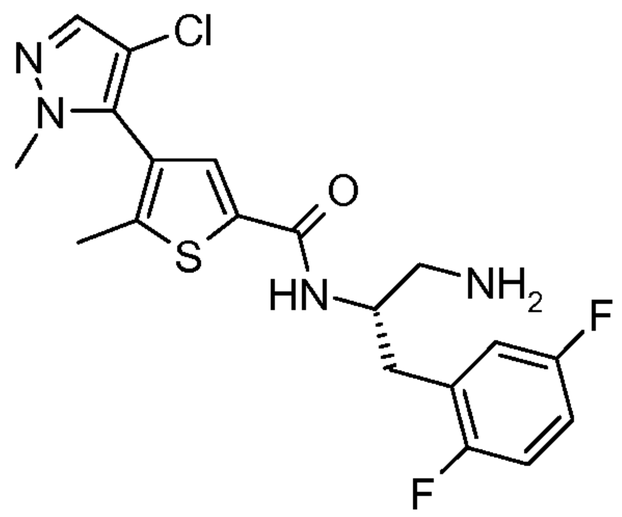
and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (106 mg, 0.16 mmol, 17%): LC-MS (ES) m/z = 557 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (106 mg, 0.19 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1.5 mL). Hydrazine (45 µL, 1.43 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

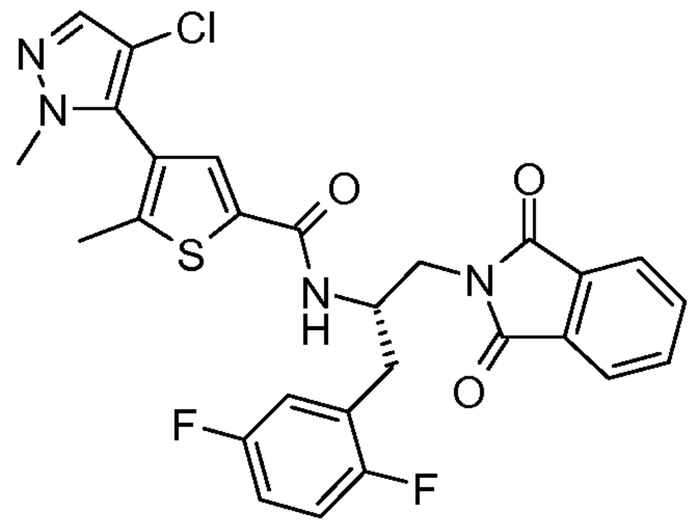
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 65 % yield): LC-MS (ES) m/z = 429 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 - 3.10 (m, 4 H) 3.77 (s, 3 H) 4.27 - 4.38 (m, 1 H) 7.11 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.68 - 7.76 (m, 1 H) 8.10 (s, 4 H) 9.11 (d, *J*=7.33 Hz, 1 H).

Example 172



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (219 mg, 0.85 mmol) [prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (290 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (481 mg, 1.03 mmol) in chloroform (8.5 mL). DIEA (750 µL, 4.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.44 mmol, 52%): LC-MS (ES) m/z = 555 $(M+H)^+$.

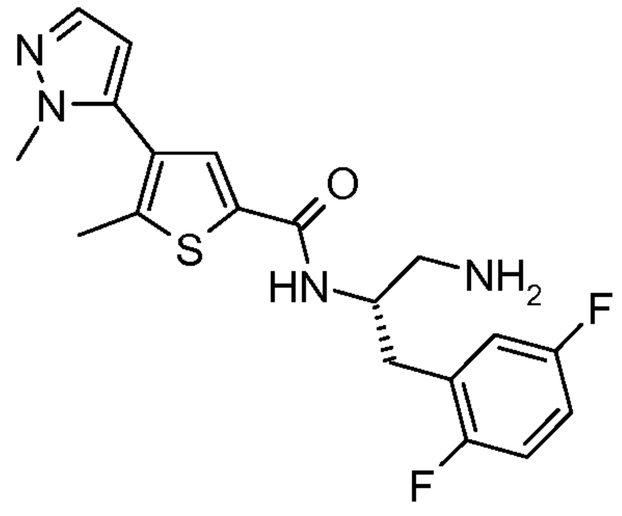
b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (246 mg, 0.44 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (100 µL, 3.19 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (147 mg, 0.28 mmol, 64 % yield): LC-MS (ES) m/z = 425 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.93 - 3.07 (m, 4 H) 3.71 (s, 3 H) 4.34 - 4.50 (m, 1 H)

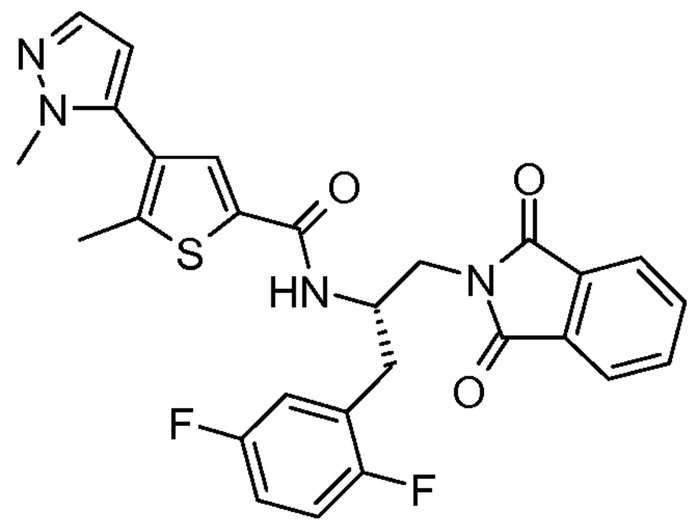
7.04 - 7.14 (m, 1 H) 7.19 (td, *J*=9.03, 4.67 Hz, 2 H) 7.69 (s, 1 H) 7.93 (s, 1 H) 8.14 (s, 3 H) 8.87 (d, *J*=8.59 Hz, 1 H).

Example 173



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



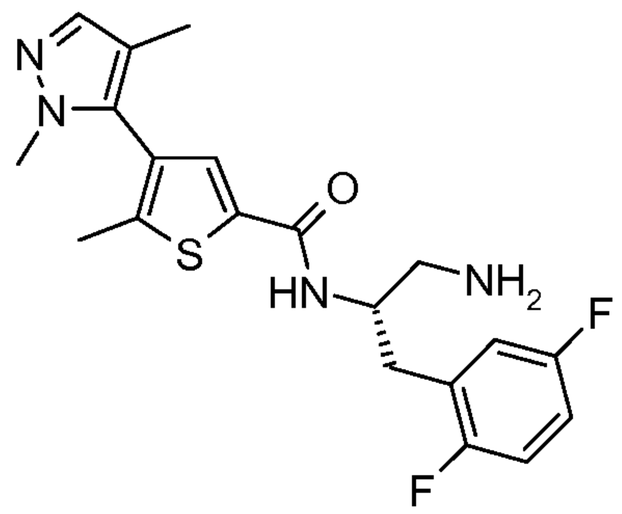
To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (171 mg, 0.77 mmol) [prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (270 mg, 0.77 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (436 mg, 0.93 mmol) in chloroform (7.5 mL). DIEA (680 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.44 mmol, 52%): LC-MS (ES) m/z = 521 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (243 mg, 0.47 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (0.103 mL, 3.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

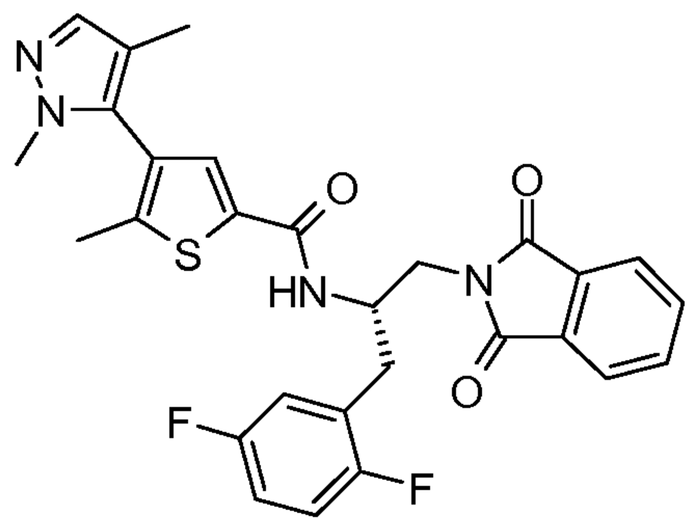
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (132 mg, 0.27 mmol, 58 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.87 - 3.10 (m, 4 H) 3.78 (s, 3 H) 4.36 - 4.47 (m, 1 H) 6.35 (d, *J*=1.77 Hz, 1 H) 7.05 - 7.13 (m, 1 H) 7.16 - 7.28 (m, 2 H) 7.52 (d, *J*=1.52 Hz, 1 H) 8.00 (s, 1 H) 8.16 (s, 3 H) 8.88 (d, *J*=8.59 Hz, 1 H).

Example 174



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



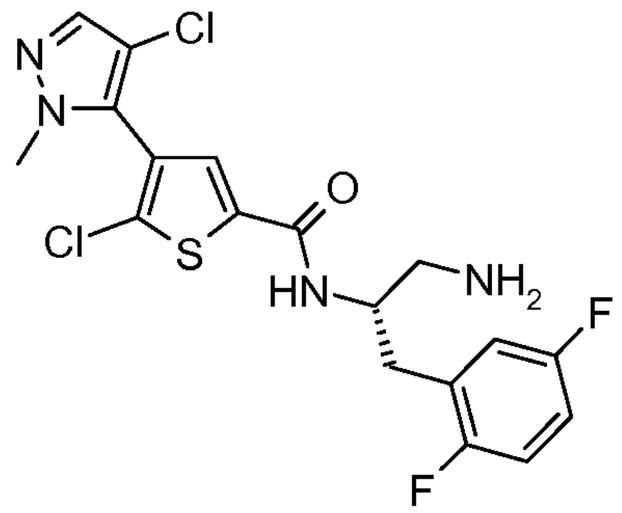
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (208 mg, 0.88 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (288 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (503 mg, 1.07 mmol) in Chloroform (8.5 mL). DIEA (770 µL, 4.41 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (292 mg, 0.55 mmol, 62%): LC-MS (ES) m/z = 535 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (292 mg, 0.55 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL) Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

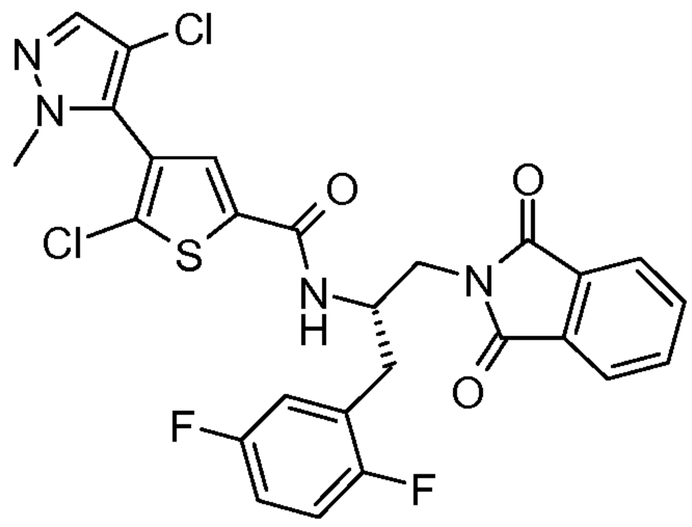
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (163 mg, 0.32 mmol, 59 % yield): LC-MS (ES) m/z = 405 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.94 - 3.06 (m, 4 H) 3.63 (s, 3 H) 4.35 - 4.49 (m, 1 H) 7.05 - 7.12 (m, 1 H) 7.16 - 7.27 (m, 2 H) 7.38 (s, 1 H) 7.86 (s, 1 H) 8.16 (s, 3 H) 8.83 (d, *J*=8.84 Hz, 1 H).

Example 175



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



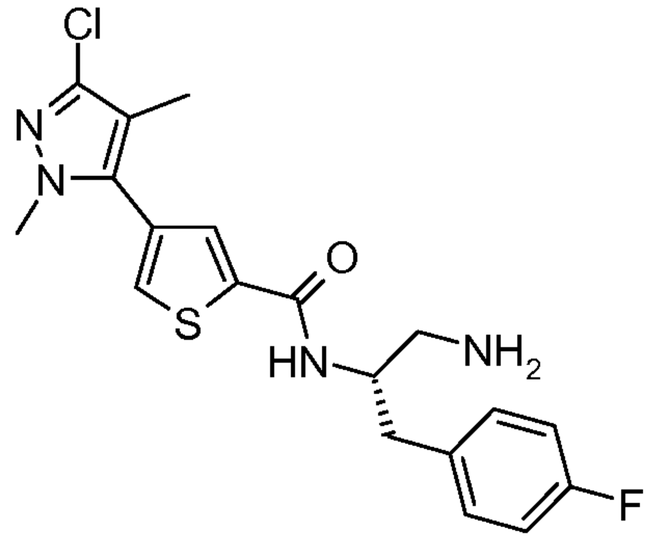
To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (235 mg, 0.85 mmol) [prepared according to the procedure of Example 96], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (290 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (479 mg, 1.02 mmol) in chloroform (8.5 mL). DIEA (742 µL, 4.25 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (174 mg, 0.30 mmol, 36%): LC-MS (ES) m/z = 575 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (174 mg, 0.30 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (1 mL). Hydrazine (70 µL, 2.23 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

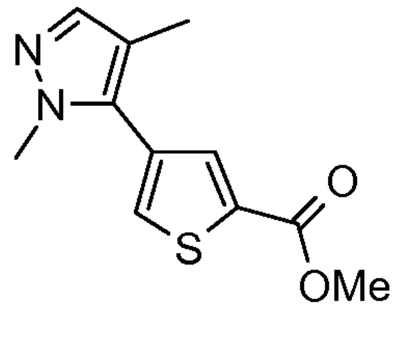
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (115 mg, 0.21 mmol, 70 % yield): LC-MS (ES) m/z = 445 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 3.09 (m, 4 H) 3.76 (s, 3 H) 4.33 - 4.48 (m, 1 H) 7.06 - 7.15 (m, 1 H) 7.20 (td, *J*=9.09, 4.55 Hz, 2 H) 7.74 (s, 1 H) 8.10 (s, 1 H) 8.13 (s, 3 H) 9.14 (d, *J*=8.84 Hz, 1 H).

Example 176



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

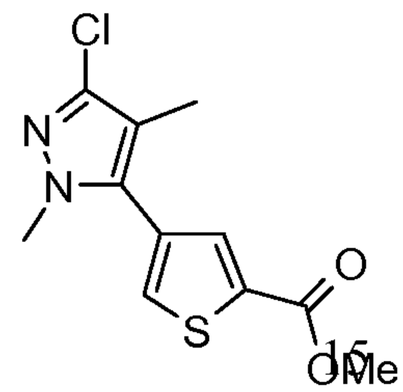
a) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 350 mL sealed flask reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (3.45 g, 11.46 mmol) [prepared according

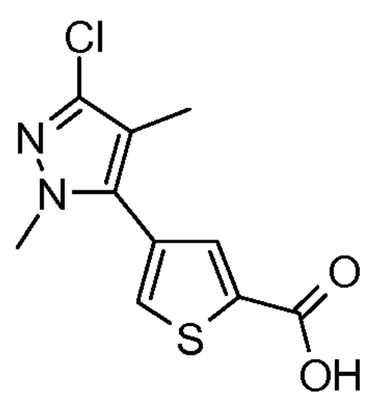
to the procedure of Example 156], trimethylboroxine (2.7 ml, 19.40 mmol), K_2CO_3 (4.75 g, 34.4 mmol) and $Pd(dppf)Cl_2$ (599 mg, 1.17 mmol) in N,N-Dimethylformamide (DMF) (57 mL). The reaction was heated at 110 °C for 1 hour, cooled to room temperature and partitioned between $CHCl_3$ / H_2O. The organic layer was separated, dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-30%EtOAc/Hexane) affording the title compound (2.07 g, 8.76 mmol, 76%): LC-MS (ES) m/z = 251 $(M+H)^+$.

b) methyl 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



NCS (1.78 g, 13.09 mmol) was added in portions to a 125 mL sealed tube reactor containing methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.07 g, 8.76 mmol) in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 100 ºC for 1 hour. Upon completion the product was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, solvents removed by vacuum distillation affording the title compound (2.18 g, 7.97 mmol, 91%) which was used without further purification: LC-MS (ES) m/z = 271 $(M+H)^+$.

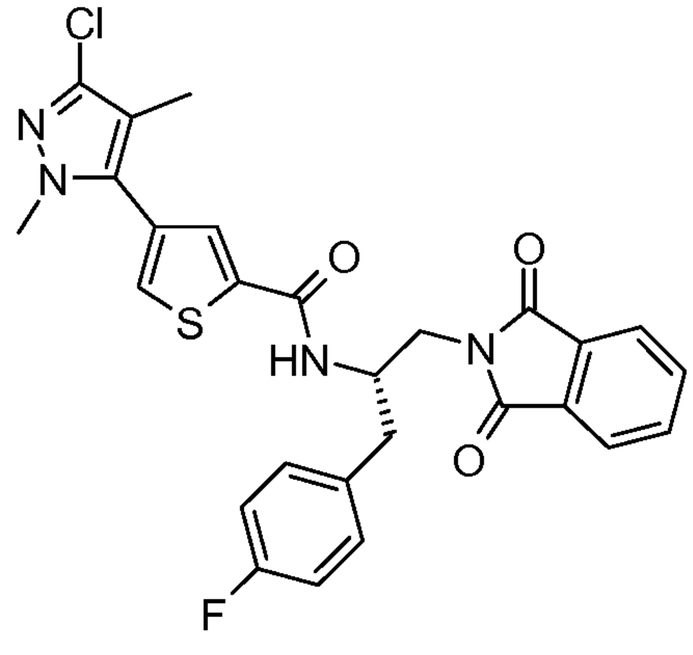
c) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.15 g, 7.94 mmol) in Tetrahydrofuran (THF) (30 ml). 6N NaOH (30 mL, 180 mmol) was added slowly and the reaction stirred at 70 ºC overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer

adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (1.35 g, 5.26 mmol, 66%) which was used in the next step without further purification LC-MS (ES) m/z = 257 $(M+H)^+$.

d) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (294 mg, 1.14 mmol), 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (409 mg, 1.22 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (645 mg, 1.38 mmol) in chloroform (10 mL). DIEA (1 mL, 5.73 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (534 mg, 0.92 mmol, 81%): LC-MS (ES) m/z = 537 $(M+H)^+$.

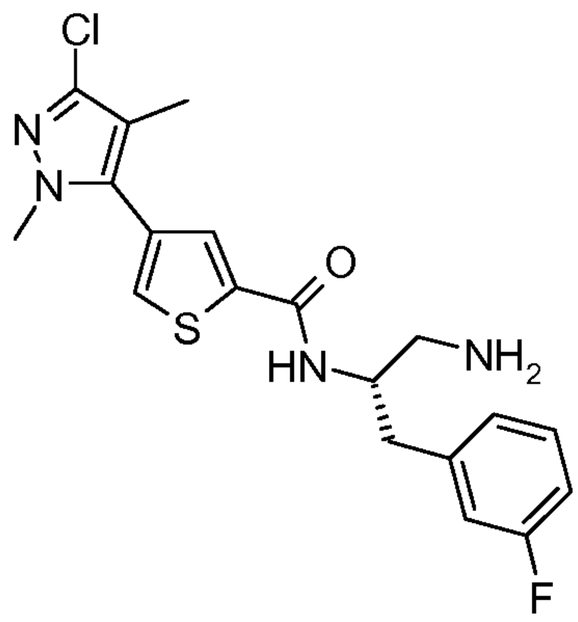
c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (534 mg, 0.994 mmol) in Tetrahydrofuran (THF) (9 mL) and Methanol (1 mL). Hydrazine (220 µL, 7.01 mmol) was added and the reaction stirred overnight at room temperature. The

reaction mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

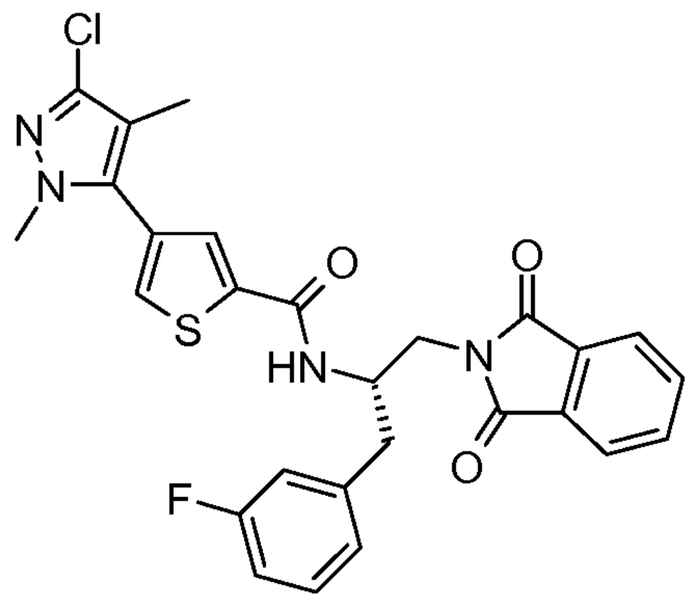
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (354 mg, 0.70 mmol, 70 % yield): LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (s, 3 H) 2.91 - 3.02 (m, 4 H) 3.79 (s, 3 H) 4.30 - 4.41 (m, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.27 - 7.36 (m, 2 H) 8.01 (d, *J*=1.26 Hz, 1 H) 8.15 (s, 3 H) 8.21 (d, *J*=1.26 Hz, 1 H) 9.04 (d, *J*=8.34 Hz, 1 H).

Example 177



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



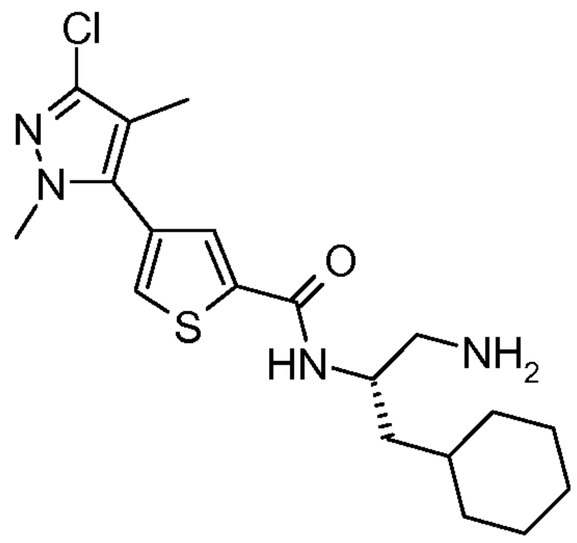
To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (291 mg, 1.13 mmol) [prepared according to the procedure of Example 176], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (409 mg, 1.22 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (654 mg, 1.39 mmol) in chloroform (10 mL). DIEA (1 mL, 5.73 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (427 mg, 0.76 mmol, 67%): LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (427 mg, 0.79 mmol) in Tetrahydrofuran (THF) (7.5 mL) and Methanol (1 mL). Hydrazine (175 µL, 5.58 mmol) was added and the solution stirred at 25 °C overnight. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

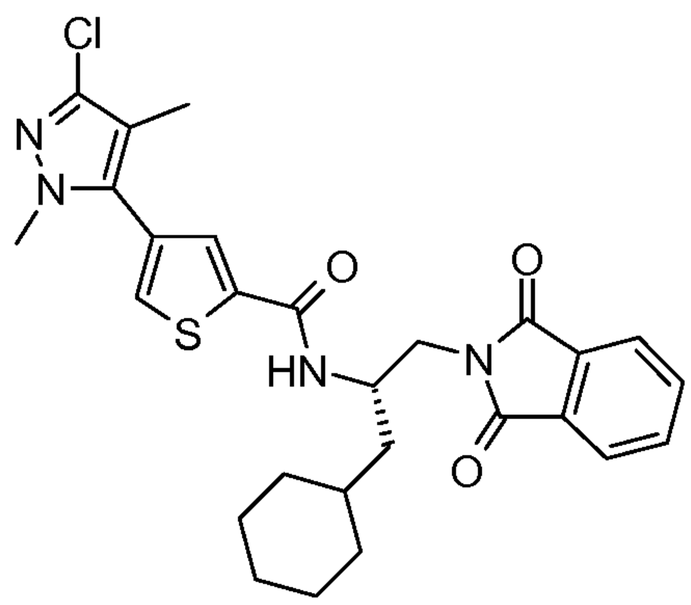
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (296 mg, 0.59 mmol, 74 % yield): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (s, 3 H) 2.95 - 3.06 (m, 4 H) 3.79 (s, 3 H) 4.33 - 4.45 (m, 1 H) 7.02 (td, *J*=8.59, 2.02 Hz, 1 H) 7.09 - 7.18 (m, 2 H) 7.26 - 7.36 (m, 1 H) 8.01 (d, *J*=1.01 Hz, 1 H) 8.16 (s, 3 H) 8.22 (s, 1 H) 9.07 (d, *J*=8.34 Hz, 1 H).

Example 178



Preparation of *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



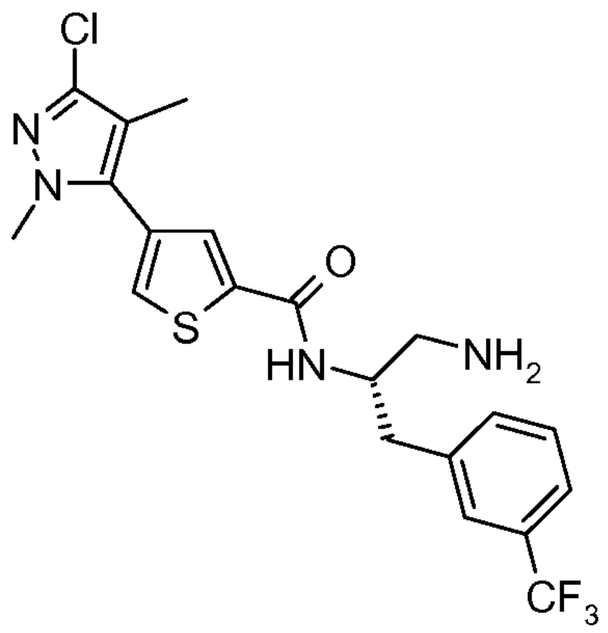
To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.58 mmol) [prepared according to the procedure of Example 176], 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (176 mg, 0.54 mmol) [prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (336 mg, 0.72 mmol) in chloroform (6 mL). DIEA (520 µL, 2.98 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (336 mg, 0.61 mmol, quant.): LC-MS (ES) m/z = 526 $(M+H)^+$.

b) *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (366 mg, 0.697 mmol) in Tetrahydrofuran (THF) (6.5 mL) and Methanol (1 mL). Hydrazine (155 µL, 4.94 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

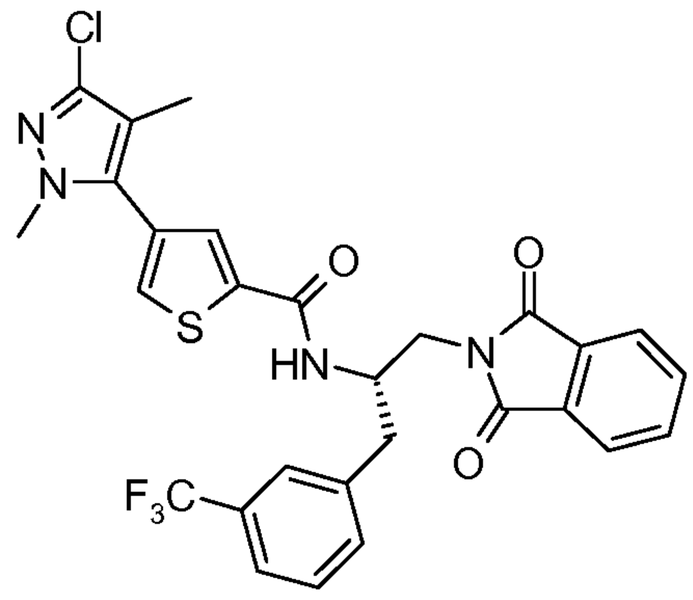
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (173 mg, 0.35 mmol, 50 % yield): LC-MS (ES) m/z = 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.92 (m, 1 H) 0.92 - 1.01 (m, 1 H) 1.13 (d, *J*=6.57 Hz, 2 H) 1.22 (d, *J*=12.88 Hz, 1 H) 1.29 (s, 1 H) 1.32 - 1.43 (m, 1 H) 1.48 - 1.56 (m, 1 H) 1.58 (d, *J*=5.05 Hz, 1 H) 1.63 (s, 3 H) 1.73 - 1.84 (m, 1 H) 1.99 (s, 3 H) 2.94 (d, *J*=5.31 Hz, 2 H) 3.78 (s, 3 H) 4.22 - 4.36 (m, 1 H) 8.03 (s, 1 H) 8.05 (s, 3 H) 8.19 (s, 1 H) 8.80 (d, *J*=8.59 Hz, 1 H).

Example 179



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (238 mg, 0.93 mmol) [prepared according to the procedure of Example 176], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (355 mg, 0.92 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (5.0 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (532 mg, 1.13 mmol) in chloroform (9.5 mL). DIEA (820 µL, 4.70 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (448 mg, 0.72 mmol, 78%): LC-MS (ES) m/z = 587 $(M+H)^+$.

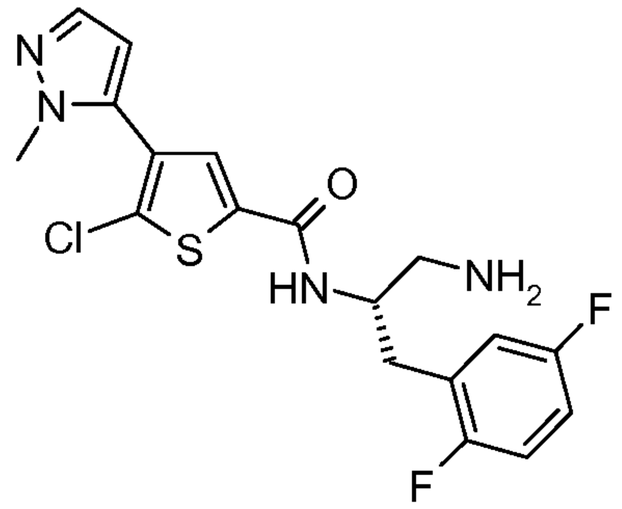
b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (468 mg, 0.80 mmol) in Tetrahydrofuran (THF) (7.5 mL) and Methanol (1 mL). Hydrazine (175 µL, 5.58 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (321 mg, 0.58 mmol, 72 % yield): LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H NMR (400 MHz,

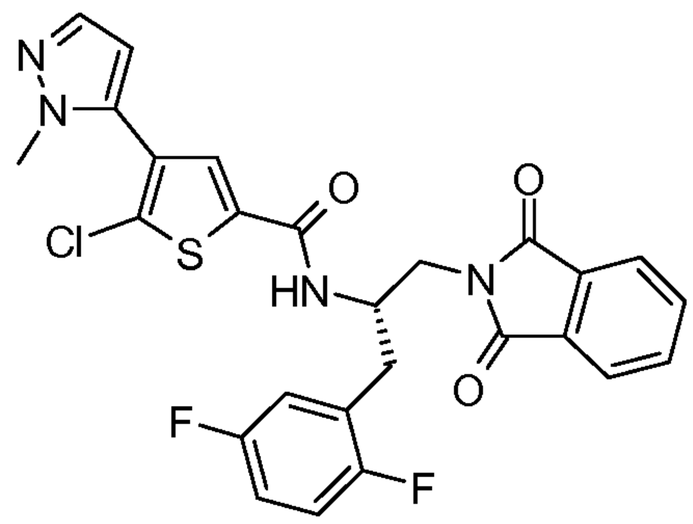
DMSO-d_6) δ ppm 1.98 (s, 3 H) 3.05 (d, *J*=7.07 Hz, 4 H) 3.77 (s, 3 H) 4.33 - 4.44 (m, 1 H) 7.49 - 7.57 (m, 2 H) 7.58 - 7.62 (m, 1 H) 7.66 (s, 1 H) 8.01 (d, *J*=1.26 Hz, 1 H) 8.11 (s, 3 H) 8.17 (d, *J*=1.26 Hz, 1 H) 9.02 (d, *J*=8.59 Hz, 1 H).

Example 180



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (147 mg, 0.61 mmol), 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (216 mg, 0.61 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (341.4 mg, 0.73 mmol) in chloroform (6 mL). DIEA (530 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70%

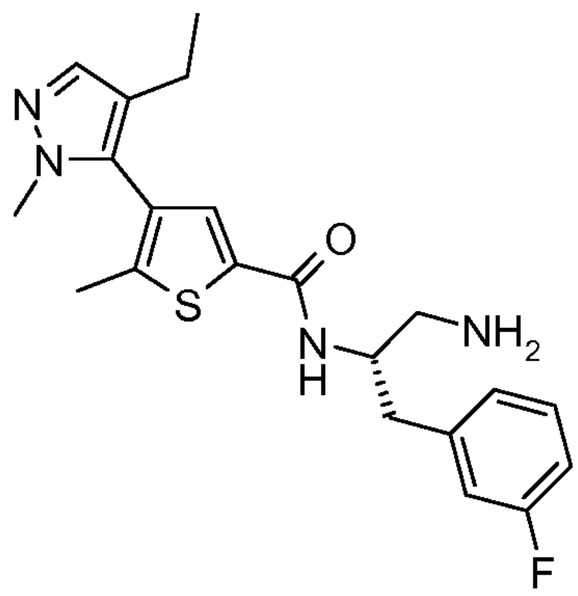
EtOAc/Hex) affording the title compound (233 mg, 0.43 mmol, 71%): LC-MS (ES) m/z = 541 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (233 mg, 0.43 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (165 mg, 0.32 mmol, 75 % yield): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 3.14 (m, 4 H) 3.85 (s, 3 H) 4.37 - 4.50 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.09 (t, *J*=8.34 Hz, 1 H) 7.19 (dt, *J*=9.09, 4.55 Hz, 1 H) 7.29 (ddd, *J*=8.84, 5.68, 3.16 Hz, 1 H) 7.55 (d, *J*=1.52 Hz, 1 H) 8.22 (s, 3 H) 8.27 (s, 1 H) 9.32 (d, *J*=8.84 Hz, 1 H).

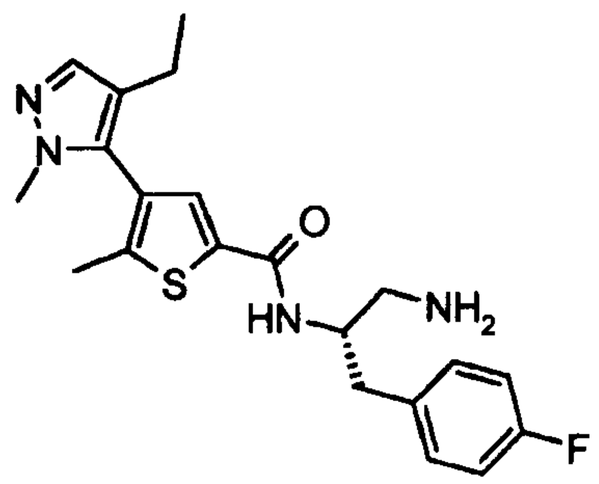
Example 181



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared according to the procedure of Example 109, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (184 mg, 0.55 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 401 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.33 Hz, 3 H) 2.13 - 2.33 (m, 5 H) 2.86 - 3.08 (m, 4 H) 3.60 (s, 3 H) 4.27 - 4.43 (m, 1 H) 6.96 - 7.07 (m, 1 H) 7.11 (d, *J*=6.32 Hz, 2 H) 7.30 (s, 1 H) 7.43 (s, 1 H) 7.85 (s, 1 H) 8.19 (s, 3 H) 8.85 (s, 1 H).

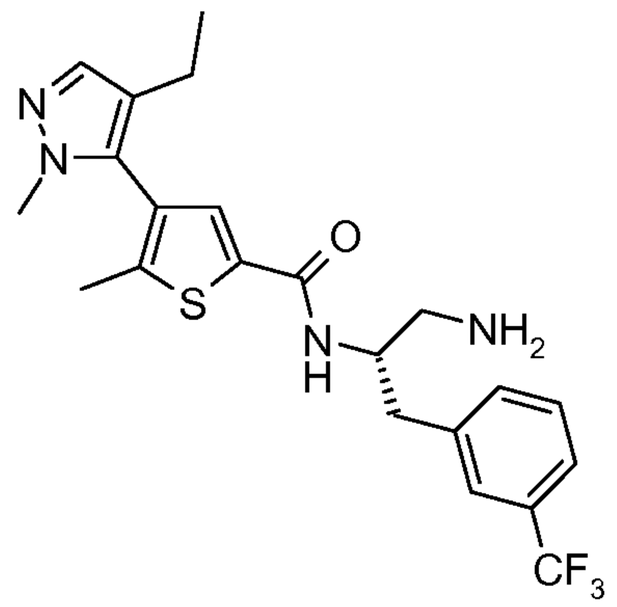
Example 182



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared according to the procedure of Example 109, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (207 mg, 0.62 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 401 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.20 Hz, 3 H) 2.25 (s, 5 H) 2.88 - 3.00 (m, 4 H) 3.61 (s, 3 H) 4.25 - 4.40 (m, 1 H) 7.01 - 7.17 (m, 2 H) 7.26 - 7.35 (m, 2 H) 7.42 (s, 1 H) 7.82 (s, 1 H) 8.17 (s, 3 H) 8.81 (s, 1 H).

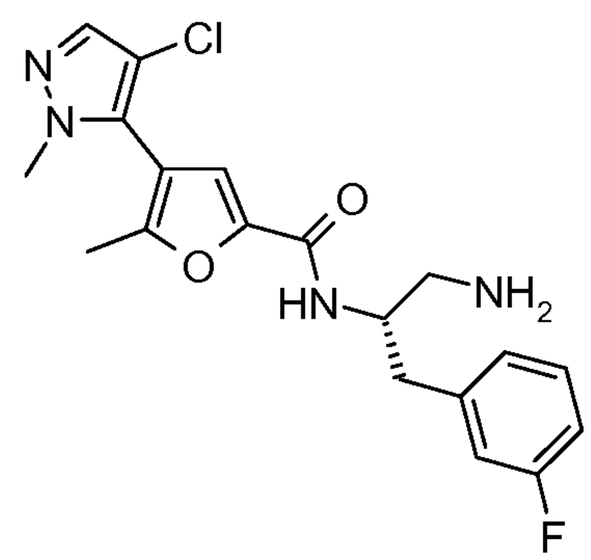
Example 183



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

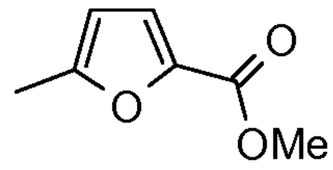
The title compound was prepared according to the procedure of Example 109, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (158 mg, 0.41 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 451 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.33 Hz, 3 H) 2.24 (s, 5 H) 3.03 (d, *J*=6.32 Hz, 4 H) 3.59 (s, 3 H) 4.35 (s, 1 H) 7.42 (s, 1 H) 7.46 - 7.57 (m, 2 H) 7.59 (d, *J*=6.57 Hz, 1 H) 7.64 (s, 1 H) 7.84 (s, 1 H) 8.20 (s, 3 H) 8.88 (s, 1 H).

Example 184



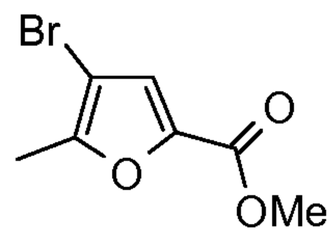
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) methyl 5-methyl-2-furancarboxylate



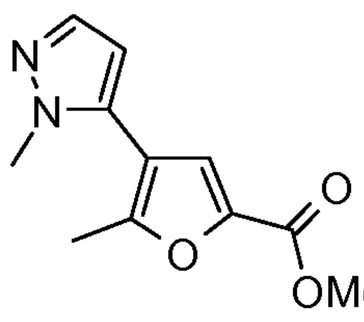
To a 200 mL round-bottomed flask with condenser was added 5-methyl-2-furancarboxylic acid (2.5 g, 19.82 mmol) in Methanol (100 mL). H_2SO_4 (10.5 mL, 197 mmol) was added slowly at room temperature. The reaction mixture was heated to 50 ºC overnight. The reaction mixture was cooled to 0 ºC and a saturated solution of $NaHCO_3$ was added to neutral pH followed by 5N NaOH to pH 10. $CHCl_3$ was added and the organic phase was separated, dried with Na_2SO_4 and concentrated affording the title compound (2.3 g, 16.3 mmol, 82%): LC-MS (ES) m/z = 141 $(M+H)^+$.

b) methyl 4-bromo-5-methyl-2-furancarboxylate



To a solution of methyl 5-methyl-2-furancarboxylate (2.33 g, 16.29 mmol) and aluminum chloride (3.3 g, 24.75 mmol) in chloroform (50 ml) at room temperature was added Br_2 (1.1 ml, 21.35 mmol). The resulting solution was stirred at room temperature in a 150 mL sealed tube reactor for 2 hours. Upon completion, the solution was cooled in an ice bath, H_2O added and reaction partitioned between $CHCl_3$ / H_2O. The organic layer was washed with $NaHCO_3$ and then $Na_2S_2O_3$. The organic layer was dried with Na_2SO_4, concentrated, adsorbed onto silica and purified via column chromatography (0-20% EtOAc/Hexanes) affording the title compound (2.13 g, 9.72 mmol, 60%): LC-MS (ES) m/z = 221 $(M+H)^+$.

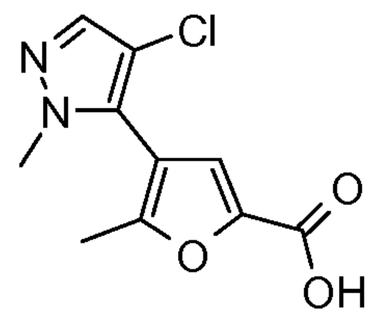
c) methyl 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a 5 mL sealed flask reactor was added methyl 4-bromo-5-methyl-2-furancarboxylate (1.13 g, 5.16 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.31 g, 6.30 mmol) [prepared according to the procedure of Preparation 7], K_3PO_4 (3.87 g, 18.23 mmol) and $Pd_2(dba)_3$ (153 mg,

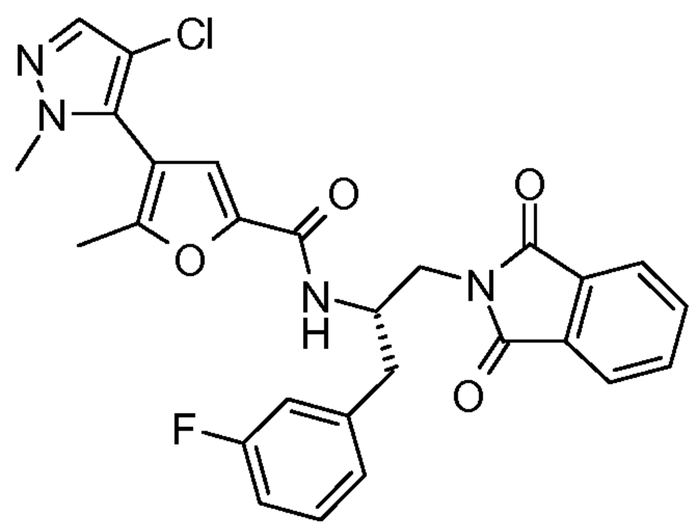
0.17 mmol) and $P(OMe)_3$ (32 µL, 0.27 mmol) in 1,4-Dioxane (23 mL). The reaction was heated at 95 °C for 4 hours, cooled to room temperature and partitioned between $CHCl_3$ / H2O. The organic layer was separated, dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-15%EtOAc/Hexanes) affording the title compound (967 mg, 4.39 mmol, 85%): LC-MS (ES) m/z = 271 $(M+H)^+$.

d) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



NCS (709 mg, 5.31 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (967 mg, 4.39 mmol) in Tetrahydrofuran (THF) (20 mL) at room temperature. The mixture was heated to 70 °C for 1 hour. 6N NaOH (20 mL, 120 mmol) was then added and the mixture stirred at 70 °C for an additional 2h. The mixture was partitioned between $CHCl_3$ and H_2O and the pH of the aqueous phase was adjusted to ~3 with 6N HCl. The organic layer was separated, dried with Na_2SO_4 and concentrated affording the title compound (1.13 g, 4.41 mmol, quant.) which was used without further purification: LC-MS (ES) m/z = 241 $(M+H)^+$.

e) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (244 mg, 0.95 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (320 mg, 0.95 mmol)

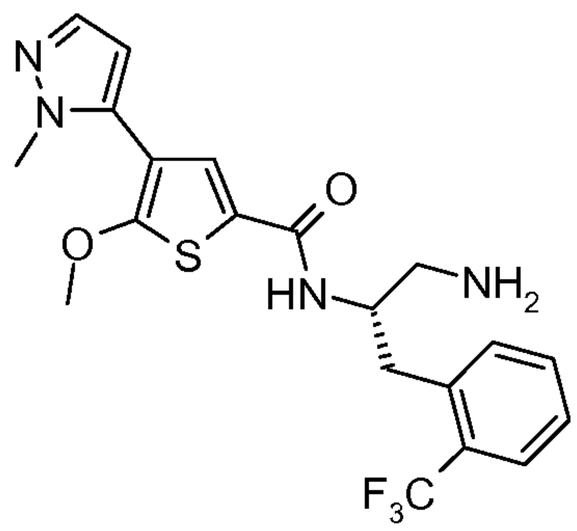
[prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.0 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (533 mg, 1.14 mmol) in chloroform (9 mL). DIEA (830 µL, 4.75 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (242 mg, 0.465 mmol, 49%): LC-MS (ES) m/z = 521 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide (238 mg, 0.46 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (1 mL). Hydrazine (100 µL, 3.19 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

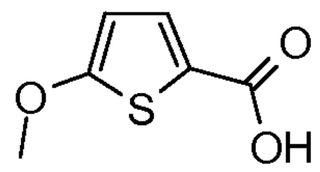
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (157 mg, 0.32 mmol, 71 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.73 (s, 3 H) 4.36 - 4.49 (m, 1 H) 7.03 (t, *J*=7.71 Hz, 1 H) 7.07 - 7.14 (m, 2 H) 7.29 - 7.37 (m, 1 H) 7.39 (s, 1 H) 7.67 (s, 1 H) 8.14 (s, 3 H) 8.65 (d, *J*=8.59 Hz, 1 H).

Example 185



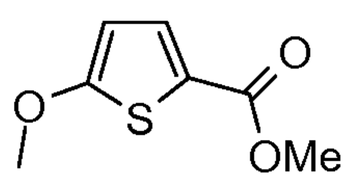
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-(methyloxy)-2-thiophenecarboxylic acid



2-(methyloxy)thiophene (1.01 g, 8.85 mmol) was added slowly over 15 min to a 100 mL round-bottomed flask containing 2.5M nBuLi in hexanes (3.8 mL, 9.50 mmol) in Tetrahydrofuran (THF) (40 mL) at -78 °C. After warming to room temperature and stirring for 2h, the mixture was cooled to -35 °C and crushed solid CO_2 was added. The mixture warmed to room temperature over 3 hours and was cooled in an ice bath and quenched with NH_4Cl(sat.). The cold reaction mixture was partitioned between $CHCl_3$ / H_2O, the aqueous layer was made acidic with 6N HCl. The separated organic layer was dried with Na_2SO_4 and concentrated affording the title compound (1.3 g, 8.05 mmol, 91%) which was used without further purification: LC-MS (ES) m/z = 159 $(M+H)^+$.

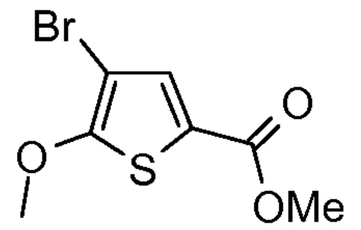
b) methyl 5-(methyloxy)-2-thiophenecarboxylate



To a 200 mL round-bottomed flask fitted with a condenser was added 5-(methyloxy)-2-thiophenecarboxylic acid (1.3 g, 8.22 mmol) in Methanol (40 mL). H_2SO_4 (5 mL, 94 mmol) was added slowly at room temperature and the reaction stirred at 50 °C overnight. The mixture was cooled to 0 °C and sat. $NaHCO_3$ was added to neutral pH followed by 5N NaOH to pH 10. The mixture was partitioned between H_2O / $CHCl_3$ and the organic phase was separated and dried over

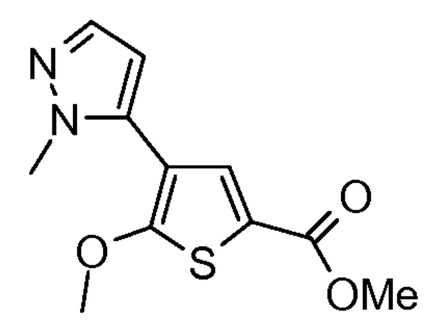
Na_2SO_4. The solution was adsorbed onto silica and purified via column chromatography (5-50% EtOAc/Hexanes) affording the title compound (827 mg, 4.56 mmol, 56%): LC-MS (ES) m/z = 173 $(M+H)^+$.

c) methyl 4-bromo-5-(methyloxy)-2-thiophenecarboxylate



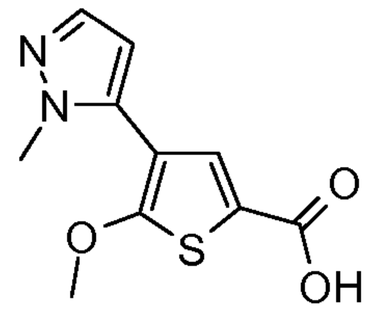
NBS (903 mg, 5.07 mmol) was added in portions to a 5 mL sealed tube reactor containing methyl 5-(methyloxy)-2-thiophenecarboxylate (0.73 g, 4.23 mmol) in N,N-Dimethylformamide (DMF) (20 mL) at room temperature and the reaction stirred for 1 hour. Additional NBS (249 mg) was added and after 1h at room temperature the product was partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-25% EtOAc/Hexanes) affording the title compound (825 mg, 3.19 mmol, 75%): LC-MS (ES) m/z = 252 $(M+H)^+$.

d) methyl 5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



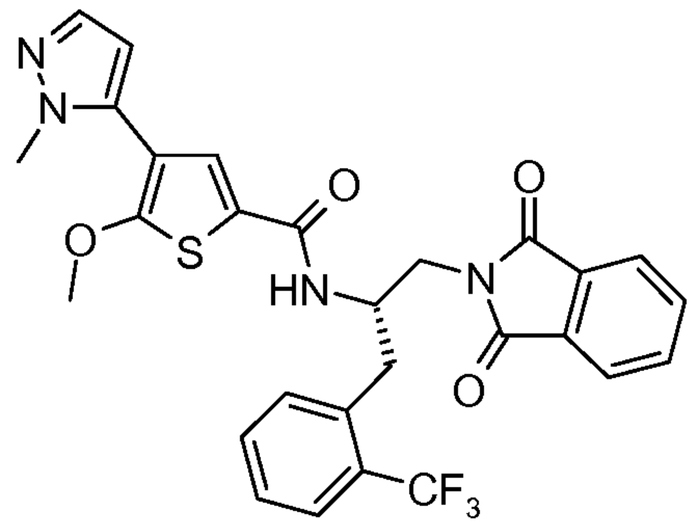
To a 350 mL sealed flask reactor was added methyl 4-bromo-5-(methyloxy)-2-thiophenecarboxylate (772 mg, 3.07 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (773 mg, 3.72 mmol) [prepared according to the procedure of Preparation 7], K_2CO_3 (1.419 g, 10.27 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (103 mg, 0.20 mmol) in 1,4-Dioxane (12 mL) and Water (3 mL). The reaction was heated at 85 ºC for 2 hours. The mixture was partitioned between $CHCl_3$ / H_2O and the aqueous layer made acidic with 6N HCl. The separated organic layer was dried over Na_2SO_4 and evaporated. The resulting material was adsorbed onto silica and purified via column chromatography (0-50%EtOAc/Hexane) affording the title compound (967 mg, 4.39 mmol, 85%): LC-MS (ES) m/z = 253 $(M+H)^+$.

e) 5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (203 mg, 0.805 mmol) in Tetrahydrofuran (THF) (4 mL). 6N NaOH (4 mL, 24.0 mmol) was added slowly, the reaction mixture stirred overnight at 70 °C. The mixture was neutralized by addition of 6N HCl and partitioned between $CHCl_3$ and H_2O. The layers were separated, the organic layer dried over Na_2SO_4 and concentrated affording the title compound (152 mg, 0.64 mmol, 79%), which was used in the next step without further purification: LC-MS (ES) m/z = 239 $(M+H)^+$.

f) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



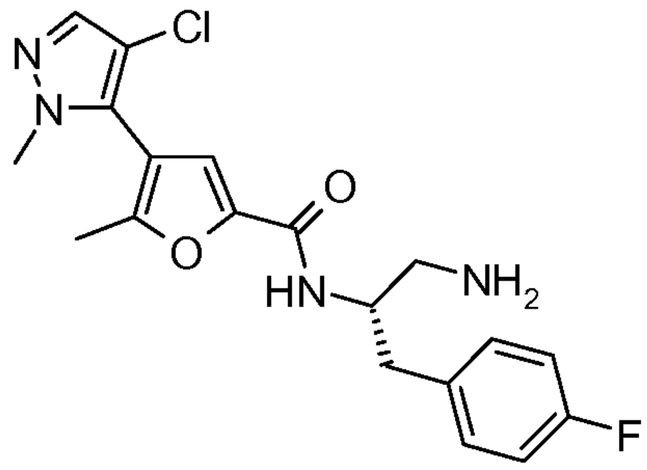
To a 50 mL round-bottomed flask was added 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (148 mg, 0.62 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (242 mg, 0.63 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (356 mg, 0.76 mmol) in Chloroform (6 mL). DIEA (550 µL, 3.15 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (303 mg, 0.51 mmol, 82%): LC-MS (ES) m/z = 569 $(M+H)^+$.

g) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (303 mg, 0.51 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL) . Hydrazine (110 µL, 3.50 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

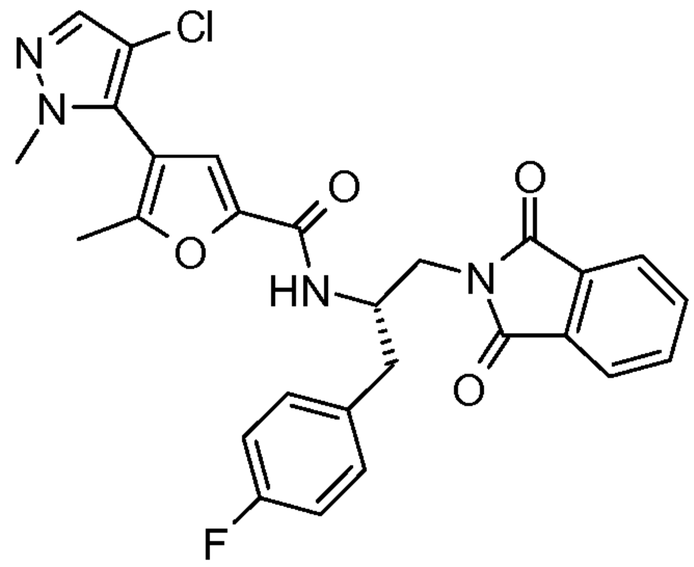
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (122 mg, 0.23 mmol, 45 % yield): LC-MS (ES) m/z = 439 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.93 - 3.02 (m, 1 H) 3.03 - 3.14 (m, 3 H) 3.82 (s, 3 H) 3.98 (s, 3 H) 4.41 - 4.53 (m, 1 H) 6.32 (s, 1 H) 7.38 - 7.49 (m, 2 H) 7.52 - 7.63 (m, 2 H) 7.68 (d, *J*=7.58 Hz, 1 H) 8.01 (s, 1 H) 8.17 (s, 3 H) 8.93 (d, *J*=8.84 Hz, 1 H).

Example 186



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (248 mg, 0.97 mmol) [prepared according to the procedure of Example 184], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (321 mg, 0.96 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (557 mg, 1.19 mmol) in chloroform (9.5 mL). DIEA (840 µL, 4.81 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (167 mg, 0.26 mmol, 67%): LC-MS (ES) m/z = 521 $(M+H)^+$.

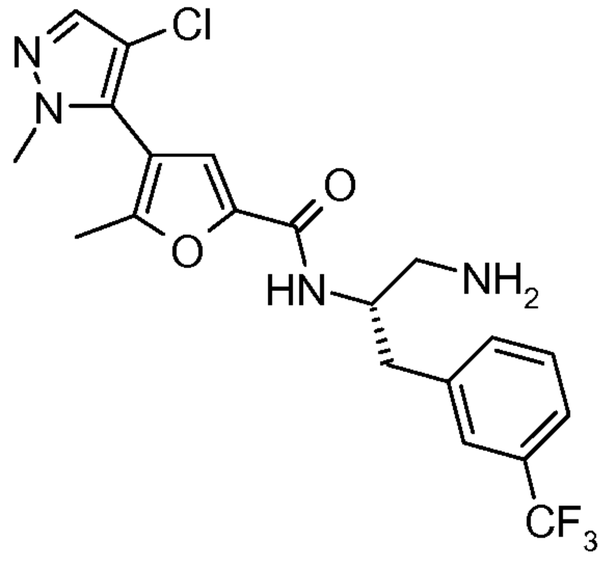
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide (144 mg, 0.27 mmol) in Tetrahydrofuran (THF) (2.5 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (100 mg, 0.21 mmol, 74 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3 H) 2.83 - 2.93 (m, 2 H) 2.94 - 3.04 (m, 2 H) 3.73 (s, 3 H)

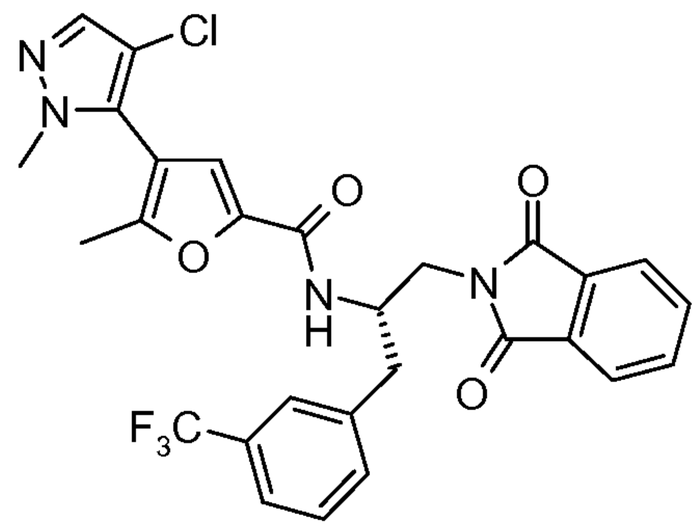
4.32 - 4.44 (m, 1 H) 7.12 (t, *J*=8.59 Hz, 2 H) 7.25 - 7.33 (m, 2 H) 7.35 (s, 1 H) 7.67 (s, 1 H) 8.07 (s, 3 H) 8.57 (d, *J*=8.59 Hz, 1 H).

Example 187



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (230 mg, 0.90 mmol) [prepared according to the procedure of Example 184], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (348 mg, 0.90 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (502 mg, 1.07 mmol) in chloroform (8.5 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture

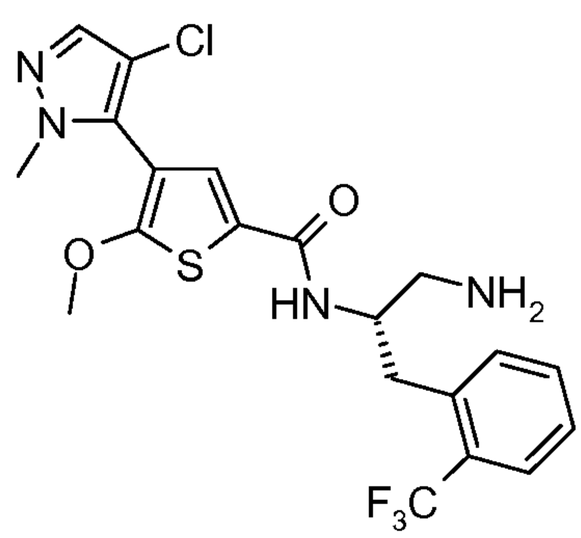
was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 0.43 mmol, 48%): LC-MS (ES) m/z = 571 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (247 mg, 0.433 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

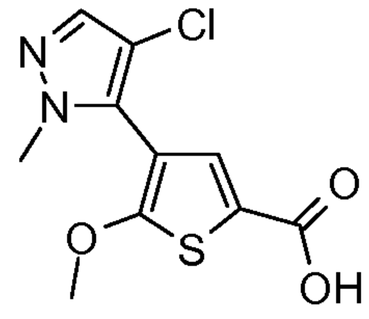
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (206 mg, 0.38 mmol, 88 % yield): LC-MS (ES) m/z = 441 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.30 (s, 3 H) 2.97 - 3.08 (m, 4 H) 3.71 (s, 3 H) 4.35 - 4.49 (m, 1 H) 7.36 (s, 1 H) 7.54 (dt, *J*=19.20, 7.20 Hz, 3 H) 7.62 - 7.68 (m, 2 H) 8.14 (s, 3 H) 8.65 (d, *J*=8.84 Hz, 1 H).

Example 188



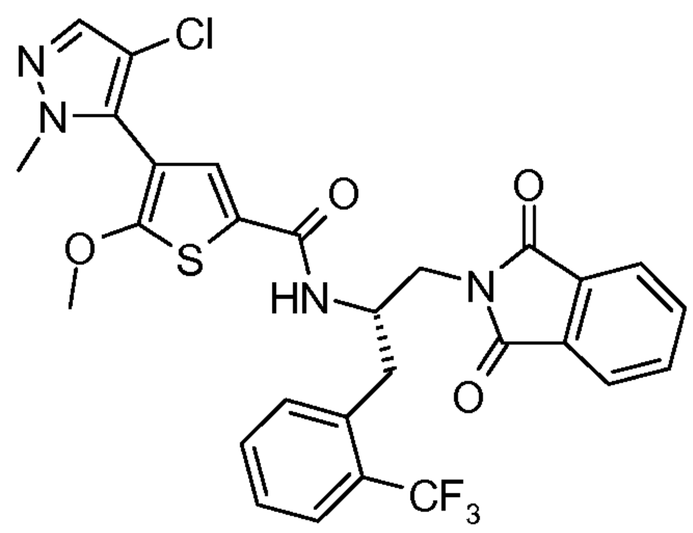
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid



NCS (382 mg, 2.80 mmol) was added in portions to a 50 mL sealed tube reactor containing methyl 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (642 mg, 2.54 mmol) [prepared according to the procedure of Example 185] in Tetrahydrofuran (THF) (12 mL) at room temperature. The mixture was heated to 70 °C for 1 hour. The reaction was cooled to room temperature, 6N NaOH (10 mL, 60.0 mmol) was added and the mixture stirred an additional 3h at 70 °C. The mixture was partitioned between $CHCl_3$ and H_2O and the aqueous layer was made acidic with 6N HCl. The organic layer was dried over Na_2SO_4 and concentrated affording the title compound (759 mg, 2.51 mmol, 98%) which was used without further purification: LC-MS (ES) m/z = 273 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (85 mg, 0.31 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (119 mg, 0.31 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (180 mg, 0.384 mmol) in chloroform (3.5 mL). DIEA (270 µL, 1.54 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70%

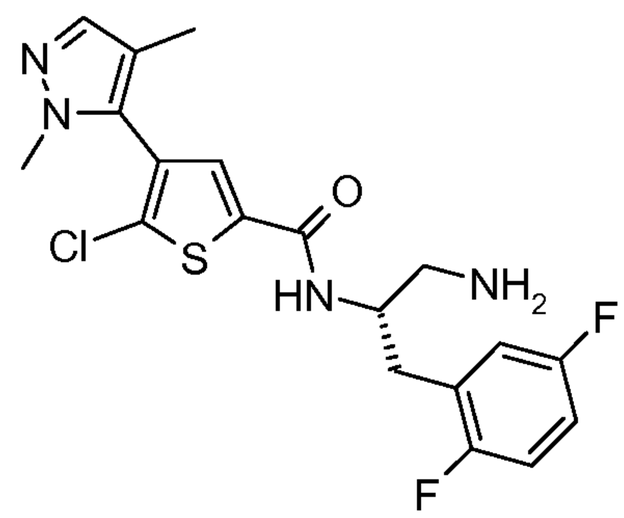
EtOAc/Hex) affording the title compound (94 mg, 0.14 mmol, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide (94 mg, 0.16 mmol) in Tetrahydrofuran (THF) (2 mL) and Methanol (1 mL). Hydrazine (35 µL, 1.12 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

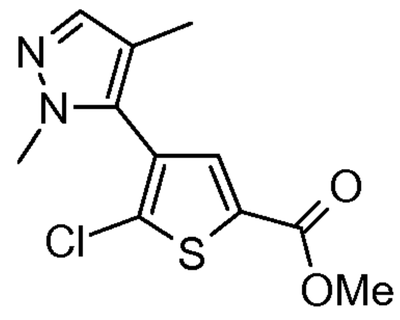
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (27 mg, 0.05 mmol, 31 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.93 - 3.14 (m, 4 H) 3.73 (s, 3 H) 4.00 (s, 3 H) 4.41 - 4.54 (m, 1 H) 7.43 (t, *J*=7.45 Hz, 1 H) 7.57 (ddd, *J*=14.59, 7.58, 7.39 Hz, 2 H) 7.62 - 7.65 (m, 1 H) 7.69 (d, *J*=7.83 Hz, 1 H) 7.82 - 7.89 (m, 1 H) 8.12 (s, 3 H) 8.80 (d, *J*=9.09 Hz, 1 H).

Example 189



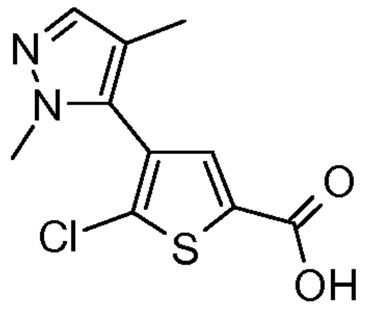
Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



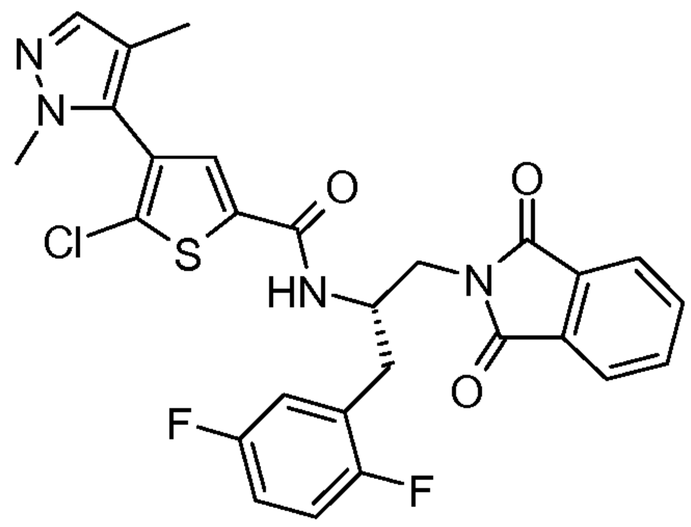
To a 350 mL sealed flask reactor was added methyl 4-bromo-5-chloro-2-thiophenecarboxylate (409 mg, 1.60 mmol) [prepared according to the procedure of Example 95], 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (388 mg, 1.75 mmol) [prepared according to the procedure of Preparation 17], K_2CO_3 (676 mg, 4.89 mmol) and $Pd(PtBu_3)_2$ (32 mg, 0.06 mmol) in 1,4-Dioxane (6 mL) and water (1.5 mL). The reaction was heated at 85 °C for 3 hours. The reaction was partitioned between $CHCl_3$ / H_2O and the pH of the aqueous layer was adjusted to ~3 with 6N HCl. The separated organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (10-65% EtOAc/Hexanes) affording the title compound (106 mg, 0.39 mmol, %); LC-MS (ES) m/z = 271 $(M+H)^+$.

b) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (106 mg, 0.39 mmol) in Tetrahydrofuran (THF) (2 mL). 6N NaOH (2 mL, 12.00 mmol) was added slowly and the reaction mixture stirred overnight at 70 °C. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried over Na_2SO_4 and concentrated affording the desired compound (96 mg, 0.37 mmol, 95%): LC-MS (ES) m/z = 257 $(M+H)^+$.

c) 5-chloro-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (96 mg, 0.37 mmol), 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (125 mg, 0.40 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (225 mg, 0.48 mmol) in chloroform (4 mL). DIEA (330 µL, 1.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (98 mg, 0.13 mmol, 34%): LC-MS (ES) m/z = 535 $(M+H)^+$.

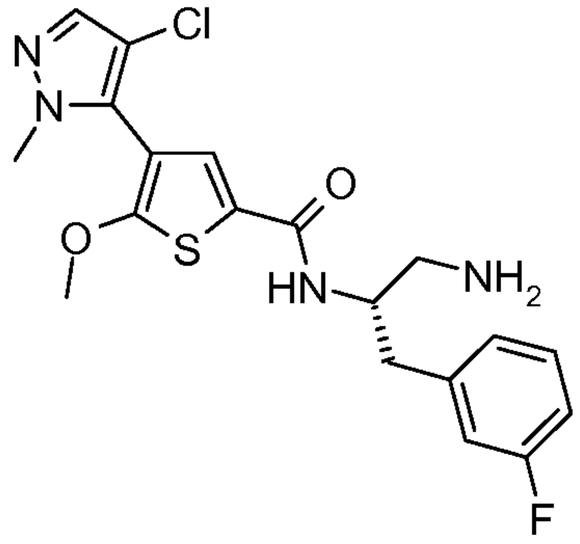
d) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (98 mg, 0.18 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 CHCl3/MeOH/NH4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (52 mg, 0.10 mmol, 56 % yield): LC-MS (ES) m/z = 425 (M+H)+, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.94 (s, 3 H) 2.87 - 3.09 (m, 4 H) 3.69 (s, 3 H) 4.42 (d, J=6.32 Hz, 1 H) 7.10 (ddd, J=12.00, 8.34, 3.41 Hz, 1 H) 7.20 (td, J=9.16, 4.67 Hz, 1 H) 7.27

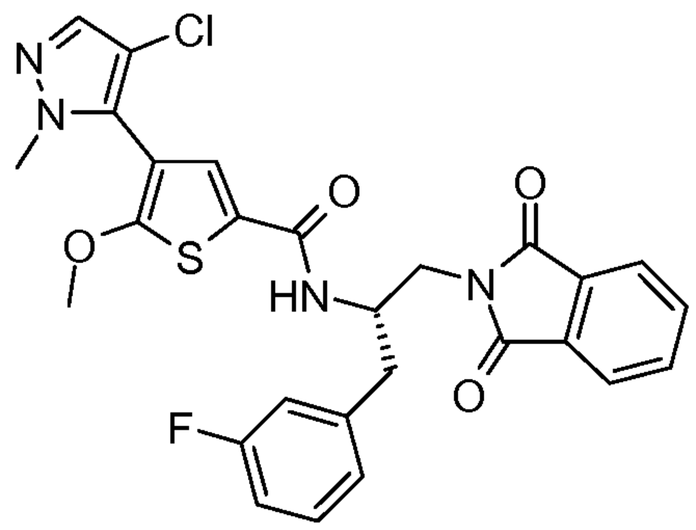
(ddd, J=8.97, 5.56, 3.16 Hz, 1 H) 7.39 (s, 1 H) 8.06 (s, 1 H) 8.13 (s, 3 H) 9.13 (d, J=8.84 Hz, 1 H).

Example 190



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (220 mg, 0.81 mmol) [prepared according to the procedure of Example 188], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (281 mg, 0.84 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (472 mg, 1.0 mmol) in Chloroform (8 mL). DIEA (710 µL, 4.07 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed

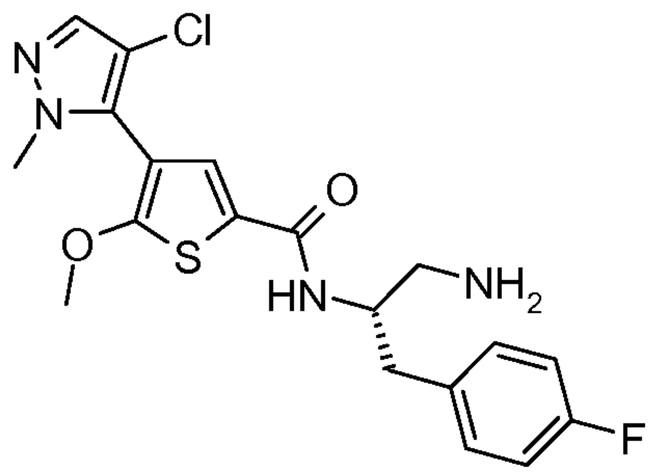
onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (281 mg, 0.51 mmol, 63%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide (281 mg, 0.51 mmol) in Tetrahydrofuran (THF) (4.5 mL) and Methanol (1 mL). Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

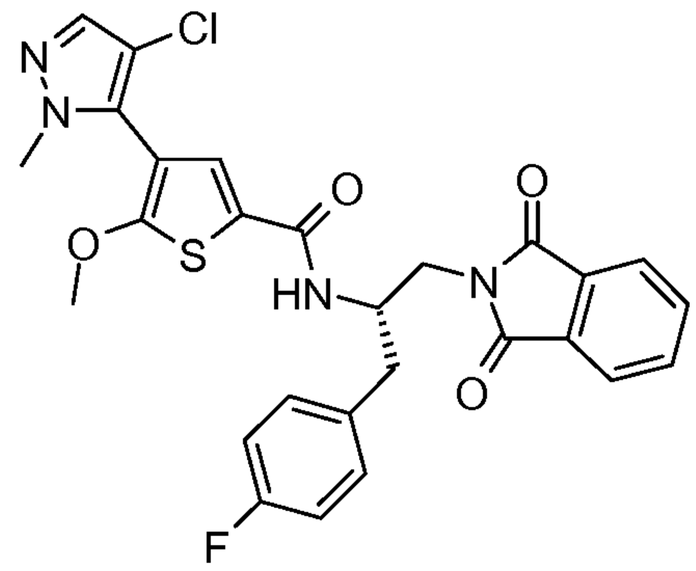
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (145 mg, 0.28 mmol, 55 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 - 3.04 (m, 4 H) 3.71 (s, 3 H) 4.02 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 (d, *J*=7.58 Hz, 2 H) 7.28 - 7.36 (m, 1 H) 7.64 (s, 1 H) 7.73 - 7.78 (m, 1 H) 7.98 (s, 3 H) 8.54 (s, 1 H).

Example 191



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide



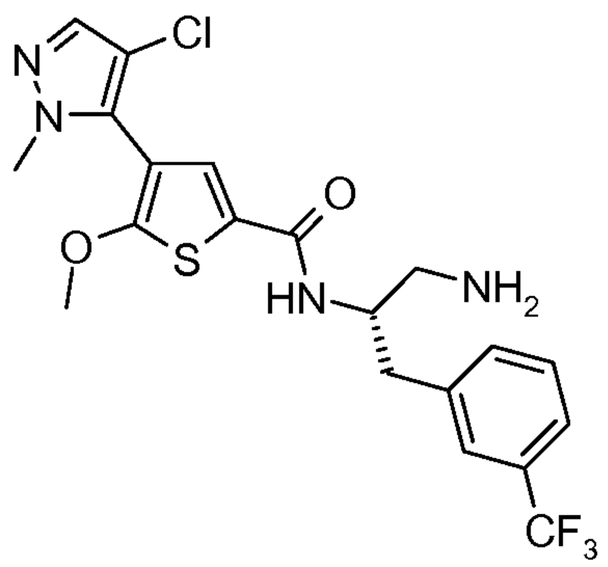
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (208 mg, 0.76 mmol) [prepared according to the procedure of Example 188], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (257 mg, 0.77 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (435 mg, 0.93 mmol) in chloroform (7.6 mL). DIEA (670 µL, 3.84 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (238 mg, 0.43 mmol, 56%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide (238 mg, 0.43 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

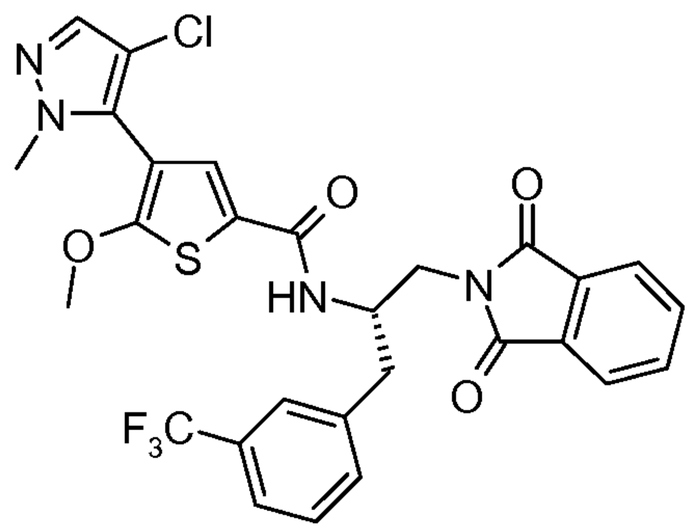
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (113 mg, 0.22 mmol, 50 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 - 2.92 (m, 2 H) 2.93 - 3.03 (m, 2 H) 3.71 (s, 3 H) 4.02 (s, 3 H) 4.26 - 4.37 (m, 1 H) 7.11 (t, *J*=8.46 Hz, 2 H) 7.26 - 7.32 (m, 2 H) 7.64 (s, 1 H) 7.69 - 7.84 (m, 1H) 7.95 (s, 3 H) 8.45 - 8.52 (m, 1H).

Example 192



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (210 mg, 0.77 mmol) [prepared according to the procedure of Example 188], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (294 mg, 0.764 mmol)

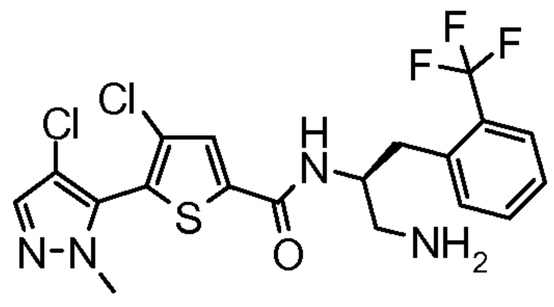
[prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (442 mg, 0.94 mmol) in chloroform (7.6 mL). DIEA (670 µL, 3.84 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (238 mg, 0.43 mmol, 56%): LC-MS (ES) m/z = 603 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide (203 mg, 0.34 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (80 µL, 2.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

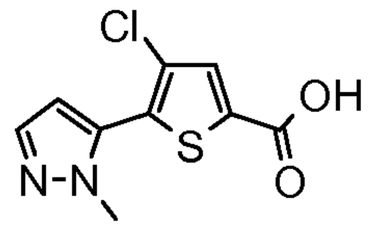
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (86 mg, 0.15 mmol, 44 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 - 3.08 (m, 4 H) 3.70 (s, 3 H) 4.01 (s, 3 H) 4.30 - 4.42 (m, 1 H) 7.50 - 7.60 (m, 3 H) 7.61 - 7.66 (m, 2 H) 7.73 - 7.81 (m, 1H) 8.00 (s, 3 H) 8.52 - 8.68 (m, 1H).

Example 193



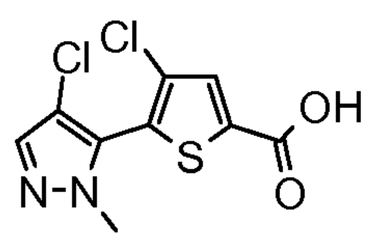
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-chloro-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



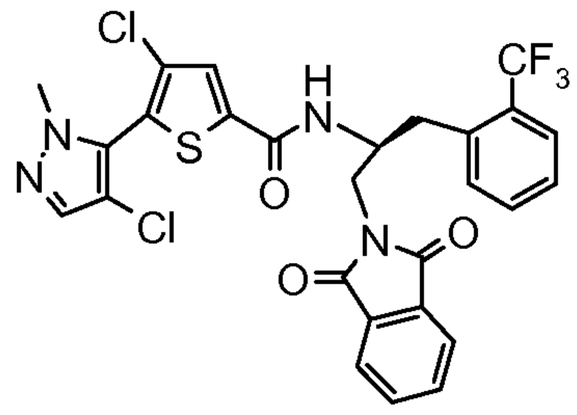
To a solution of 5-bromo-4-chloro-2-thiophenecarboxylic acid (482 mg, 2 mmol) in dioxane/H_2O (4:1, 10 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro Palladium (II) dichloromethane complex (16.3 mg, 0.02 mmol), potassium carbonate (828 mg, 6 mmol) and 5-(5,5-dimethyl-1,3,2-dooxaborinan-2-yl)-1-methyl-1*H*-pyrazole (832 mg, 4 mmol)[prepared according to Preparation 7]. The reaction mixture was heated to 80 °C in a sealed tube for 20 hrs. The reaction mixture was poured into H_2O (100 mL) and extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated and purified using silica (EtOAc / hexane (0 – 45% gradient)) affording the title compound as a white solid (401.7 mg, 83%): LC-MS (ES) m/z= 243 $(M+H)^+$.

b) 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of 4-chloro-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (121 mg, 0.5 mmol) and N-chlorosuccinimide (67mg, 0.5 mmol) in THF (5 mL) was stirred in a sealed tube at 70 °C. After 4 hrs, the solution was concentrated and partitioned between DCM and H_2O. The aqueous layer was extracted several times with DCM. The organic fractions were combined, concentrated and azeotropically dried with toluene to give the title compound as a brown oil (136 mg, 98%): LC-MS (ES) m/z= 278 $(M+H)^+$.

c). 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

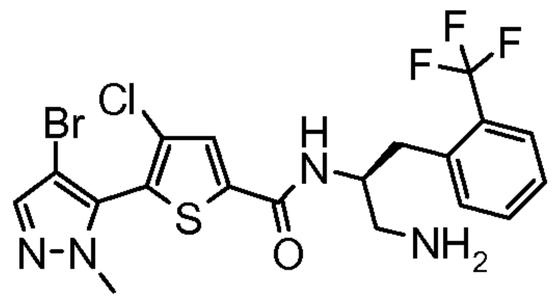


To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (136.1 mg, 0.49 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (179 mg, 0.51 mmol)[prepared according to Preparation 6], diisopropylethyl amine (260 uL, 1.5 mmol) in DCM (5 mL) was added PyBrop (341 mg, 0.75 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (242 mg, 82%) as a white solid: LCMS (ES) m/z = 607 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (242 mg, 0.4 mmol) in THF-MeOH (1:1, 4 mL) was added hydrazine (75 uL, 2.42 mmol). After 12h, the solution was concentrated. The resulting residue was partitioned between DCM and H_2O. The organics were washed three times with water and acidified to pH ~ 1 with 6N aqueous HCl solution. The resulting mixture was extracted with water. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the desired product as a light yellow solid (77 mg, 40%): LCMS (ES) m/z 477 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.08-3.11 (m, 4 H) 3.75 (s, 3 H) 4.50 (br. s., 1 H) 7.45 (t, *J*=6.95 Hz, 1H) 7.55 - 7.63 (m, 2H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.78 (s, 1 H) 8.02 - 8.10 (m, 3 H) 8.12 (s, 1 H) 9.12 (d, *J*=9.09 Hz, 1 H)

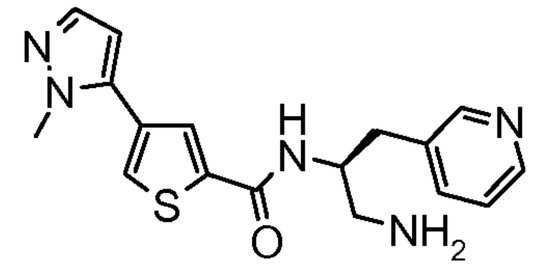
Example 194



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 193, except substituting N-bromosuccinimide (89 mg, 0.5 mmol) for and N-chlorosuccinimide: LCMS (ES) m/z 522 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0-3.13 (m, 4 H) 3.76 (s, 3 H) 4.50 (br. s., 1 H) 7.46 (d, *J*=7.58 Hz, 1 H) 7.55 - 7.66 (m, 2 H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.78 (s, 1 H) 8.04 (br. s., 4 H).

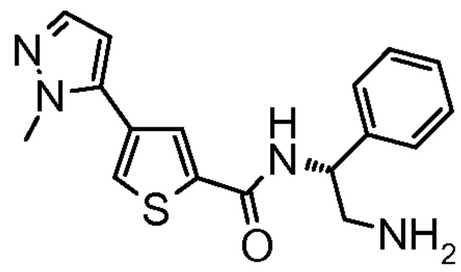
Example 195



Preparation of *N*-[(1*S*)-2-amino-1-(3-pyridinylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (62 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione -HCl (84 mg, 0.3 mmol)[prepared according to Preparation 19] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 342 $(M+H)^+$, ^{1}H NMR (CD_3OD, 400 MHz) δ ppm 3.17 (dd, *J*=13.89, 10.86 Hz, 1 H) 3.33 - 3.36 (m, 2 H) 3.36 - 3.44 (m, 1 H) 3.96 (s, 3 H) 4.70 (dd, *J*=14.02, 6.19 Hz, 1 H) 6.47 (s, 1 H) 7.51 (s, 1 H) 7.88 (d, *J*=1.26 Hz, 1 H) 7.94 (s, 1 H) 8.02 (t, *J*=6.32 Hz, 1 H) 8.61 (d, *J*=7.83 Hz, 1 H) 8.76 (br. s., 1 H) 8.89 (br. s., 1 H).

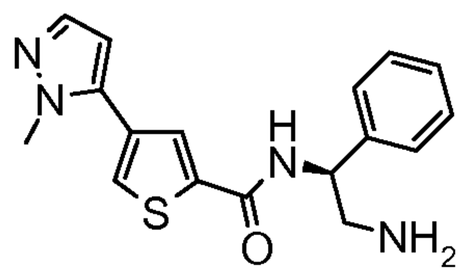
Example 196



Preparation of *N*-[(1*R*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (83 mg, 0.4 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [(2*R*)-2-amino-2-phenylethyl]carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z = 327 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.44 (d, *J*=4.29 Hz, 1 H) 3.63 (br. s., 1 H) 4.18 (s, 3 H) 5.47 (dd, *J*=10.36, 4.55 Hz, 1 H) 6.88 (d, *J*=2.78 Hz, 1 H) 7.38 (d, *J*=7.07 Hz, 1 H) 7.44 (t, *J*=7.33 Hz, 2 H) 7.55 (d, *J*=7.83 Hz, 2 H) 8.08 (d, *J*=2.53 Hz, 1 H) 8.18 (d, *J*=1.26 Hz,1 H) 8.42 (d, *J*=1.26 Hz, 1 H).

Example 197

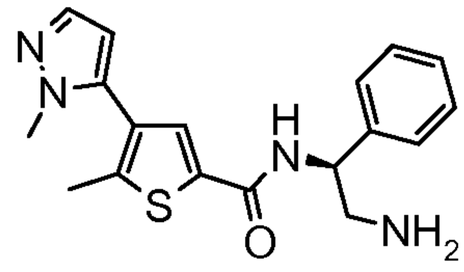


Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (83 mg, 0.4 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 327 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ

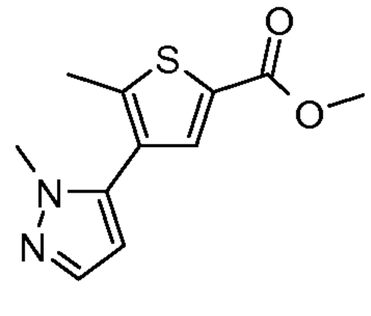
ppm 3.44 (d, J=2.78 Hz, 1 H) 3.60 (br. s., 1 H) 4.06 (br. s., 3 H) 5.47 (dd, J=10.36, 4.29 Hz, 1 H) 6.70 (br. s., 1 H) 7.38 (d, J=6.82 Hz, 1 H) 7.44 (t, J=7.20 Hz, 2 H) 7.53 (d, J=7.58 Hz, 2 H) 7.79 (br. s., 1 H) 8.04 (br. s.,1 H) 8.32 (br. s., 1 H).

Example 198



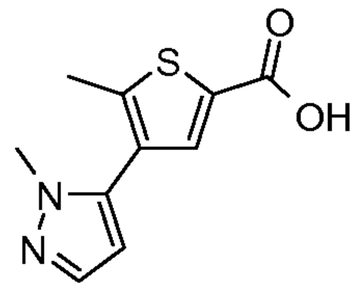
Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



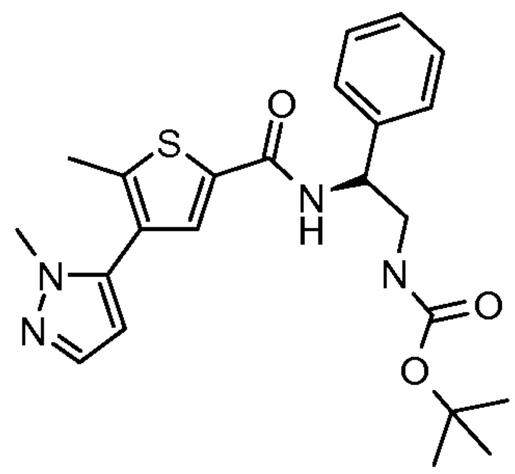
A solution of methyl 4-bromo-5-methyl-2-thiophenecarboxylate (2g, 8.51 mmol)[prepared in Preparation 10], potassium carbonate (5.88 g, 42.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.12 g, 10.21 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.22 g, 0.43 mmol) in 1,4-Dioxane (35 ml) and H_2O (7 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 25% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate. This reaction was run in several batches (1g, 3 x 2g) which were combined for workup and purification affording the title compound (5.5 g, 78% combined yield) as a viscous yellow oil: LC-MS (ES) m/e 236 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (94 mg, 0.4 mmol) in 6N sodium hydroxide (0.67 ml, 4 mmol) and tetrahydrofuran (4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~3 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the desired product (67 mg, 0.3 mmol, 75 % yield) as a yellow oil: LC-MS (ES) m/e 223 (M+H)+.

c) 1,1-dimethylethyl [(2S)-2-({[5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



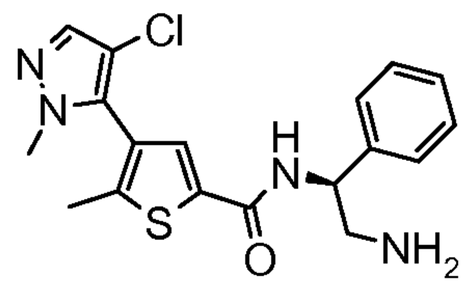
To a solution of 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (67 mg, 0.3 mmol), 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (71 mg, 0.3 mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.16 ml, 0.9 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (210 mg, 0.45 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (87 mg, 0.2 mmol, 65 % yield) as a yellow foam: LC-MS (ES) m/e 441 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (87 mg, 0.2 mmol) in DCM (2

mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol) which stirred at ambient temperature for 15 h. The solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (26 mg, 0.06 mmol, 32%): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.49 (br. s., 3 H) 3.43 (d, *J*=4.80 Hz, 1 H) 3.55 (d, *J*=10.36 Hz, 1 H) 3.95 (s, 3 H) 5.41-5.43 (m, 1 H) 6.66 (d, *J*=2.27 Hz, 1 H) 7.38 (d, *J*=7.07 Hz, 1 H) 7.44 (t, *J*=7.33 Hz, 2 H) 7.48 - 7.53 (m, 2 H) 7.94 - 8.02 (m, 2 H).

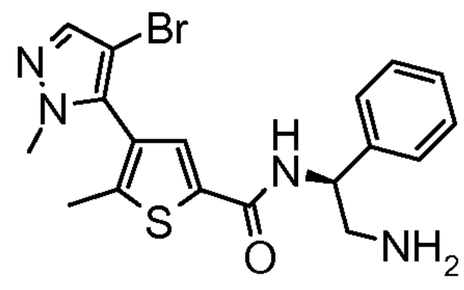
Example 199



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (89 mg, 0.4 mmol) [prepared according to Example 198] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.38-2.41 (m, 1H), 3.38 (d, *J*=1.52 Hz, 1 H) 3.49 (d, *J*=10.86 Hz, 1 H) 3.73 (br. s., 3 H) 5.41 (d, *J*=3.54 Hz, 1 H) 7.30 - 7.50 (m, 5 H) 7.54 - 7.62 (m, 1 H) 7.81 (br. s., 1 H).

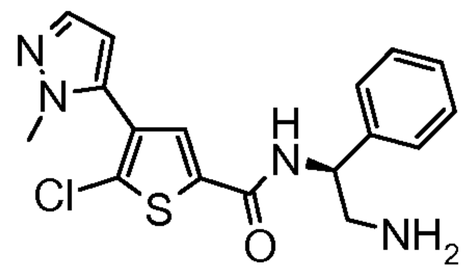
Example 200



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

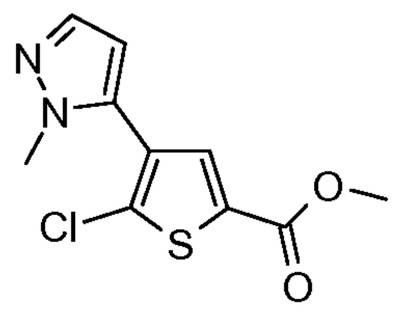
The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (168 mg, 0.5 mmol) [prepared according to Example 198] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid, N-bromosuccinimide (88.5 mg, 0.5 mmol) for N-chlorosuccinimide and 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (71 mg, 0.3 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.39 (d, *J*=4.04 Hz, 3 H) 3.42 (br. s., 1 H) 3.55 (br. s., 1 H) 3.75-3.78 (m, 3 H) 5.45 (m, 1 H) 7.37 (d, *J*=7.07 Hz, 1 H) 7.40 - 7.46 (m, 2 H) 7.49 (br. s., 2 H) 7.59 - 7.68 (m, 1 H) 7.80 - 7.88 (m, 1 H).

Example 201



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

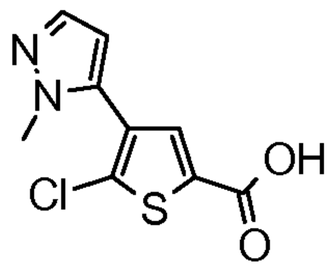
a) methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (2.56 g, 10.00 mmol)[prepared according to Example 95], 5-(5,5-dimethyl)-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (3.88 g, 20.0 mmol)[prepared according to Preparation 7], potassium carbonate (4.15 g, 30.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.073 g, 0.1 mmol) in 1,4-Dioxane (12 mL) and water (3.00 mL) were heated at 80 °C in a sealed tube. After 3 hrs, another batch of 5-(5,5-dimethyl)-1,3,2-

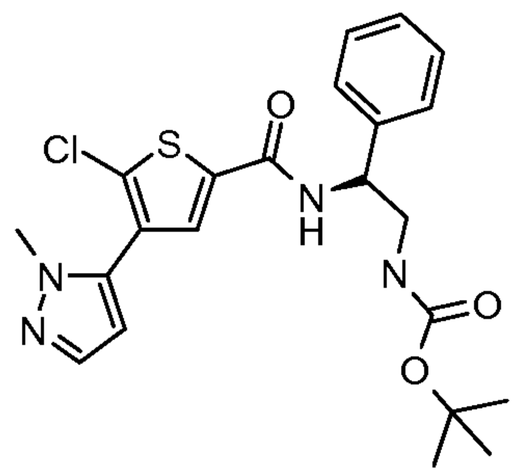
dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.94 g, 10.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.073 g, 0.1 mmol) were added. After 2 hr, the mixture was concentrated and purified by silica gel eluting with 0-35% ethyl acetate / hexane affording the title compound as a yellow solid (1.74 g, 3.35 mmol, 34%): LC-MS (ES) m/z 257 $(M+H)^+$.

b) 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (304 mg, 1.18 mmol) in 6N sodium hydroxide (2 ml, 12 mmol) and Tetrahydrofuran (10 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~3 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the desired product (276 mg, 1.14 mmol, 96 % yield) as a yellow oil: LC-MS (ES) m/e 244 $(M+H)^+$.

c) 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



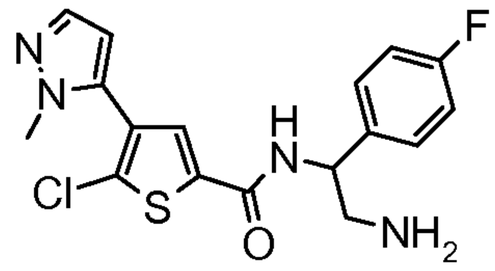
To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (60 mg, 0.25 mmol), 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (58 mg, 0.25 mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.12 ml, 0.75 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (190 mg, 0.41 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column

chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (90 mg, 0.20 mmol, 79 % yield) as a colorless oil: LC-MS (ES) m/e 461 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (90 mg, 0.20 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol). After 15 h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (63 mg, 0.14 mmol, 74%): : LC-MS (ES) m/z 361 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.41 (dd, *J*=13.01, 4.17 Hz, 1 H) 3.63 (d, *J*=10.86 Hz, 1 H) 4.08 (s, 3 H) 5.45 (dd, *J*=10.48, 4.17 Hz, 1 H) 6.87 (d, *J*=2.27 Hz, 1 H) 7.36 (d, *J*=7.33 Hz, 1 H) 7.42 (t, *J*=7.33 Hz, 2 H) 7.54 (d, *J*=7.07 Hz, 2 H) 8.14 (d, *J*=2.27 Hz, 1 H) 8.27 (s, 1 H).

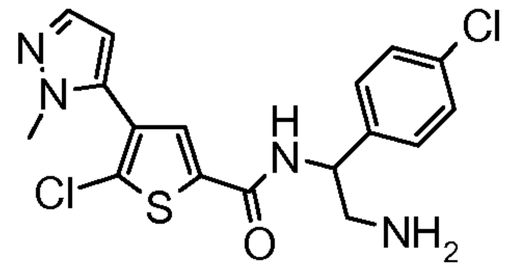
Example 202



Preparation of *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate (63 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 379 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.40 (dd, *J*=13.01, 4.42 Hz, 1 H) 3.66 (d, *J*=2.02 Hz, 1 H) 4.03 - 4.15 (m, 3 H) 5.46 (dd, *J*=10.36, 4.29 Hz, 1 H) 6.84 (d, *J*=2.53 Hz, 1H) 7.15 (t, *J*=8.72 Hz, 2 H) 7.60 (dd, *J*=8.59, 5.05 Hz, 2 H) 8.10 (d, *J*=2.53 Hz, 1 H) 8.29 (s, 1 H).

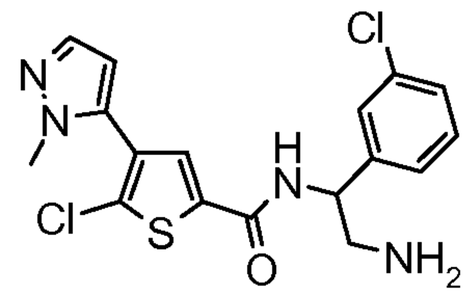
Example 203



Preparation of *N*-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(4-chlorophenyl)ethyl]carbamate (45 mg, 0.17 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.40 (d, *J*=4.55 Hz, 1 H) 3.58 (d, *J*=10.36 Hz, 1 H) 3.98 (s, 3 H) 5.41 (d, *J*=4.55 Hz, 1 H) 6.71 (s, 1 H) 7.43 (dt, *J*=4.74, 2.31 Hz, 2 H) 7.47 - 7.56 (m, 2 H) 7.92 (br. s., 1 H) 8.13 (s, 1 H).

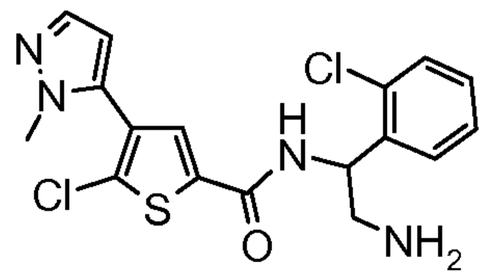
Example 204



Preparation of *N*-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.41 (dd, *J*=12.76, 4.93 Hz, 5 H) 3.36 - 3.47 (m, 3 H) 3.63 (s, 2 H) 3.59 (d, *J*=10.61 Hz, 6 H) 3.95 (s, 9 H) 4.02 (d, *J*=3.03 Hz, 15 H) 5.41 (dd, *J*=9.09, 3.79 Hz, 8 H) 6.67 (d, *J*=2.27 Hz, 3 H) 6.78 (br. s., 4 H) 7.33 - 7.49 (m, 23 H) 7.56 (br. s., 7 H) 8.06 (br. s., 8 H) 8.16 (d, *J*=16.93 Hz, 6 H).

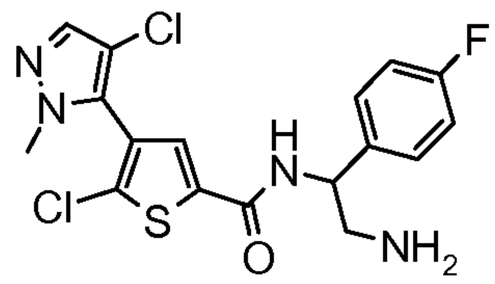
Example 205



Preparation of *N*-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

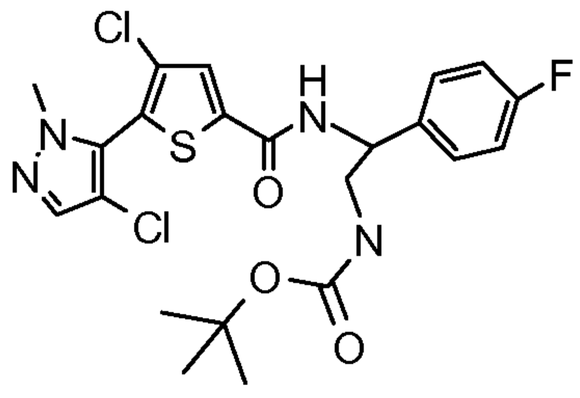
The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(2-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^{1}H NMR (CD_3OD, 400 MHz) δ ppm 3.39 (br. s., 1 H) 3.56 (d, *J*=10.86 Hz, 1 H) 4.05 (d, *J*=3.03 Hz, 3 H) 5.87 (dd, *J*=10.74, 3.41 Hz, 1 H) 6.81 (br. s., 1 H) 7.39 (br. s., 2 H) 7.50 (d, *J*=6.57 Hz, 1 H) 7.70 (d, *J*=7.07 Hz, 1 H) 8.04 (br. s., 1 H) 8.26 (br. s., 1 H).

Example 206



Preparation of *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-(4-fluorophenyl)ethyl]carbamate

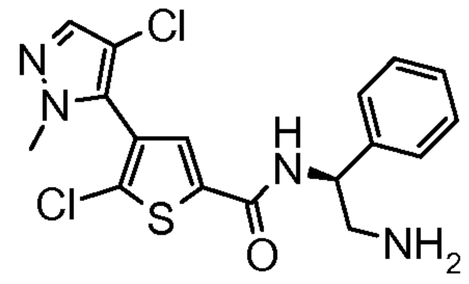


To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (67 mg, 0.24 mmol) [prepared according to Example 193], 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate (61 mg, 0.24 mmol) [prepared according to the procedure of Preparation 16], diisopropylethyl amine (126 uL, 0.72 mmol) in DCM (5 mL) was added PyBrop (168 mg, 0.36 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (93 mg, 0.18 mmol, 76%) as a white solid: LCMS (ES) m/z = 514 $(M+H)^+$.

b). *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [2-({[4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-(4-fluorophenyl)ethyl]carbamate (90 mg, 0.17 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.43 mL, 1.75 mmol). After 15h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (39.6 mg, 0.09 mmol, 52%): LC-MS (ES) m/z 414 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.42 (d, *J*=2.78 Hz, 1 H) 3.56 (br. s., 1 H) 3.79 (s, 3 H) 5.43 (dd, *J*=10.23, 4.67 Hz, 1 H) 7.11 - 7.22 (m, 2 H) 7.49 - 7.57 (m, 2 H) 7.60 (s, 1 H) 7.93 (br. s., 1 H).

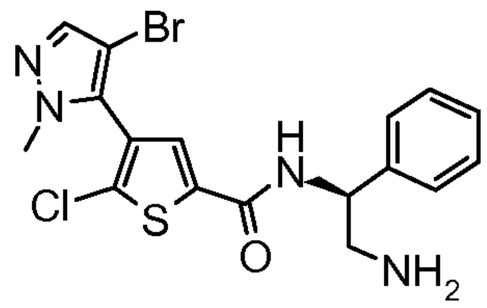
Example 207



Preparation *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

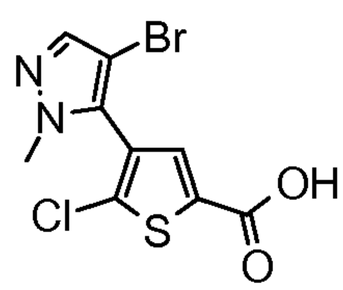
The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [(2S)-2-amino-2-phenylethyl]carbamate (57 mg, 0.24 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 396 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.42 (br. s., 1 H) 3.57 (d, *J*=11.12 Hz, 1H) 3.80 (s, 3 H) 5.44 (dd, *J*=10.36, 4.29 Hz, 1 H) 7.37 (d, *J*=2.53 Hz, 1 H) 7.40 - 7.47 (m, 2 H) 7.48 - 7.55 (m, 2 H) 7.60 (s, 1 H) 7.95 (br. s., 1 H).

Example 208



Preparation *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

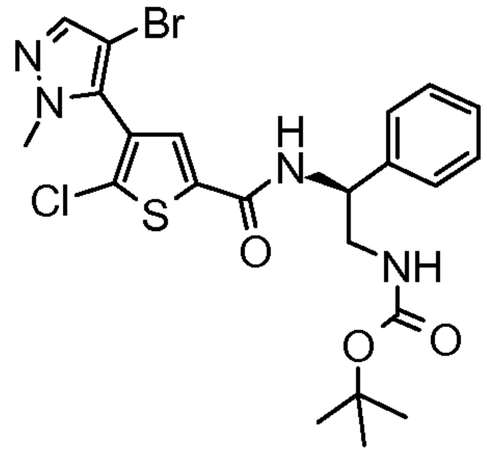
a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.169 mmol)[prepared according to the procedure of Example 193] in THF (10 ml) was added *N*-bromosuccinimide (212 mg, 1.19 mmol). The mixture was sealed and heated at 70 °C. After 2h, a solution of 6N NaOH (2.0 ml, 6.0 M, 11.84 mmol) was added in one portion. The resulting mixture

stirred for an additional 2h and was partitioned between DCM-H_2O. The pH of the aqueous phase was adjusted to ~3 and extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated affording the title compound as a colorless oil (105 mg, 28%): LC-MS (ES) m/z= 322 $(M+H)^+$.

b) 1,1-dimethylethyl [(2*S*)-2-({[4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



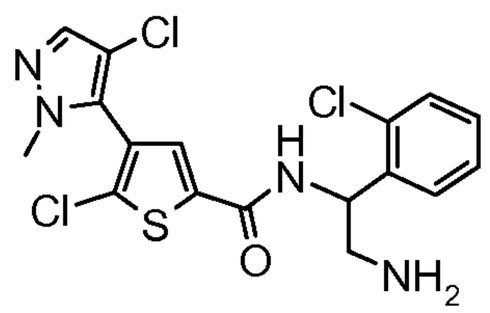
To a solution of 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (80 mg, 0.25 mmol), 1,1-dimethylethyl [(2S)-2-amino-2-phenylethyl]carbamate (59 mg, 0.25 mmol) [prepared according to the procedure of Preparation 1], diisopropylethyl amine (128 uL, 0.75 mmol) in DCM (5 mL) was added PyBrop (168 mg, 0.36 mmol) in one portion. After 3h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (110 mg, 0.18 mmol, 73%) as a white solid: LCMS (ES) m/z = 540 $(M+H)^+$.

c). *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (81 mg, 0.15 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.38 mL, 1.5 mmol) After 15h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (18.3 mg, 0.04 mmol, 26%): LC-MS (ES) m/z 440 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.40 (d, *J*=13.89 Hz, 1H) 3.60 (br. s., 1

H) 3.80 (br. s., 3 H) 5.38 - 5.50 (m, 1 H) 7.37 (d, *J*=7.33 Hz, 1 H) 7.43 (t, *J*=7.45 Hz, 2 H) 7.52 (d, *J*=7.58 Hz, 2 H) 7.61 (s, 1 H) 8.02 (br. s., 1 H)

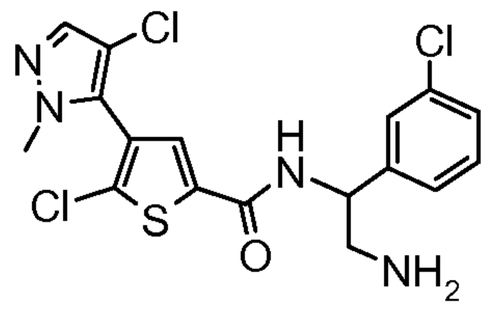
Example 209



Preparation *N*-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 430 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.45 (d, *J*=5.56 Hz, 2 H) 3.72 - 3.81 (m, 3 H) 5.86 (dd, *J*=9.22, 4.42 Hz, 1H) 7.41 (d, *J*=2.02 Hz, 2 H) 7.48 - 7.55 (m, 1 H) 7.58 (br. s., 2 H) 7.83 (s, 1 H)

Example 210

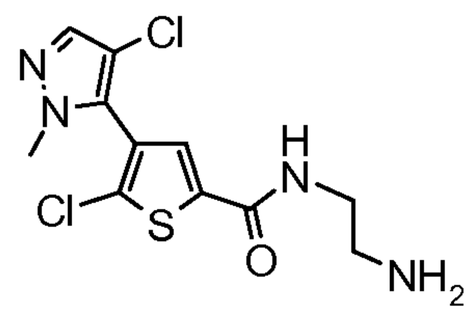


Preparation *N*-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.44 (d, *J*=3.54 Hz, 1 H) 3.55 (d, *J*=10.61 Hz, 1 H) 3.80 (s, 3 H) 5.42

(dd, *J*=10.36, 4.29 Hz, 1 H) 7.35 - 7.49 (m, 3 H) 7.55 (s, 1 H) 7.59 (s, 1 H) 7.95 (d, *J*=14.40 Hz, 1 H)

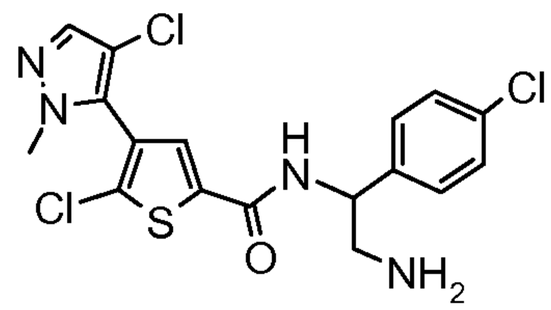
Example 211



Preparation *N*-(2-aminoethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl (2-aminoethyl)carbamate (58 mg, 0.36 mmol) for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 320 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.17 (d, *J*=5.81 Hz, 2 H) 3.66 (br. s., 2 H) 3.78 (s, 3 H) 7.60 (s, 1 H) 7.66 (s, 1H)

Example 212

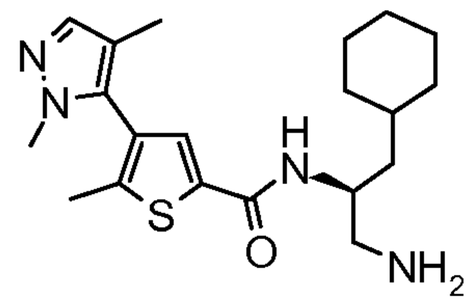


Preparation *N*-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(4-chlorophenyl)ethyl]carbamate (65 mg, 0.24 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 431 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.43 (d, *J*=4.55 Hz, 1 H) 3.53 (d, *J*=10.11 Hz, 1 H) 3.79 (s, 3 H) 5.43

(dd, *J*=10.36, 4.55 Hz, 1H) 7.43 - 7.47 (m, 2 H) 7.48 - 7.53 (m, 2 H) 7.60 (s, 1 H) 7.94 (s,1 H)

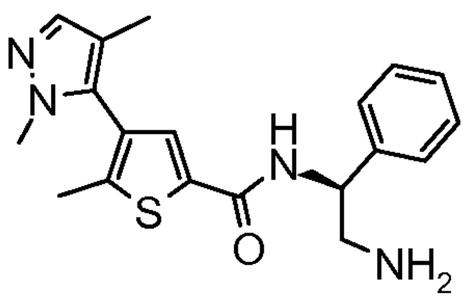
Example 213



Preparation *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

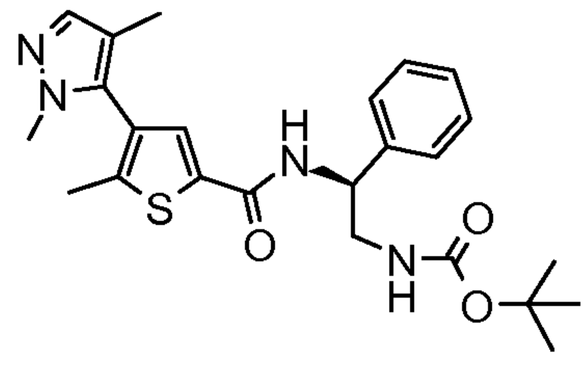
The title compound was prepared as an off-white solid according to the procedure of Example 99, except substituting 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (73 mg, 0.25 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 0.91- 0.99 (m, 1H), 1.01-1.10 (m., 1 H) 1.39-1.47 (m., 3 H) 1.37-1.48 (m, 2 H) 1.65 - 1.77 (m, 5 H) 1.89 (br. s., 1 H) 2.10 (s, 3 H) 2.45 (s, 3 H) 3.07 - 3.16 (m, 2 H) 3.91 - 3.98 (m, 3 H) 4.42 (br. s., 1 H) 7.91 (br. s., 1 H) 8.24 (s, 1 H)

Example 214



Preparation *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate

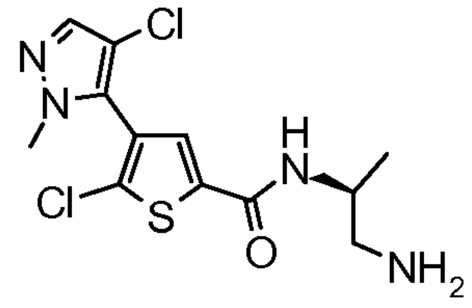


To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (110 mg, 0.4 mmol) [prepared in Experiment 99], 2-[(2S)-2-amino-4-methylpentyl]-1H-isoindole-1,3(2H)-dione (99 mg, 0.4mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.2 ml, 1.2 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (280 mg, 0.6 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (113 mg, 0.22 mmol, 56 % yield) as a colorless oil: LC-MS (ES) m/e 506 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (99 mg, 0.22 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol). After 15 h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as an off-white solid (40 mg, 0.11 mmol, 52%): LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.99 - 2.14 (m, 3 H) 2.43 (s, 3 H) 3.39 (d, *J*=9.85 Hz, 1 H)) 3.60 (d, *J*=9.85 Hz, 1 H) 3.92 (br. s., 3 H) 5.44 (d, *J*=8.84 Hz, 1 H) 7.36 (d, *J*=2.53 Hz, 1 H) 7.43 (t, *J*=5.94 Hz, 2 H) 7.49 - 7.57 (m, 2 H) 8.03 (br. s., 1 H) 8.14 (br. s., 1H).

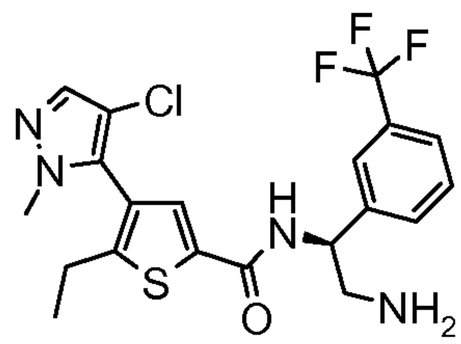
Example 215



Preparation *N*-[(1*S*)-2-amino-1-methylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-aminopropyl]-1H-isoindole-1,3(2H)-dione (74 mg, 0.36 mmol) for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 333 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.37 (d, *J*=6.82 Hz, 3 H) 3.11 - 3.14 (m, 2 H) 3.79 (s, 3 H) 4.38 – 4.40 (m, 1 H) 7.60 (br. s., 1 H) 7.83 (d, *J*=2.27 Hz, 1 H).

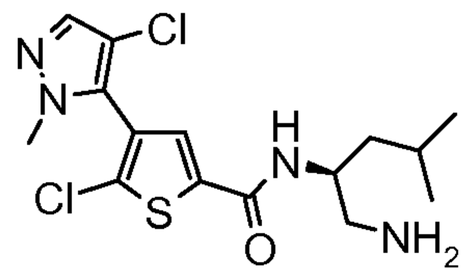
Example 216



Preparation *N*-{(1*S*)-2-amino-1-[3-(trifluoromethyl)phenyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 100, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (348 mg, 1.0 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 471 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.24 (t, *J*=7.33 Hz, 3 H) 2.54 (d, *J*=8.84 Hz, 2 H) 2.74 (q, *J*=7.24 Hz, 2 H) 3.05 - 3.16 (m, 1 H) 3.26 (d, *J*=4.80 Hz, 1 H) 3.66 - 3.79 (m, 3 H) 4.54 (br. s., 1 H) 7.47 - 7.56 (m, 2 H) 7.57 - 7.76 (m, 4 H).

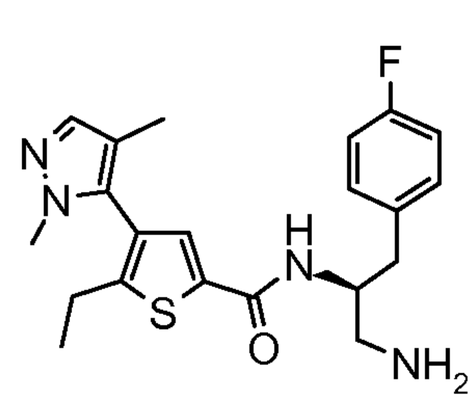
Example 217



Preparation *N*-[(1*S*)-1-(aminomethyl)-3-methylbutyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

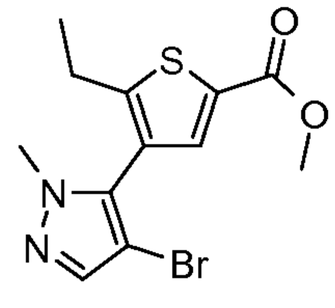
The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-amino-4-methylpentyl]-1H-isoindole-1,3(2H)-dione (99 mg, 0.4 mmol) for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 376 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 0.99 (t, *J*=6.44 Hz, 6 H) 1.42 (s, 1 H) 1.63 - 1.80 (m, 2 H) 3.04 (br. s., 1 H) 3.14 (d, *J*=3.54 Hz, 1 H) 3.80 (s, 3 H) 4.42 (br. s., 1 H) 7.59 (s, 1 H) 7.84 (d, *J*=6.06 Hz, 1 H).

Experiment 218



Preparation *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

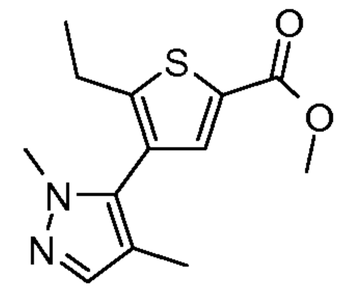
a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



To a solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (600 mg, 2.40 mmol) [prepared according to Example 98] in Tetrahydrofuran (THF) (10 ml) was added N-bromosuccinimide (512 mg, 2.88 mmol). The mixture stirred in a sealed tube at 70 °C for 2h. The reaction mixture was then concentrated and purified with silica gel using a 0-5% gradient (ethyl

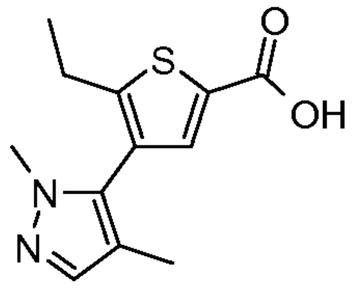
acetate / hexane) to afford the title compound as an off-white solid: LC-MS (ES) m/z 330 $(M+H)^+$.

b) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



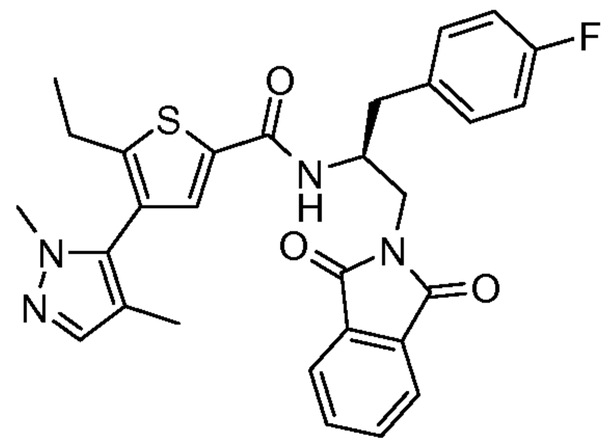
A solution of methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (635 mg, 1.93 mmol), potassium carbonate (1.33 g, 9.64 mmol), $PdCl_2$(dppf) (141 mg, 0.19 mmol) and trimethylboroxine (0.54 ml, 3.86 mmol) in N,N-dimethylformamide (3 ml) was stirred at 110 °C in a sealed tube for 2h. This reaction mixture was concentrated and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording the title compound (488 mg, 96%) as a yellow oil: LCMS (ES) m/e 265 (M+H)+.

c) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



A solution of methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (488 mg, 1.85 mmol) in 6N sodium hydroxide (3.08 ml, 18.5 mmol) and Tetrahydrofuran (10 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound as a yellow foam (448 mg, 1.79 mmol, 96 % yield) as a yellow oil: LCMS (ES) m/e 251(M+H)+.

d) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-ethyl-2-thiophenecarboxamide

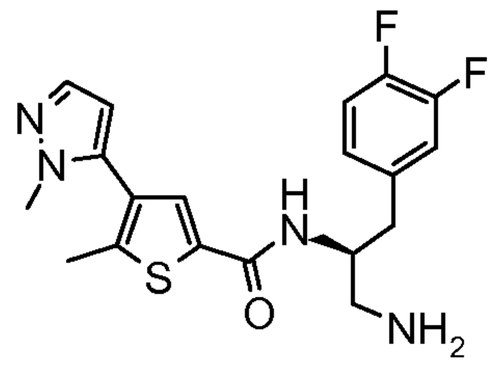


To a solution of 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (250 mg, 1.0 mmol), 2-{(2S)-2-amino-3-[4-(fluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (313 mg, 1.05 mmol)[prepared according to the procedure of Preparation 6] and diisopropylethylamine (0.52 ml, 3 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (746 mg, 1.6 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound as a yellow solid (490 mg, 0.92 mmol, 92 % yield) as a yellow foam: LCMS (ES) m/e 531 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

To a solution of 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-ethyl-2-thiophenecarboxamide (400 mg, 0.75 mmol) in methanol (8 ml) at 25 °C was added hydrazine (0.12 ml, 3.77 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as a yellow solid: LC-MS (ES) m/z 401 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.58 Hz, 3 H) 2.07 (s, 3 H) 2.75 (m, 2 H) 3.02 (d, *J*=6.32 Hz, 2 H) 3.22 (br. s., 2 H) 3.92 (d, *J*=2.27 Hz, 3 H) 4.53 (br. s., 1 H) 7.02 (t, *J*=8.59 Hz, 2 H) 7.34 (m, 2H), 7.80 (s, 1 H) 8.13 - 8.25 (m, 1 H).

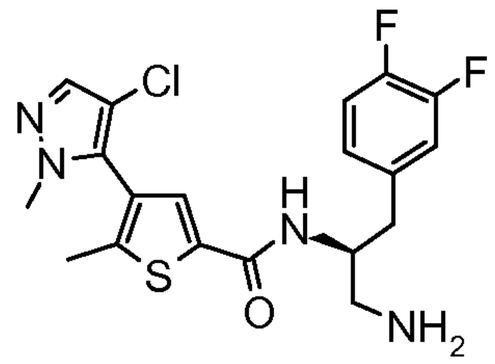
Example 219



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 103, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 391 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.44 (s, 3 H) 2.91 - 3.02 (m, 2 H) 3.16 (d, *J*=10.11 Hz, 1 H) 3.24 (dd, *J*=13.14, 3.54 Hz, 1H) 3.82 (s, 3 H) 4.50 (d, *J*=3.54 Hz, 1 H) 6.44 (d, *J*=2.02 Hz, 1H) 7.05 - 7.13 (m, 1 H)7.15-7.25 (m, 2H), 7.67-7.70 (m, 2 H) .

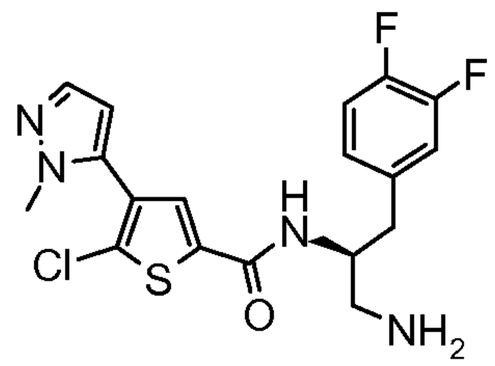
Example 220



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 102, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 425 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.40 (s, 3 H) 2.95 - 3.03 (m, 2 H) 3.23 - 3.26 (m, 2 H) 3.76 (br, s, 3H) 4.96 - 4.52 (m, 1H), 7.07 - 7.15 (m, 2H) 7.22 -7.28 (m, 1H) 7.55 - 7.77 (m, 2H).

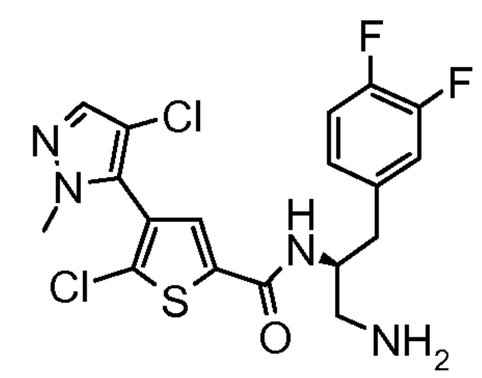
Example 221



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 104, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 411 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.02 (d, *J*=7.33 Hz, 2 H) 3.24 (d, *J*=6.82 Hz, 2 H) 4.01 (d, *J*=7.58 Hz, 3 H) 4.52 (d, *J*=7.07 Hz, 1 H) 6.78 (d, *J*=11.87 Hz, 1 H) 7.08 - 7.21 (m, 1 H) 7.26 - 7.28 (m, 1 H) 7.94 - 8.08 (m, 2 H).

Example 222

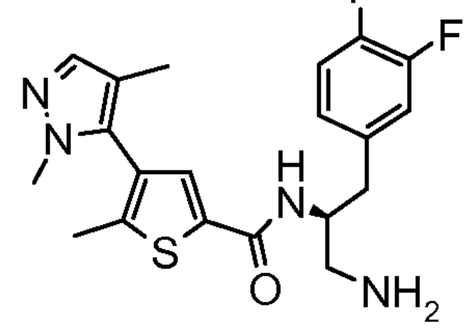


Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 446 $(M+H)^+$, ^1H

NMR (400 MHz, MeOD) δ ppm 2.95 - 3.05 (m, 2 H) 3.22 - 3.23 (m, 2 H) 3.79 (s, 3 H) 4.52 (br. s., 1 H) 7.08 - 7.21 (m, 2 H) 7.27 - 7.26 (m, 2 H) 7.60 (s, 1 H) 7.83 (br. s., 1 H) .

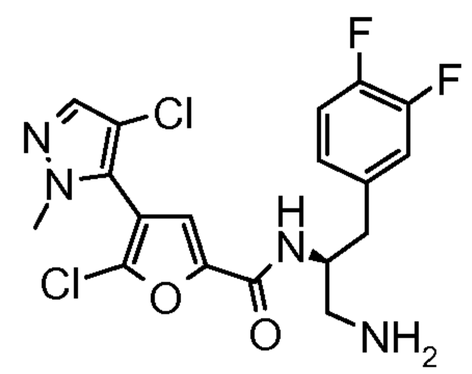
Example 223



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

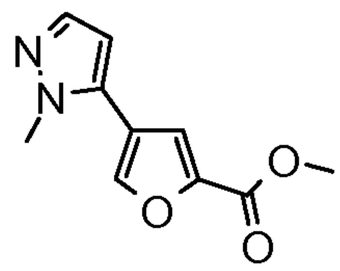
The title compound was prepared as a yellow solid according to the procedure of Example 99, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [prepared according to Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 405 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.09 (s, 15 H) 2.42 (s, 3 H) 3.04 (d, *J*=7.07 Hz, 2 H) 3.27 (d, *J*=4.80 Hz, 2 H) 3.88 - 4.01 (m, 3H) 4.54 (br. s., 1 H) 7.08 - 7.21 (m, 2 H) 7.29 (d, *J*=7.58 Hz, 1 H) 7.92 (br. s., 1H) 8.15 - 8.26 (m, 1 H).

Example 224



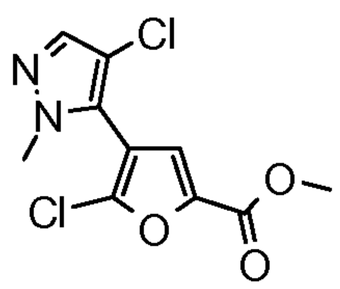
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



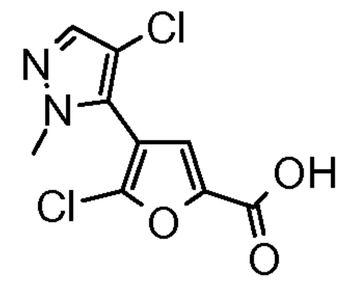
A solution of methyl 4-bromo-2-furancarboxylate (470 mg, 2.29 mmol), potassium carbonate (1584 mg, 11.46 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (525 mg, 2.52 mmol)[prepared according to Preparation 7] and bis-(tri-t-butylphosphine)Palladium (0) (58.6 mg, 0.12 mmol) in 1,4-dioxane (9.55 ml) and water (1.9 ml) was stirred at 80 °C. After 1hr, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (30% EtOAc in hexanes) affording the title compound (124 mg, 0.60 mmol, 26 % yield) as a white powder: LCMS (ES) m/e 206 $(M+H)^+$.

b) methyl 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (412 mg, 2.0 mmol) and N-chlorosuccinimide (267 mg, 2.0 mmol) in DMF (10 mL) was heated at 75 °C for 30 minutes. Another batch of N-chlorosuccinimide (267 mg, 2.0 mmol) was added. After 1 hr, the mixture was concentrated and purified using silica gel and eluting with 0-55% ethyl acetate / hexane to afford the title compound as a white solid (225 mg, 0.82 mmol, 71% yield) : LCMS (ES) m/e 276 $(M+H)^+$.

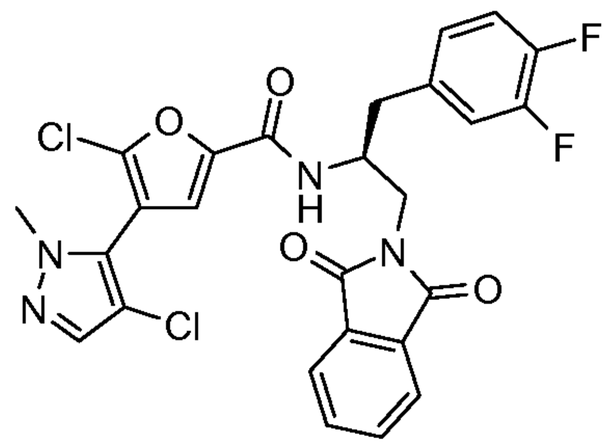
c) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (224 mg, 0.82 mmol) in 6N sodium hydroxide (1.36 ml, 8.2 mmol) and tetrahydrofuran (5 ml) was stirred at 70 °C in a sealed tube for 1h. The

resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound (201 mg, 0.77 mmol, 94 % yield) as a yellow oil: LCMS (ES) m/e 262 $(M+H)^+$.

d) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide



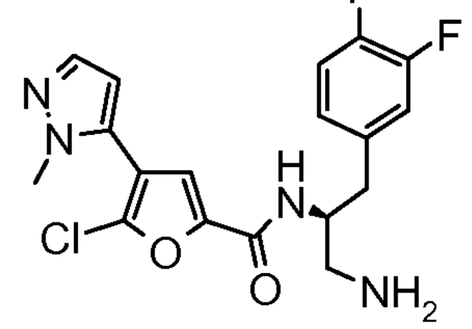
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (200 mg, 0.77 mmol)[prepared according to the procedure of Preparation 6], 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (254 mg, 0.80 mmol) and N,N-diisopropylethylamine (0.40 ml, 2.30 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (536 mg, 1.15 mmol). After stirring at ambient temperature for 20 hrs, the mixture was concentrated and purified with silica gel column eluting with gradient (0-50% ethyl acetate/hexanes) to afford the title compounds as an off-white foamy solid (304 mg, 0.54 mmol, 71% yield): LCMS (ES) m/e 560(M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide (304 mg, 0.54 mmol) in methanol (5 ml) at 25 °C was added hydrazine (0.08 ml, 2.7 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as a yellow solid: LC-MS (ES) m/z 430$(M+H)^+$, ^1H NMR (400 MHz,

MeOD) δ ppm 2.91 - 3.05 (m, 2 H) 3.17 - 3.28 (m, 2 H) 3.81 (s, 3 H) 4.57 (d, *J*=9.60 Hz, 1 H) 7.12 (br. s., 1 H) 7.18-7.28 (m., 2 H) 7.36-7.39 (m, 1 H) 7.58 (s, 1 H).

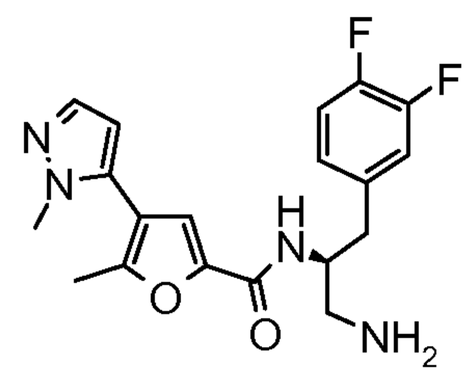
Example 225



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

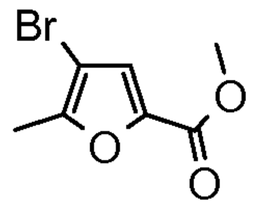
The title compound was prepared as an off-white solid according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (147 mg, 0.46 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.90 - 3.06 (m, 2 H) 3.18-3.24 (m, 2 H) 3.98 (d, *J*=17.68 Hz, 3 H) 4.52 - 4.64 (m, 1 H) 6.67 (d, *J*=1.77 Hz, 1 H) 7.19 (dd, *J*=10.11, 8.59 Hz, 2 H) 7.26 (td, *J*=9.73, 2.27 Hz, 1 H) 7.51 (d, *J*=19.96 Hz, 1 H) 7.93 (br. s., 1 H).

Example 226



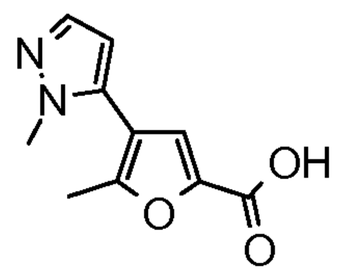
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-bromo-5-methyl-2-furancarboxylate



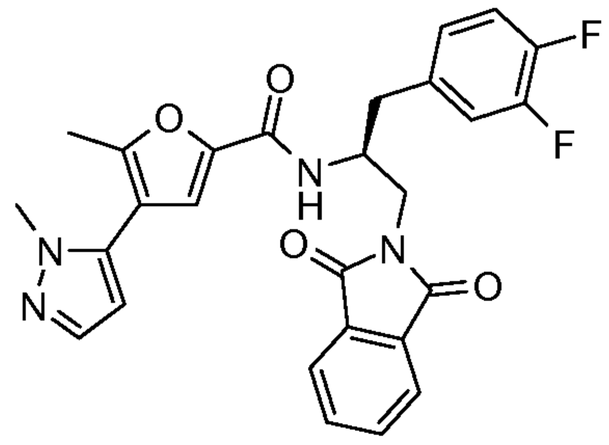
Methyl 4,5-dibromo-2-furancarboxylate (3.7 g, 13.03 mmol) [prepared according to Example 127] and trans-dichlorobis(triphenylphosphine)Palladium (II) (0.46 g, 0.65 mmol) were combined in THF (50ml) to give a yellow suspension. A THF solution of methylzinc chloride (11.40 ml, 22.81 mmol) was added dropwise at room temperature. After stirring at ambient temperature for 20h, the solution was concentrated and purified using silica gel and eluting with 0-30% ethyl acetate / hexane to generate the title compound as a white solid (1.45 g, 6.61 mmol, 51% yield): LC-MS (ES) m/z 220 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid



To a solution of methyl 4-bromo-5-methyl-2-furancarboxylate (500 mg, 2.28 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (950 mg, 4.57 mmol)[prepared according to Preparation 7] and potassium carbonate (315 mg, 2.28 mmol) in 1,4-dioxane (8 mL) and water (2.0 mL) was added bis(tri-t-butylphosphine)Palladium (0) (117 mg, 0.23 mmol). The mixture was heated to 80 °C and after 15h the reaction mixture was concentrated. The residue was partitioned between DCM and water. The organic layer was concentrated and dissolved in tetrahydrofuran (THF) (8.0 mL). The solution was treated with 6N aqueous solution of sodium hydroxide (3.80 mL, 22.83 mmol) and heated to 75 °C. After 15h, the reaction mixture was concentrated and partitioned between DCM and water. The aqueous layer was acidified to pH ~ 3 with 2N HCl aqueous solution and extracted several times with DCM. The organic fractions were combined and concentrated to afford the title compound as a yellow solid (401 mg, 1.95 mmol, 85% yield): LC-MS (ES) m/z 207 $(M+H)^+$.

c) *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

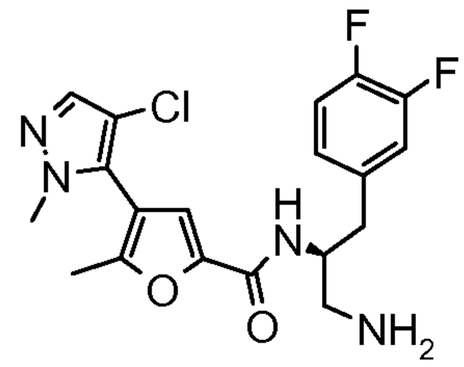


To a solution of 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid (200 mg, 0.97 mmol), 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (322 mg, 1.02 mmol)[prepared according to the procedure of Preparation 6] and N,N-diisopropylethylamine (0.51 ml, 2.91 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (678 mg, 1.46 mmol). After stirring at ambient temperature for 20h, the mixture was concentrated and purified using silica gel and eluting with a 0-50% ethyl acetate/hexane gradient to afford the title compound as an off-white foamy solid (181 mg, 0.36 mmol, 37% yield): LCMS (ES) m/e 505 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

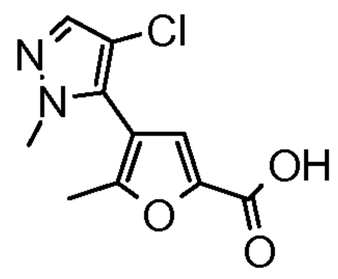
To a solution of *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide
(176 mg, 0.35 mmol) in methanol (5 ml) at 25 ºC was added hydrazine (0.22 ml, 0.7 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as an off-white solid:
LC-MS (ES) m/z 430$(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.91 - 3.05 (m, 2 H) 3.17 - 3.28 (m, 2 H) 3.81 (s, 3 H) 4.57 (d, *J*=9.60 Hz, 1 H) 7.12 (br. s., 1 H) 7.18-7.28 (m., 2 H) 7.36-7.39 (m, 1 H) 7.58 (s, 1 H)

Example 227



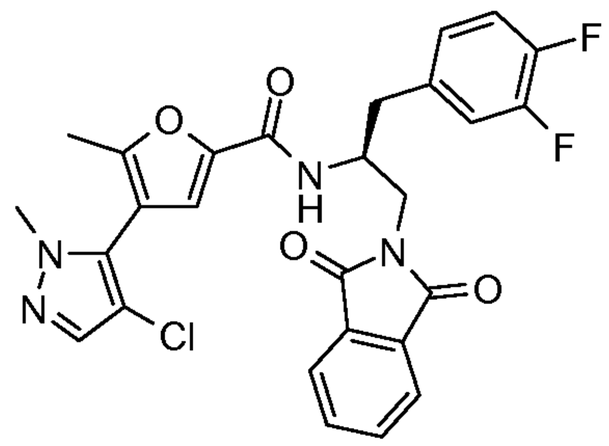
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (150 mg, 0.73 mmol)[prepared in Example 126] in THF (10 ml) was added N-chlorosuccinimide (97 mg, 0.73 mmol). After stirring at 70 °C for 20h in a sealed tube, the mixture was partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound as an off-white foamy solid (152 mg, 0.63 mmol, 87% yield): LC-MS (ES) m/z 241$(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide



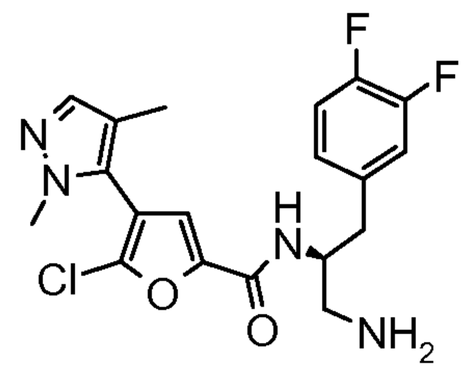
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (150 mg, 0.62 mmol) , 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (207 mg, 0.65 mmol)[prepared according to the procedure of Preparation 6] and N,N-diisopropylethyl amine (0.33 ml, 1.87 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium

hexafluorophosphate (436 mg, 0.94 mmol). After stirring at ambient temperature for 20h, the mixture was concentrated and purified using silica gel and eluting with a gradient of 0-50% ethyl acetate/hexane to afford the title compound as an off-white foam (200 mg, 0.35 mmol, 57% yield): LC-MS (ES) m/z 539 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a solution of 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide (210 mg, 0.39 mmol) in methanol (5 ml) at 25 °C was added hydrazine (0.02 ml, 0.78 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as an off-white solid: LC-MS (ES) m/z 409$(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.38 (s, 3 H) 2.98 (d, *J*=9.35 Hz, 1 H) 3.01 (d, *J*=5.56 Hz, 1 H) 3.23 (dd, *J*=13.01, 8.97 Hz, 2 H) 3.73 - 3.83 (m, 3 H) 4.56 (d, *J*=9.35 Hz, 1H) 7.17 (s, 1 H) 7.18 - 7.32 (m, 3 H) 7.57 (s, 1 H).

Example 228

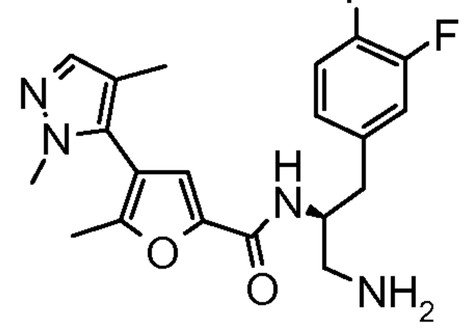


Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 118, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (253 mg, 0.8 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 409

(M+H)$^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.05 - 2.15 (m, 3H) 2.91 - 3.07 (m, 2 H) 3.16 - 3.26 m., 2 H) 3.91 (br. s., 3 H) 4.57 - 4.59 (m., 1 H) 7.09 - 7.31 (m, 3 H) 7.51 (br. s., 1 H) 8.07 (br. s., 1 H)

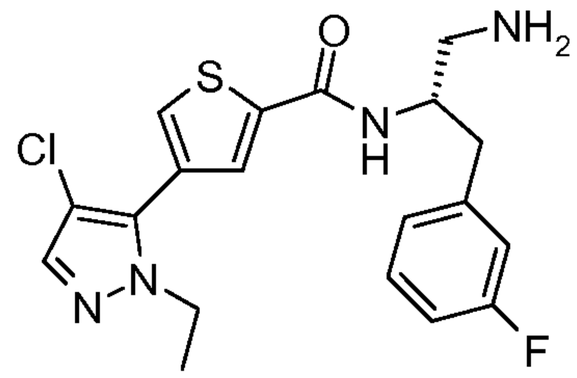
Example 229



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

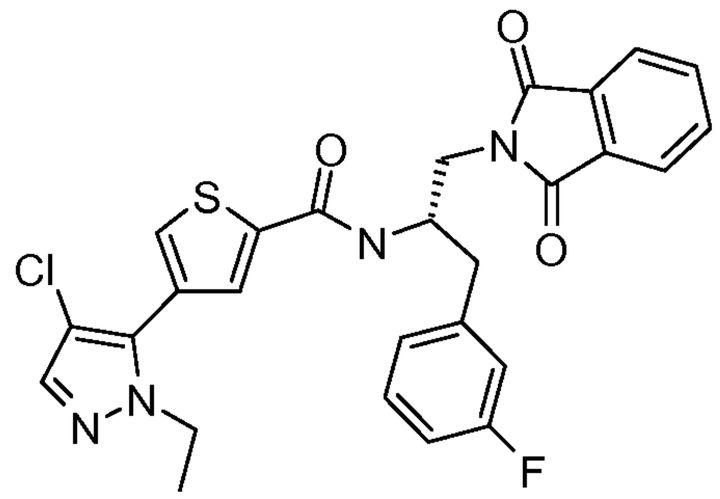
The title compound was prepared as a yellow solid according to the procedure of Example 119, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (302 mg, 0.95 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 389 (M+H)$^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.04 - 2.15 (m, 3 H) 2.35 - 2.47 (m, 3 H) 2.99 - 3.02 (m,, 2 H) 3.18 - 3.24 (m, 2 H) 3.86 - 3.96 (m, 3 H) 4.56 - 4.62 (m, 1H) 7.16 - 7.26 (m, 4 H) 8.07 (s, 1 H).

Example 230



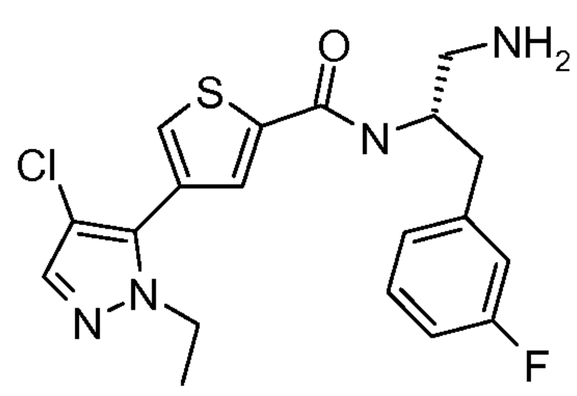
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (220 mg, 0.857 mmol) [from Example 92] in DCM (5 mL) at 25 °C was added PyBrOP (440 mg, 0.857 mmol) in one portion, followed by addition of DIPEA (1.5 mL, 8.59 mmol). After 10 min, diamine 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (256 mg, 0.857 mmol) was added to above solution. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.39 g, 81%) as a white solid: LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



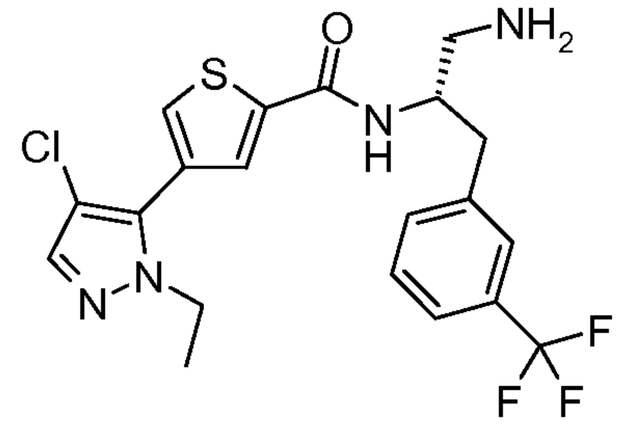
At RT, NH_2NH_2 (0.11 mL, 3.54 mmol) was added to 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (380 mg, 0.708 mmol) in MeOH (4 mL). After 10h, the solvent was removed under vaccum to give a residue, which was dissolved in DCM (15 mL), and washed with H_2O (10 mL x 3).

To the above DCM solution was added aqueous HCl (12 N, 2.95 mL, 35.4 mmol). After 1h, the aqueous phase was separated, and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (160 mg, 47%) as a white solid: LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 9.18-8.8(m, 1H), 8.28-8.08 (m, 4H), 8.04 (s, 1H), 7.27-7.43 (m, 1),

7.08-7.24 (m, 2H), 6.91-7.08 (m, 1H), 4.4-4.34 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.15-2.80 (m, 4H), and 1.29 (t, J = 7.3 Hz, 3H).

Example 231

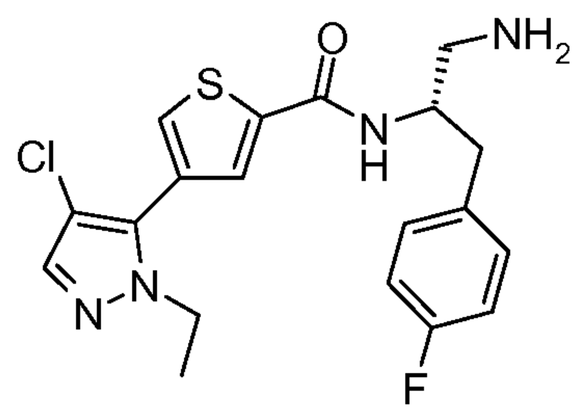
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (339 mg, 0.97 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.92 (br s, 1H), 7.89-7.80 (m, 1H), 7.63-7.59 (m, 3H), 7.56-7.48 (m, 2H), 4.61-4.53 (m, 1H), 4.21-4.15 (m, 2H), 3.46-3.21 (m, 2H), 3.18-3.02 (m, 2H), and 1.35 (t, J = 7.3 Hz, 3H).

Example 232

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

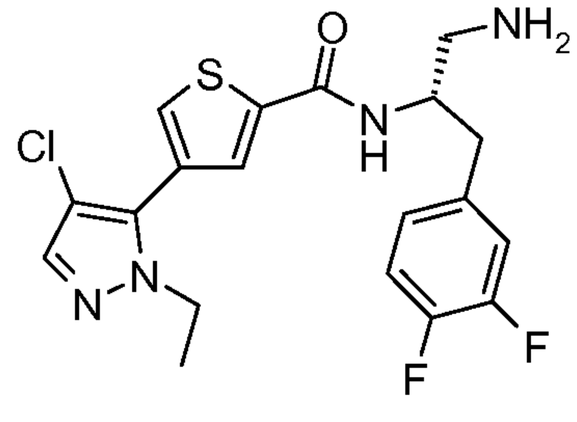


The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (584 mg, 1.95 mmol) for 2-[(2S)-2-

amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.93 (d, J = 1.3 Hz, 1H), 7.85 (d, J = 1.3 Hz, 1H), 7.59 (s, 1H), 7.34-7.31 (m, 2H), 7.05-7.01 (m, 2H), 4.52 (m, 1H), 4.19 (q, J = 7.3 Hz, 2H), 3.26-3.12 (m, 2H), 3.05-2.94 (m, 2H), and 1.36 (t, J = 7.3 Hz, 3H).

Example 233

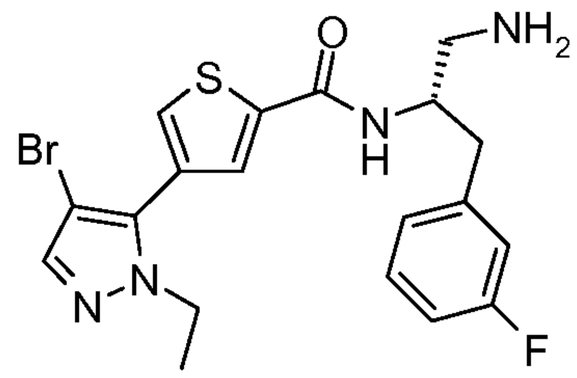
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



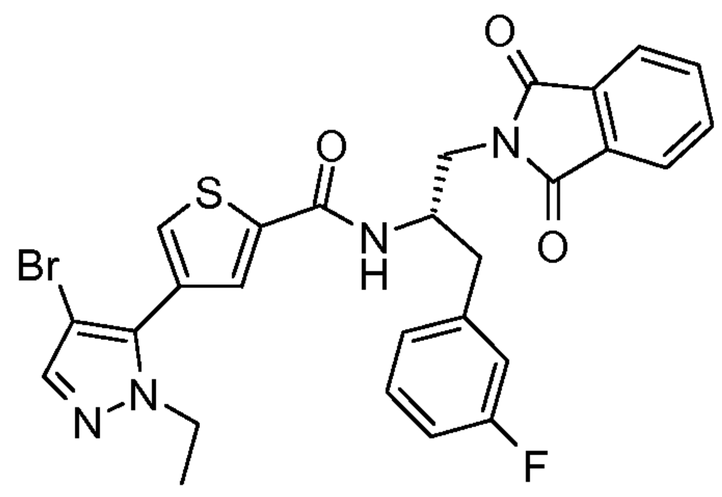
The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (200m g, 0.63 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 425$(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.88 (d, J = 8.3 Hz, 1H), 8.16-8.06 (m, 4H), 7.71 (s, 1H), 7.39-7.30 (m, 2H), 7.12 (m, 1H), 4.35 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.08-2.87 (m, 4H), and 1.29 (t, J = 7.1 Hz, 3H).

Example 234

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

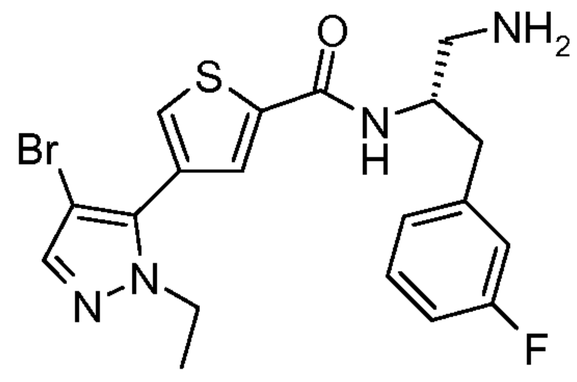


a) 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 93, except substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (149 mg, 0.50 mmol) for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z = 582 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

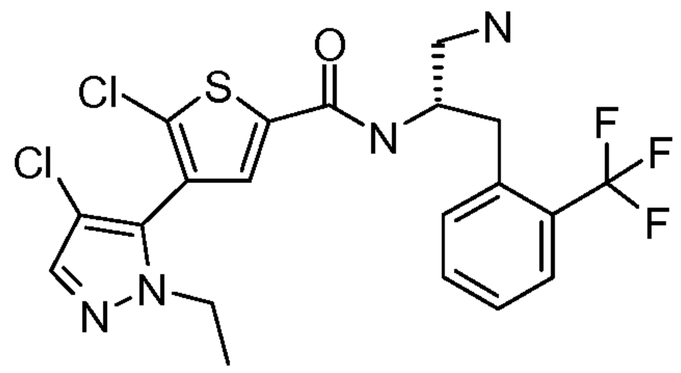


The title compound was prepared as an off-white solid according to the procedure of Example 230(b), except substituting *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (240 mg, 0.41 mmol) for 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide: LC-MS (ES) m/z = 452$(M+H)^+$,

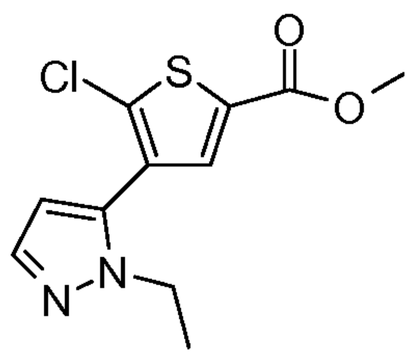
^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.24-8.85 (m, 1H), 8.26-8.13 (m, 4H), 8.03 (s, 1H), 7.03 (s, 1H), 7.34 -7.29 (m, 1H), 7.16-7.13 (m, 2H), 7.05-7.00 (m, 1H), 4.39 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.06-2.96 (m, 4H), and 1.28 (t, J = 7.3 Hz, 3H).

Example 235

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

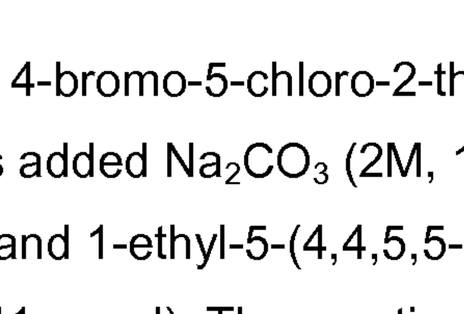


a) Methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



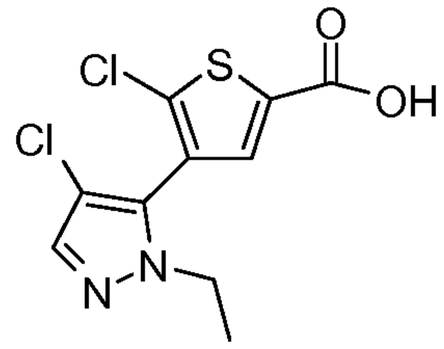
To a solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (300 mg, 1.17 mmol) in THF (2 mL) was added Na_2CO_3 (2M, 1.76 mL, 3.52 mmol), $Pd(dppf)Cl_2$ (86, 0.117 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (313 mg, 1.41 mmol). The reaction mixture was heated to 80 °C in a sealed tube under N_2. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-50%) to afford the title compound (0.272 g, 82%) as a light yellow syrup: LC-MS (ES) m/z = 271 $(M+H)^+$.

b) Methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



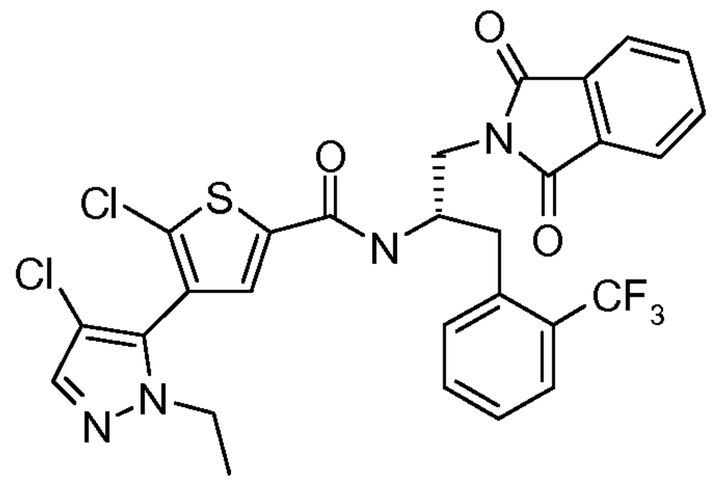
Methyl 5-chloro-4-[(1Z)-1-(1-ethyl-2-methylidenehydrazino)-1-propen-1-yl]-2-thiophenecarboxylate (260 mg, 0.96 mmol) and 1-chloro-2,5-pyrrolidinedione (154 mg, 1.15 mmol) in THF (4 mL) were heated at 70 °C under N_2 for 2 h, concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.281g, 83%) as a syrup: LC-MS (ES) m/z = 305 $(M+H)^+$.

c) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (260 mg, 0.85 mmol) in THF/H_2O (4 mL/1 mL) was added KOH (478 mg, 8.52 mmol). The reaction mixture was heated to 50° C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without further purification.

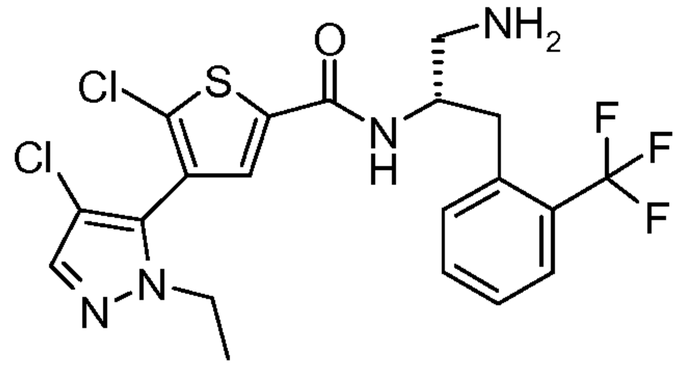
d) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (~0.85 mmol) in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (477 mg, 1.02 mmol) in one portion, followed by the addition of DIPEA (0.744 mL, 4.26 mmol). After stirring for 10 min, diamine 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (356 mg, 1.02 mmol) was added to the above solution.

After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.416 g, 79%) as a white solid: LC-MS (ES) m/z = 621 $(M+H)^+$.

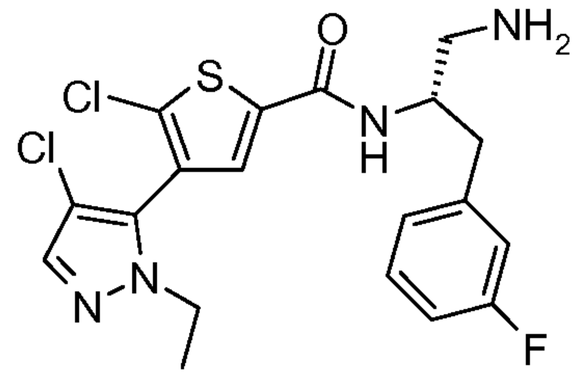
e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



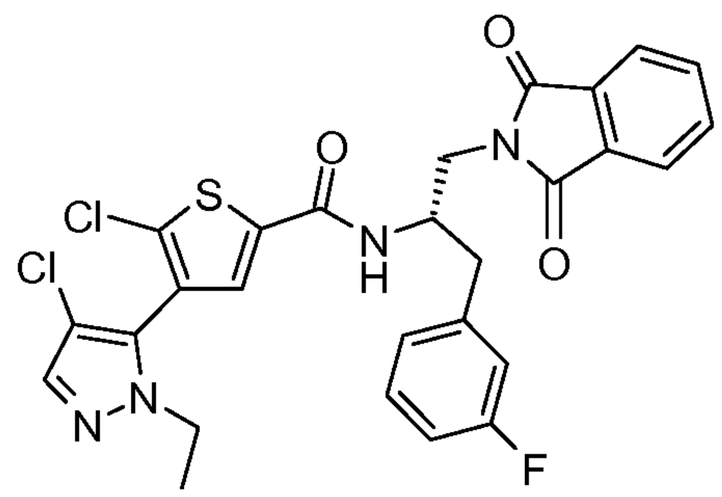
5-Chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (410 mg, 0.66 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (1.04mL, 33 mmol). The reaction was stirred over 5h at RT, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95 -5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water and neutralized by ammonium hydroxide. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound, which was dissolved in MeOH (2 mL), and treated with HCl (4 M in dioxane, 1.6 mL). After stirring overnight, the reaction solution was concentrated to give the title compound (160 mg, 42 %) as a di-HCl salt: LC-MS: m/z = 491 $(M+H)^+$,^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.34 (J = 8.8 Hz, 1H), 8.38-8.03 (m, 3H), 7.77 (s, 1H), 7.69-7.59 (m, 2H), 7.53 (dd, J = 7.3, 7.3 Hz, 1H), 7.42(dd, J = 7.6, 7.6 Hz, 1H), 4.48 (m, 1H), 4.13-4.00 (m, 2H), 3.17-2.90 (m, 4H), and 1.29 (m, 3H).

Example 236

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

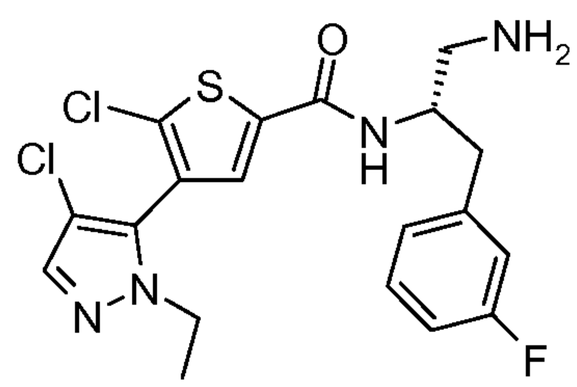


a) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (180 mg, 0.618 mmol) [from Example 235(c)] in DCM (5 mL) at 25 °C was added PyBrOP in one portion, followed by addition of DIPEA (0.54 mL, 3.09 mmol). After stirring for 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (203 mg, 0.68 mmol) was added to above solution in one portion. After stirring for 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (285 mg, 77%) as a white solid: LC-MS (ES) m/z = 571 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

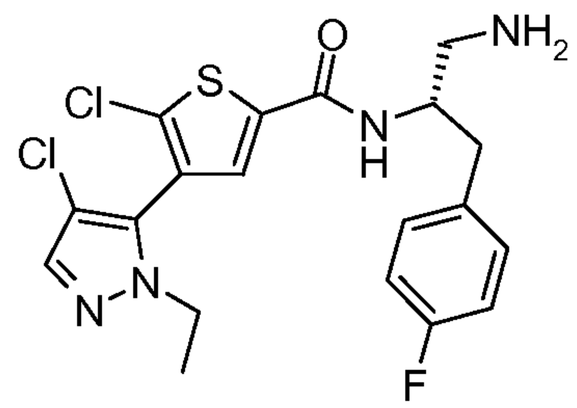


At RT, NH_2NH_2 (0.15 ml, 4.78 mmol) was added to 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (280 mg, 0.49 mmol) in MeOH

(5 mL). After 10h the solvent was removed under vaccum. The resulting residue was dissolved in DCM (15 mL), and washed with H_2O (10 mL x 3). To the DCM solution was added HCl (12 N, 1.0 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the tilte compound (179 mg, 67.5%) as an off-white solid: LC-MS (ES) m/z = 441 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.72-7.67 (m, 1H), 7.62 (s, 1H), 7.35-7.29 (m, 1H), 7.14-7.17 (m, 2H), 7.00-6.96 (m, 1H), 4.53 (m, 1H), 4.14-3.97 (m, 2H), 3.37-3.15 (m, 2H), 3.07-2.97 (m, 2H), and 1.33 (t, J = 7.1 Hz, 3H).

Example 237

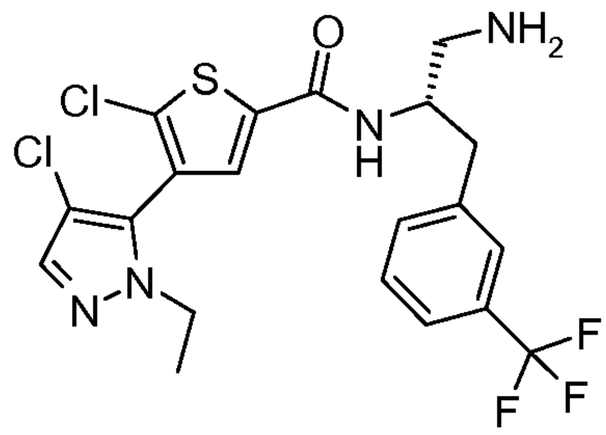
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound (190 mg, 70%) was prepared as an off-white solid according to the procedure of Example 236, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (231 mg, 0.77 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 441$(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz, no calibration of chemical shift of MeOD solvent peak) δ ppm 6.09 (s, 1H), 6.08 (s, 1H), 5.78-5.75 (m, 2H), 5.53-5.48 (m, 2H), 2.96 (m, 1H), 2.51 (m, 2H), 1.71-1.67 (m, 1H), 1.62-1.54 (m, 1H), 1.49-1.38 (m, 2H), and -0.21 (t, J = 7.3 Hz, 3H).

Example 238

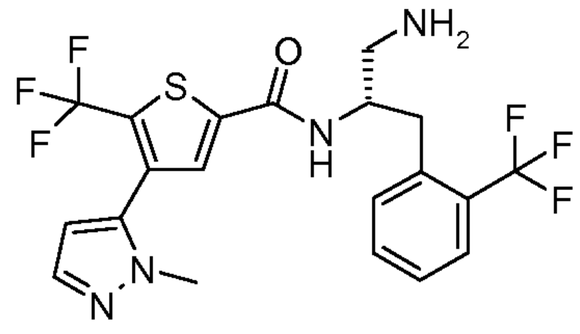
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound (228 mg, 58.2%) was prepared as an off-white solid according to the procedure of Example 236, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (156 mg, 0.45 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 491$(M+H)^+$, ^{1}H NMR (d_4-MeOD, 400 MHz) δ ppm 7.66-7.49 (m, 6H), 4.60-4.47 (m, 1H), 4.09-4.01 (m, 2H), 3.36-3.18 (m, 2H), 3.16-3.01 (m, 2H), and 1.33 (t, J = 7.1 Hz, 3H).

Example 239

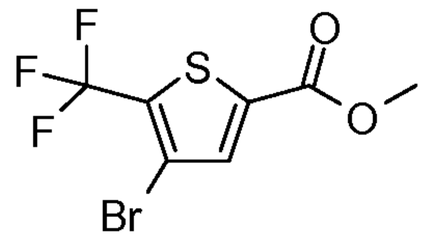
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide



a) methyl 4-bromo-5-iodo-2-thiophenecarboxylate

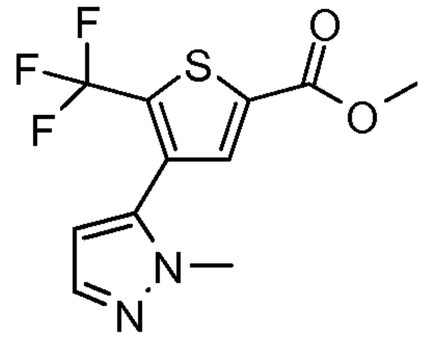
At -78 °C, nBuLi (2.05 mL, 5.13 mmol) was added to a solution of methyl 4,5-dibromo-2-thiophenecarboxylate (1.4 g, 4.67 mmol) in THF (10 mL). After the mixture was stirred for 30 min, I_2 (1.185 g, 4.67 mmol) was added in 3 mL THF. After the resulting solution was stirred at -78 °C for 1h, it was quenched with $Na_2S_2O_3$ at -78 °C, and warmed to RT. The reaction mixture was extracted with DCM, dried over Na_2SO_4, and concentrated. The crude product was purified on silica (EtOAc/Hex, 0-10%) to give the title compound (1.3 g, 56 %) as a yellow solid: LC-MS (ES) m/z 348$(M+H)^+$.

b) methyl 4-bromo-5-(trifluoromethyl)-2-thiophenecarboxylate



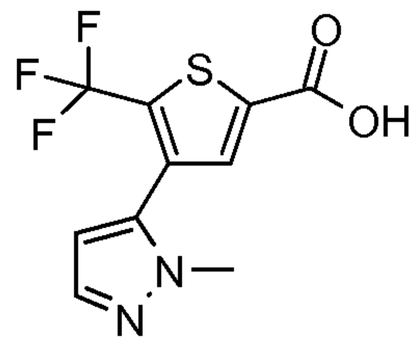
To a solution of methyl 4-bromo-5-iodo-2-thiophenecarboxylate (500 mg, 1.44 mmol), copper (I) iodide (137 mg, 0.72 mmol) and potassium fluoride (251 mg, 4.32 mmol) in DMF/HMPA (5 ml/5 mL) was added methyl difluoro(fluorosulfonyl)acetate (1.1g, 5.76 mmol). The mixture was heated at 70 °C under N_2 in a sealed tube. After 1h, the reaction was quenched with NH_4Cl (sat'd) (2 mL), extracted with ether (5 mL x 5) and washed with distilled water (5 mL x 5). The combined organic phase was dried over Mg_2SO_4 and purified on silica (EtOAc/Hex, 20-50%) to afford the title compound (0.82 g) containing a 60% inseparable impurity: LC-MS m/z (ES) 290 $(M+H)^+$.

c) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylate



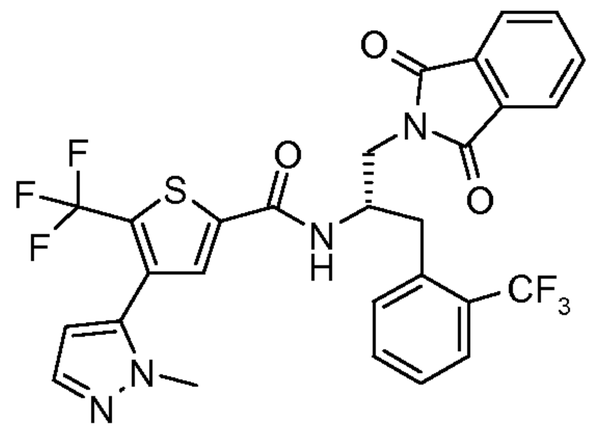
A mixture of methyl 4-bromo-5-(trifluoromethyl)-2-thiophenecarboxylate (0.8 g, 40% purity, 1.11 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.299 g, 1.434 mmol), tetrakis (0.128 g, 0.11 mmol) and K_2CO_3 (0.459 g, 3.32 mmol) in dioxane/H_2O (5 mL/1 mL) was heated to 70° C in a sealed tube. After 12h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 40-60%) to afford the title compound (0.25 g, 70%) as a light yellow solid: LC-MS (ES) m/z 291 $(M+H)^+$.

d) 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylic acid



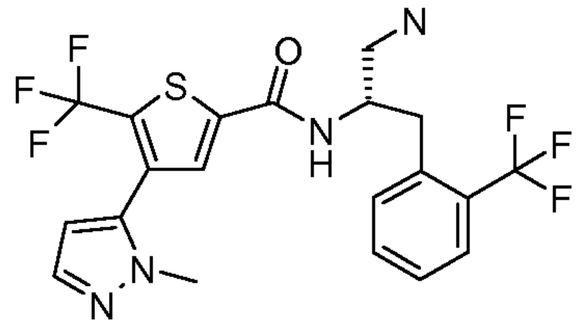
To a solution of methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylate (250 mg, 0.77 mmol), in THF/H_2O (3 mL/0.3 mL), was added KOH (217 mg, 3.88 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give crude acid (235 mg, 80% pure) which was used directly in the next step without further purification: LC-MS (ES) 277 $(M+H)^+$.

e) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide



At room temperature, a mixture of 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylic acid (235 mg, 80% purity, 0.68 mmol), phosphoniumhexafluorophosphate (PyBrOP) (381 mg, 0.19 mmol), DIPEA (0.59 mL, 3.4 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (261 mg, 0.75 mmol) in DCM (5 mL) was stirred for 2h. The reaction solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (386 mg, 86%) as a white solid: LC-MS (ES) 607 $(M+H)^+$.

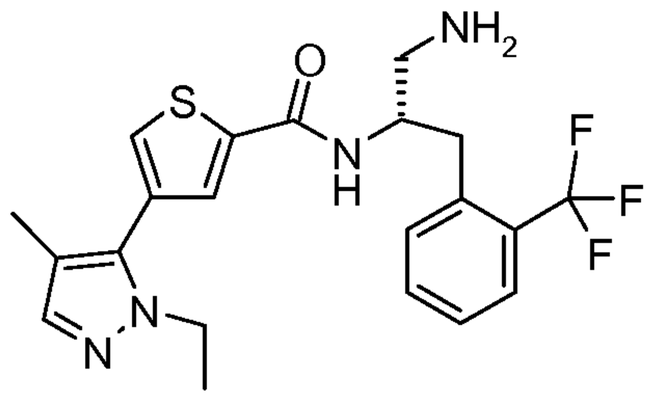
f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide



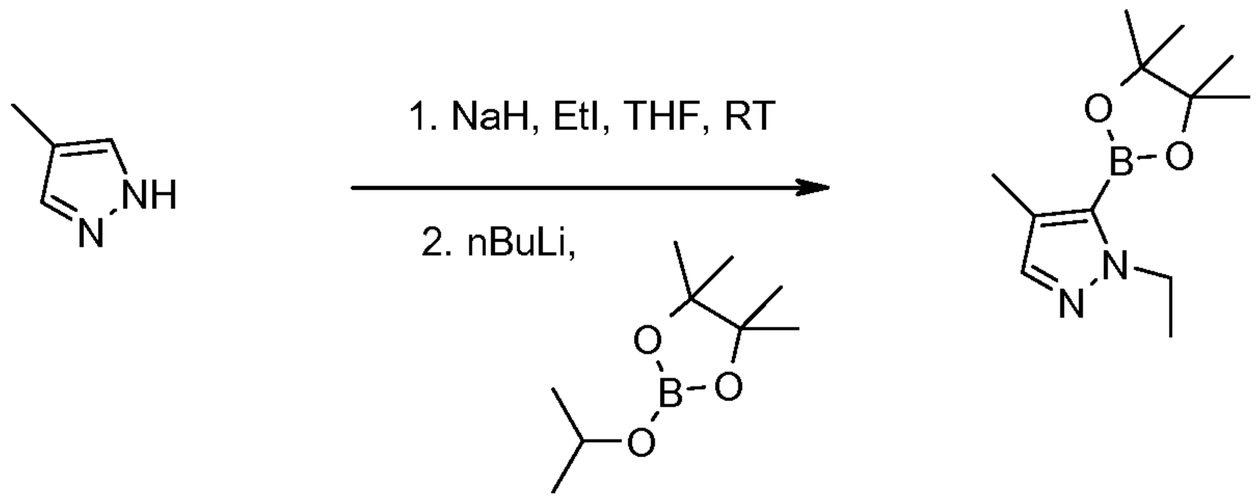
N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide (150 mg, 0.25 mmol) was dissolved in MeOH (5 mL) and was treated with NH_2NH_2 (0.76 mL, 24.2 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95 -5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and ammonium hydroxide (0.32 mL, 30% wt%, 2.46 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL), and treated with HCl (4 M in dioxane, 0.62 mL, 2.48 mmol). After stirring overnight, the reaction solution was concentrated to give the title compound (90 mg, 66%) as a white solid: LC-MS (ES) m/z 477 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.00 (d, J = 1.1 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.59-7.52 (m, 2H), 7.44 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 4.67 (m, 1H), 3.87 (s, 3H), and 3.37-3.14 (m, 4H).

Example 240

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



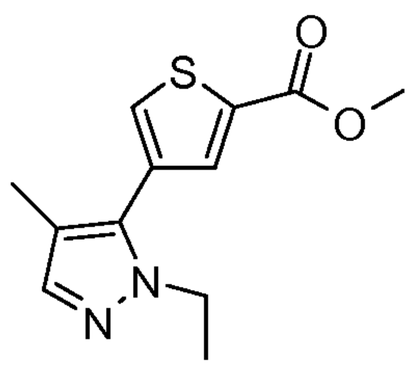
a) 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



To a suspension of NaH (4.3 g, 60%, 108 mmol) in THF (200 mL) at RT was added 4-methyl-1H-pyrazole (6.8 g, 83 mmol) dropwise. After 30 min, EtI (8.03 mL, 99 mmol) was added dropwise. After the reaction was complete (2h), the reaction solution was diluted with saturated aqueous NH_4Cl and extracted with ether. The ether fractions, were washed with water (3 x 100 mL), and dried over $MgSO_4$.

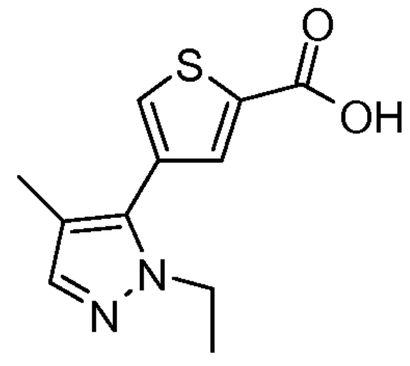
At 0°C, to the above ether solution of 4-methyl pyrazole was added n-BuLi (36.4 mL, 2.5 M in Hexane, 91 mmol) dropwise. The reaction solution was stirred for 1 hour at RT and then cooled to -78 °C [*J. Heterocyclic Chem*. **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.49 g, 99 mmol). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (16 g, 80% purity) as a syrup which was used without further purification: LC-MS (ES) m/z 155 $(M+H)^+$ for [RB(OH)2].

b) methyl 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



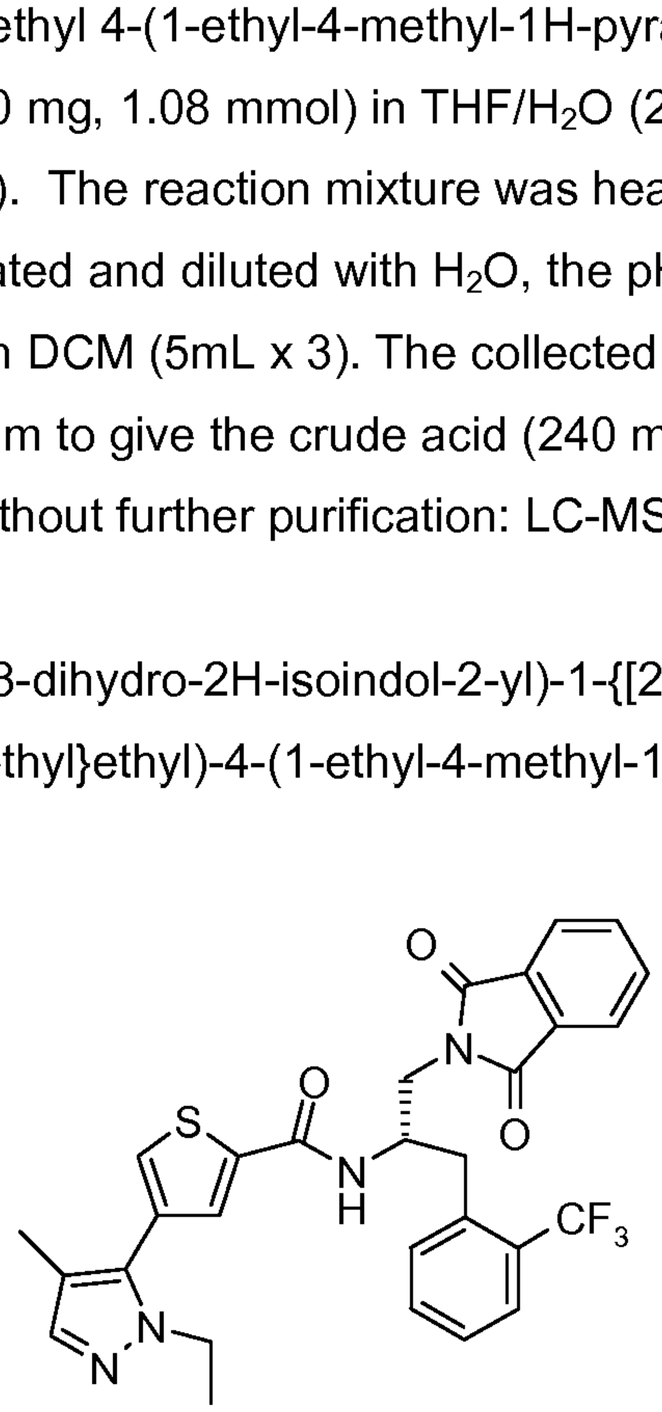
A mixture of methyl 4-bromo-2-thiophenecarboxylate (300 mg, 1.36 mmol), 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (449 mg, 1.9 mmol), $Pd(Ph_3P)_4$ (157mg, 0.136 mmol), and K_2CO_3 (536 mg, 4.07 mmol) was heated at 70 ^oC for 2h, concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.27 g, 79%) as a syrup: LC-MS m/z = 251 $(M+H)^+$.

c) 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



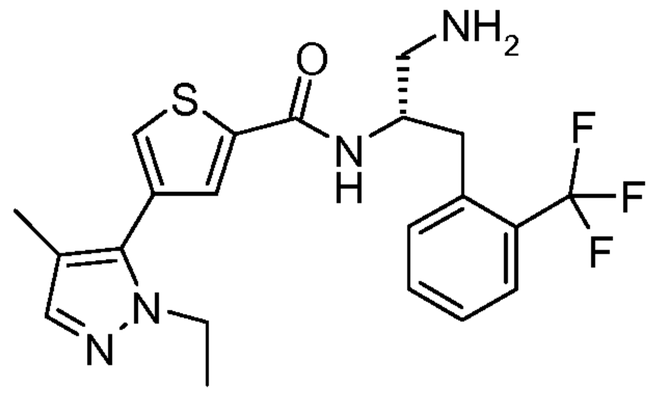
To a solution of methyl 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (270 mg, 1.08 mmol) in THF/H_2O (2 mL/0.4 mL) was added KOH (303 mg, 1.79 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid (240 mg), which was used directly in the next step without further purification: LC-MS m/z = 237 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a mixture of 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (240 mg, 1.02 mmol) and bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (Pybrop) (568 mg, 1.22 mmol) was added DIPEA (1.77 ml, 10.16 mmol). After 10 min, 2-{(2S,4Z)-2-amino-4-[(1E)-1-(trifluoromethyl)-1-propen-1-yl]-4,6-heptadien-1-yl}-1H-isoindole-1,3(2H)-dione (425 mg, 1.22 mmol) was added. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (365 mg, 63%) as a white solid: LC-MS (ES) m/z 567 $(M+H)^+$.

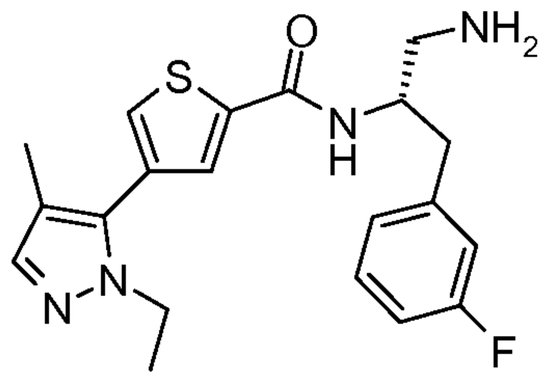
e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



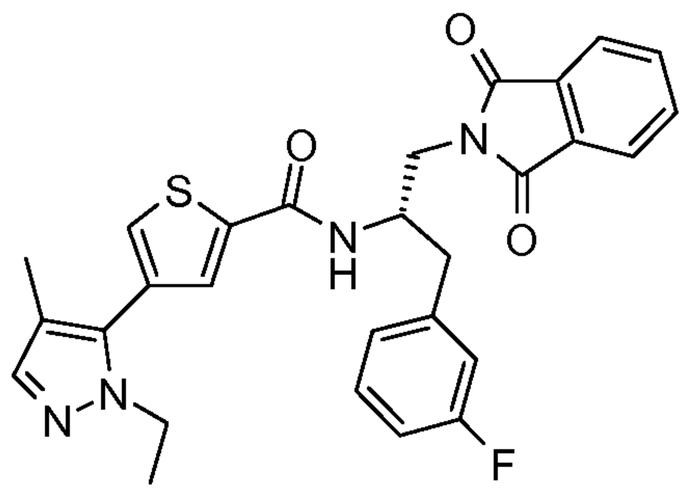
N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (365 mg, 0.64 mmol) was dissolved in MeOH (8 mL) and was treated with NH_2NH_2 (0.1 mL, 3.22 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and ammonium hydroxide (4.18 mL, 30% wt%, 32.2 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (4 M in dioxane, 3.22 mL, 12.88 mml). After stirring overnight, the reaction solution was concentrated to give the title compound (190 mg, 56.7%) as a white solid: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.96 (m, 1H), 8.17-8.04 (m, 4H), 7.87 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.62 (m, 1H), 7.53 (dd, J = 7.3, 7.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 4.50 (m, 1H), 4.09 (q, J = 7.3 Hz, 2H), 3.18-2.98 (m, 4H), 2.00 (s, 3H), and 1.27 (t, J = 7.3 Hz, 3H).

Example 241

(*N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

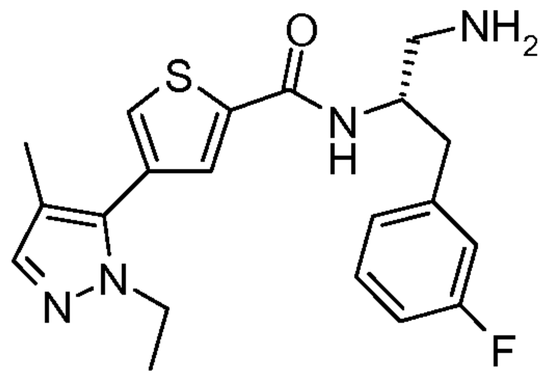


a) N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (125 mg, 0.53 mmol) [from Example 240(c)] in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate(PyBrOP) in one portion (350 mg, 0.75 mmol), followed by addition of DIPEA (0.7 ml, 4.0 mmol). After 10 min, 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (180 mg, 0.60 mmol) was added to above solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (258 mg, 94%) as a white solid: LC-MS (ES) m/z 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



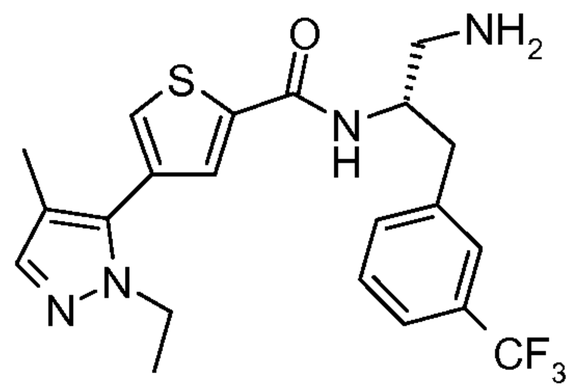
At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (252 mg, 0.49 mmol) in MeOH (5 ml). After 10h, the solvent was removed under vacuum. The resulting residue was dissolved in DCM (10 mL) and washed with H_2O (10 mL x 3).

To the above DCM solution was added HCl (36%, 2 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was

removed under high vacuum to give the title compound (170 mg, 72%) as an off-white solid: LC-MS(ES) m/z 387 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.87 (d, J = 8.9 Hz, 1H), 8.08 (br s, 2H), 8.01 (s, 1H), 7.08 (s, 1H), 7.37 (s, 1H), 7.35-7.29 (m, 1H), 7.16-7.10 (m, 2H), 7.05-7.00 (m, 1H), 4.38 (m, 1H), 4.07 (q, J = 7.3 Hz, 2H), 3.04-2.94 (m, 4H), 2.00 (s, 3H), and 1.26 (t, J = 7.3 Hz, 3H).

Example 242

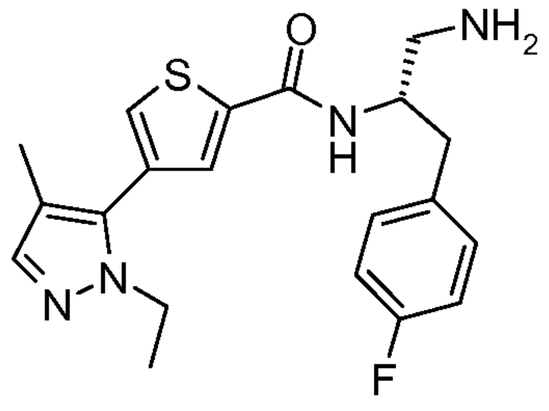
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound (180 mg, 67%) was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (220 mg, 0.63 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.96 (d, J = 8.84 Hz, 1H), 8.15 (m, 2H), 8.04 (d, J =1.3 Hz, 1H), 7.86 (d, J = 1.3 Hz, 1H), 7.69-7.49 (m, 4H), 7.36 (s, 1H), 4.39 (m, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.11-3.00 (m, 4H), 1.99 (s, 3H), and 1.25 (t, J = 7.1 Hz, 3H).

Example 243

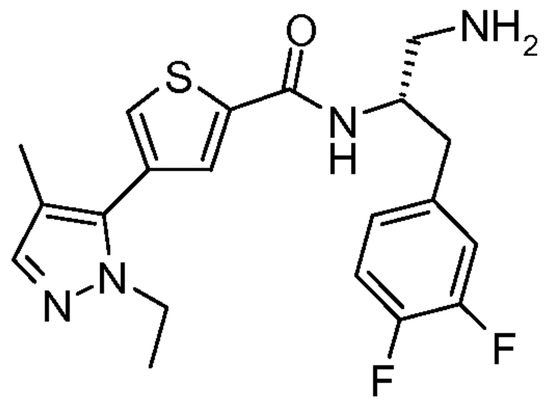
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (160 mg, 0.536 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 387 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.90 (d, J = 8.6 Hz, 1H), 8.13 (m, 2H), 8.03 (d, J =1.3 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.38-7.30 (m, 3H), 7.12-7.08 (m, 2H), 4.36 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.07-2.97 (m, 2H), 2.96-2.88 (m, 2H), 2.00 (s, 3H), and 1.25 (t, J = 7.1 Hz, 3H).

Example 244

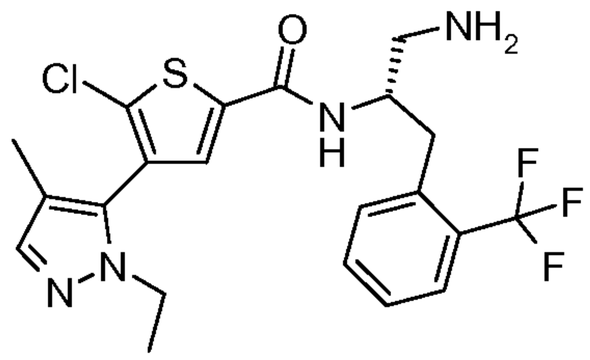
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



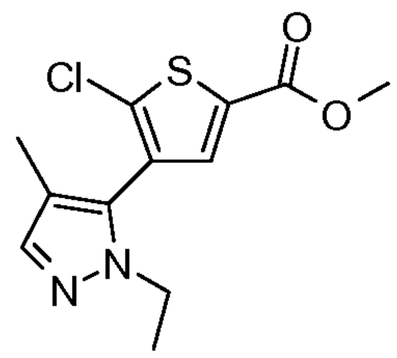
The title compound (210 mg, 72%) was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (240 mg, 0.76 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 405 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.99 (d, J = 8.34 Hz, 1H), 8.16 (m, 2H), 8.09 (d, J =1.0 Hz, 1H), 7.87 (d, J = 1.0 Hz, 1H), 7.40-7.30 (m, 3H), 7.13 (br s, 1H), 4.36 (m, 1H), 4.08 (q, J = 7.3 Hz, 2H), 3.06-2.99 (m, 2H), 2.96-2.33 (m, 2H), 2.00 (s, 3H), and 1.26 (t, J = 7.3 Hz, 3H).

Example 245

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

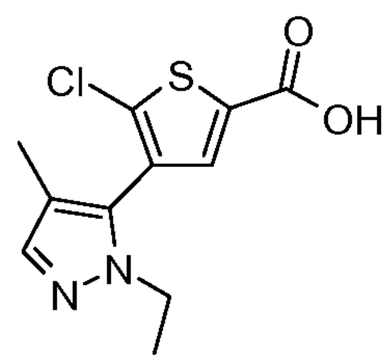


a) Methyl 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (230 mg, 0.9 mmol), 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (425 mg, 1.8 mmol), $PdCl_2$(dppf) (65.9 mg, 0.09 mmol), and sodium carbonate (2N aq, 1.35 mL, 2.7 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. Afte 5h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 40-60%) to afford the title compound (241 mg, 92%) as a light yellow solid: LC-MS (ES) m/z = 285 $(M+H)^+$.

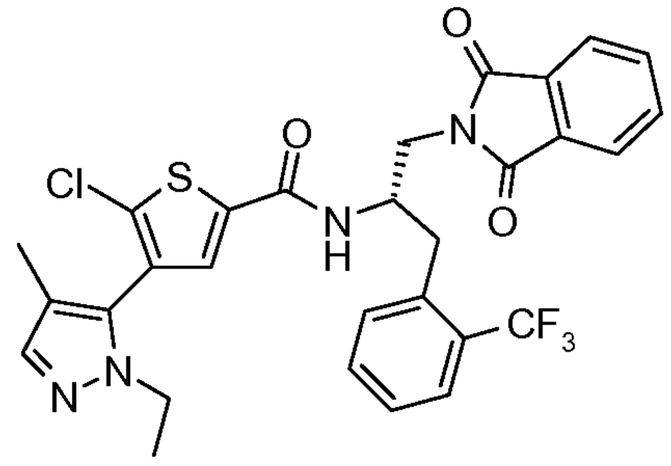
b) 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (260 mg, 0.90 mmol) in THF/H_2O (2 mL/2 mL) was added KOH (201 mg, 3.6 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were

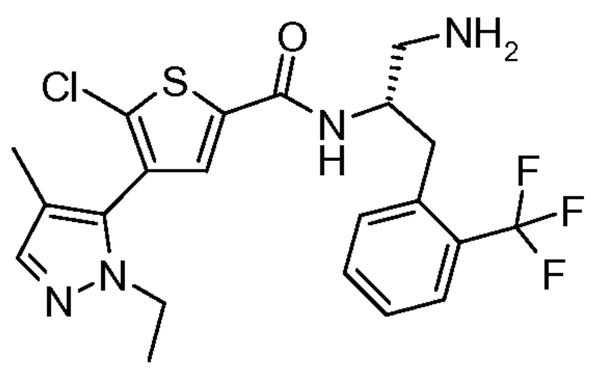
concentrated under vacuum to give crude 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly without further purification: LC-MS (ES) m/z 271 $(M+H)^+$.

c) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (542 mg, 1.16 mmol) in one portion, followed by addition of DIPEA (0.16 mL, 0.90 mmol). After 10 min, 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (312 mg, 0.90 mmol) was added in one portion. After 2h, the reaction solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (278 mg, 49 % for two steps) as a white solid: LC-MS (ES) m/z 601 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

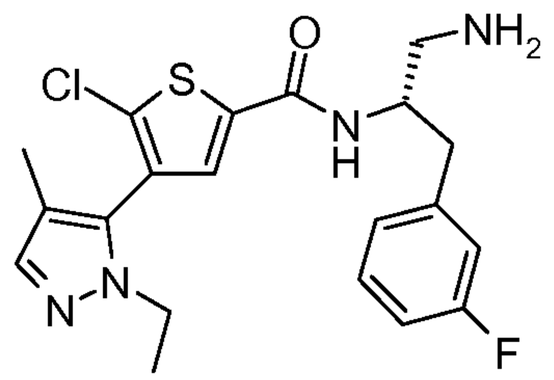


5-Chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (255 mg, 0.42 mmol) was dissolved in MeOH (2mL) and was treated with NH_2NH_2 (0.13 mL, 4.2 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-

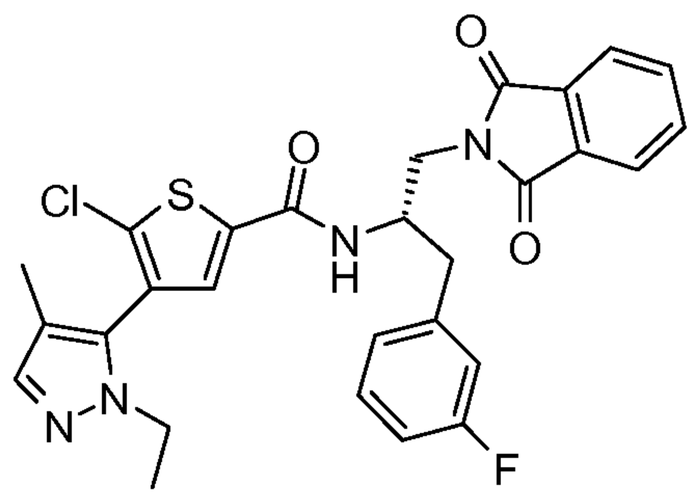
5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water and ammonium hydroxide was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (1 mL) and treated with HCl (4 M in dioxane, 2.1 mL). After stirring overnight, the mixture was concentrated to give 120 mg of the title compound (120 mg, 49%) as an off-white solid: LC-MS (ES) m/z 471 (M+H)+, ^{1}H NMR (d_4-MeOD, 400 MHz) δ ppm 7.91 (br s, 2h), 7.71 (m, 1H), 7.59 (m, 1H), 7.53 (m, 1H), 7.44 (m, 1H), 4.65 (m, 1H), 4.21(m, 2H), 3.37-3.14 (m, 4H), 2.07 (s, 3H), and 1.40 (m, 3H).

Example 246

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



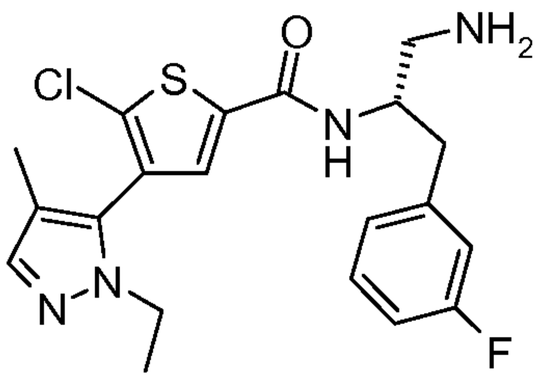
a) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (130 mg, 0.48 mmol) [from Example 245(b)] in DCM (5 mL) at 25 °C was added PyBrOP (250 mg, 0.54 mmol) in one portion, followed by addition of DIPEA (0.7 mL, 4.01 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-

fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (150 mg, 0.50 mmol) was added to above solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (210 mg, 79%) as a white solid: LC-MS m/z (ES) 551 $(M+H)^+$.

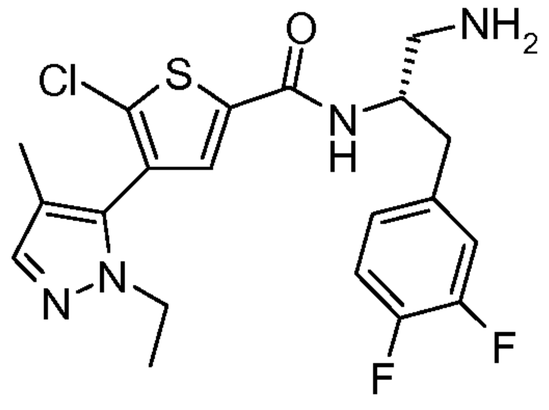
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (201 mg, 0.36 mmol) in MeOH (3 mL) . After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (10 mL) and washed with H_2O (10 mL x 3). To the DCM solution was added HCl (36%, 2 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (101 mg, 53%) as an off-white solid: LC-MS (ES) m/z 421 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 9.02 (d, J = 8.3 Hz, 1H), 8.08 (s, 2H), 7.97 (s, 1H), 7.42 (s, 1H), 7.32 (m, 1H), 7.15-7.09 (m, 1H), 7.06-7.01 (m, 1H), 4.35 (m, 1H), 3.95 (m, 2H), 3.05-2.98 (m, 2H), 2.96-2.88 (m, 2H), and 1.92 (s, 3H), and 1.24 (t, J = 6.6 Hz, 3H).

Example 247

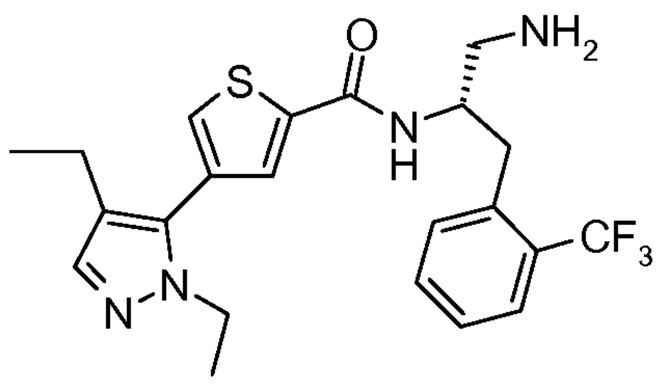
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



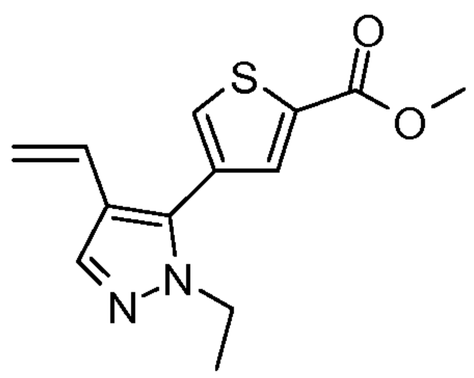
The title compound (95 mg, 50.2%) was prepared according to the procedure of Example 246, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (152 mg, 0.48 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 439 $(M+H)^+$,^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.10 (d, J = 8.6 Hz, 1H), 8.13 (s, 2H), 8.03 (s, 1H), 7.42 (s, 1H), 7.39-7.30 (m, 2H), 7.15-7.10 (m, 1H), 4.33 (m, 1H), 3.95 (m, 2H), 3.05-2.99 (m, 2H), 2.96-2.88 (m, 2H), 1.92, and 1.24 (t, J = 6.3 Hz, 3H).

Example 248

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



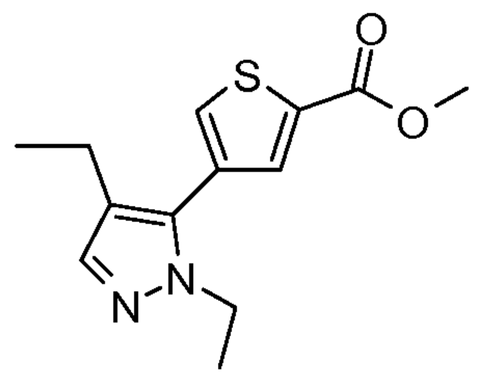
a) Methyl 4-(4-ethenyl-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-(4-bromo-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (200 mg, 0.64 mmol), $Pd(Ph_3P)_4$ (73.3 mg, 0.06 mmol), and tributyl(ethenyl)stannane (302 mg, 0.95 mmol) was heated at 90 °C for 1 h under N_2

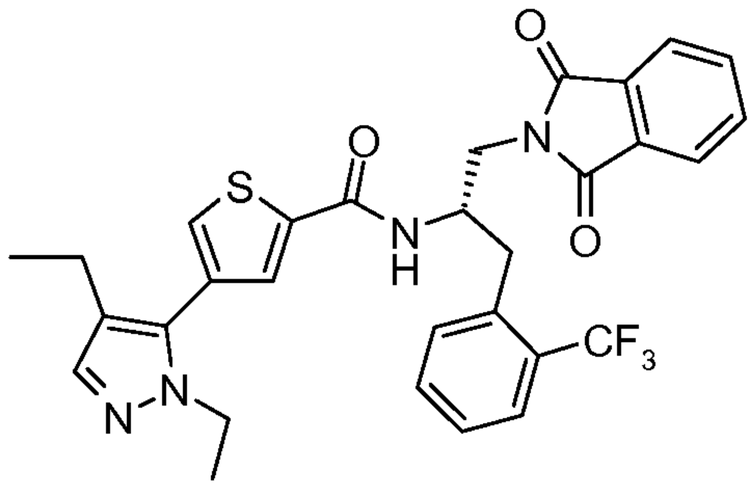
in a sealed tube. The mixture was purified on Silica (10%-20% EtOAc in Hex) to give the title compound (151 mg, 76%): LC-MS (ES) m/z 263 $(M+H)^+$.

b) Methyl 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



Pd/C (12 mg, 10%) was added to a solution of ethyl 4-(4-ethenyl-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (150 mg, 0.57 mmol) in EtOH. The air in the system was removed by vacuum. The reaction mixture was stirred for 10h under a balloon of hydrogen gas. The reaction was diluted with MeOH (2 mL) and filtered through Celite. Concentration of the reaction solution gave the title compound (149 mg, 94%) as a yellow oil: LC-MS (ES) m/z 265 $(M+H)^+$.

c) 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

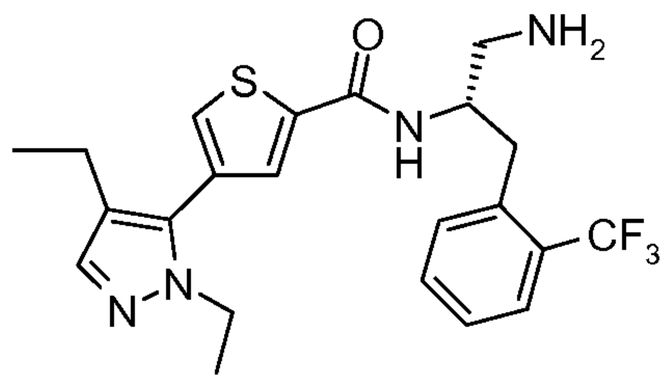


To a solution of methyl 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (149 mg, 0.56 mmol) in THF/H_2O (5 mL/5 mL) was added KOH (158 mg, 2.82 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without of further purification: LC-MS (ES) m/z 251 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (315 mg, 0.68 mmol) in one portion,

followed by the addition of DIPEA (0.98 mL, 5.64 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (196 mg, 0.56 mmol). After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.315 g, 94%) as a white solid: LC-MS (ES) m/z 581 $(M+H)^+$.

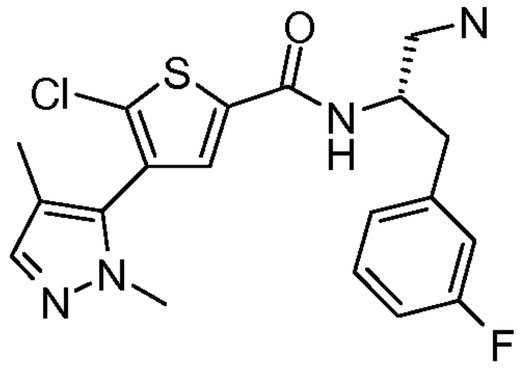
d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



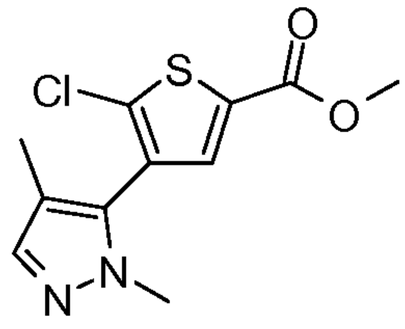
4-(1,4-diethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (310 mg, 0.53 mmol) was dissolved in MeOH (1 mL) and was treated with NH_2NH_2 (0.34 mL, 10.68 mmol) . The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water (2 mL) and ammonium hydroxide (3.47 mL, 30%, 26.7 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the tile compound. The free base was dissolved in MeOH (1 mL) and treated with HCl (4 M in dioxane, 2.1 mL). After stirring overnight, the reaction solution was concentrated to give the title compound (140 mg, 48%) as an off-white solid: LC-MS (ES) m/z 451 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.25-8.23 (m, 1H), 8.16-8.14 (m, 1H), 8.10-8.08 (m, 1H), 7.71-7.67 (m, 1H), 7.65-7.61 (m, 1H), 7.52-7.47 (m, 1H), 7.44-7.39 (m, 1H), 4.69 (m, 1H), 4.45-4.37 (m, 2H), 3.39-3.18 (m, 4H), 2.63-2.55 (m, 2H), 1.49-1.44 (m, 3H), and 1.24-1.19 (m, 3H).

Example 249

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



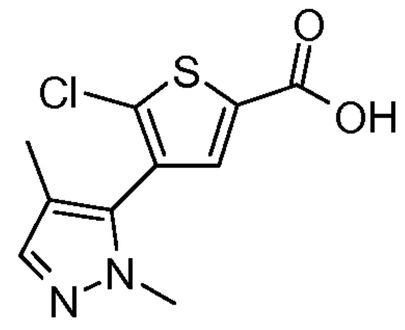
Method A:

To a solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (500 mg, 1.96 mmol) in THF(10 mL) was added aqueous Na_2CO_3 (2N, 3mL, 6.0 mmol), $PdCl_2$(dppf) (143 mg, 0.196 mmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (522 mg, 2.35 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 10-20%) to afford the title compound (410 mg,77%) as a tan solid: LC-MS (ES) m/z 271 $(M+H)^+$.

Method B:

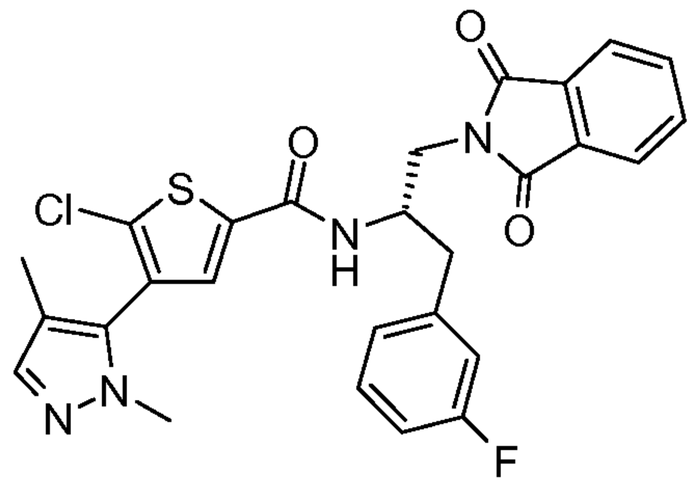
To a 250 mL sealed flask was added 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10.43 g, 47.0 mmol), potassium carbonate (16.23 g, 117 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (10 g, 39.1 mmol) and bis(tri-t-butylphosphine)palladium(0) (1.6 g, 3.13 mmol) in 1,4-dioxane (120 mL) and H_2O (20ml). After stirring for 90 min at 70 ºC, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (hexanes/EtOAC, 10-30%) to give the title compound (7.6 g, 72%) as a tan solid: LC-MS (ES) m/z 271 $(M+H)^+$.

b) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



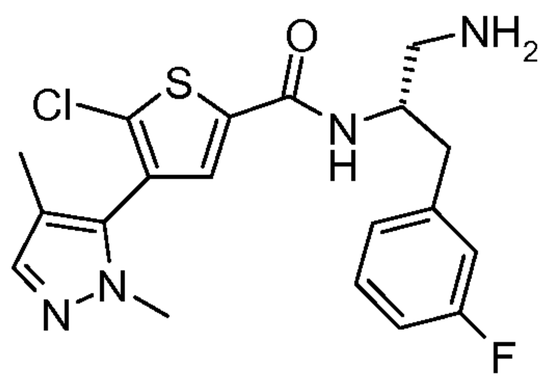
To a solution of methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (7.6 g, 28.1 mmol) in THF/H_2O (30 mL/5 mL) was added KOH (4.72 g, 84 mmol). The reaction mixture was heated to 50 °C for 1 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (50 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid (6.8 g, 94%), which was used directly in the next step without further purification: LCMS (ES) m/z 257 $(M+H)^+$.

c) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 500 mL round-bottomed flask was added 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (6.8 g, 26.5 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (8.69 g, 29.1mmol), N,N-diisopropyl ethylamine (14 mL, 80 mmol) and Pybrop (18.52 g, 39.7 mmol) in dichloromethane (DCM) (100 mL). After stirring at RT for 1h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with (EtOAc/hexanes, 1:1) to give the title compound (6.1g, 42.9%) as a white solid: LCMS (ES) m/z 537 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

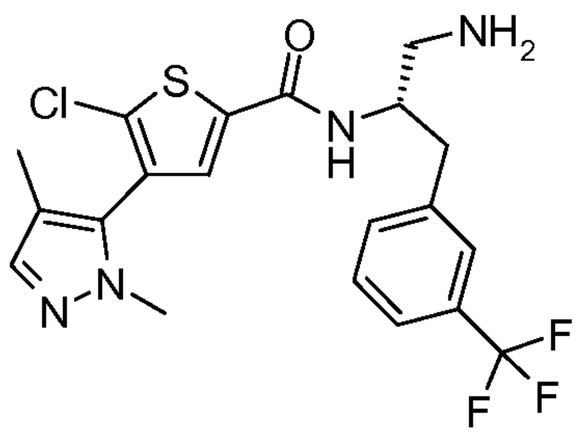


At RT, NH_2NH_2 (4 mL, 127 mmol) was added to 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (5.2 g, 9.68 mmol) in MeOH (30 ml). After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (200 mL) and washed with H_2O (50 mL x 5).

To the above DCM solution was added HCl (36%, 50 mL, 600 mmol). After 1h, the aqueous phase was separated and washed with DCM (50 ml x 5). Water was removed under high vacuum to give the title compound (3.8 g, 79%) as a white solid: LC-MS (ES) m/z 407 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 8.75 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 7.85 (m, 1H), 7.34-7.29 (m, 1H), 7.15-7.09 (m, 2H), 7.00-6.95 (m, 1H), 4.54 (m, 1H), 3.88 (s, 3H), 3.26-3.18 (m, 2H), 3.09-2.98 (m, 2H), and 2.08 (s, 3H).

Example 250

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

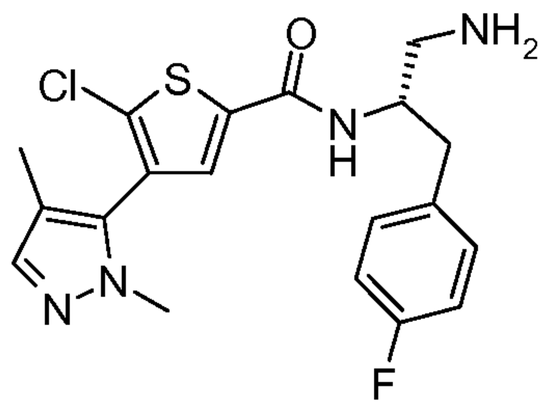


The title compound was prepared as a white solid (180 mg, 68%) according to the procedure of Example 249, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (209 mg, 0.6 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 457 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.94 (s, 1H), 7.90 (s, 1H), 7.65-

7.60 (m, 2H), 7.55-7.48 (m, 2H), 4.55 (m, 1), 3.89 (s, 3H), 3.37-3.27 (m, 2H), 3.16-3.06 (m, 2H), and 2.08 (s, 3H).

Example 251

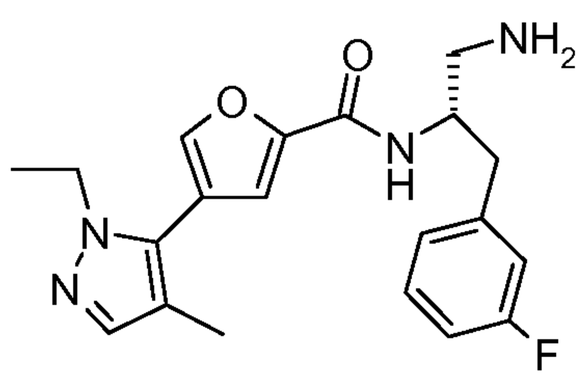
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



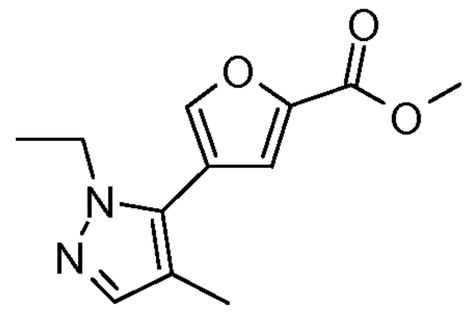
The title compound was prepared as white solid (95 mg, 39%) according to the procedure of Example 249, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (584 mg, 1.96 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 407 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.81 (s, 2H), 7.35-7.31 (m, 2H), 7.06-7.01 (m, 2H), 4.51 (m, 1H), 3.89 (s, 3H), 3.25-3.16 (m, 2H), 3.05-2.94 (m, 2H), and 2.07 (s, 3H).

Example 252

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

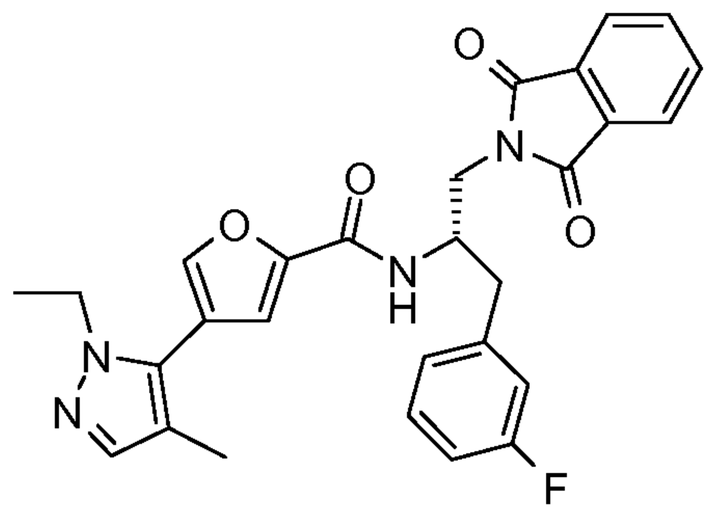


a) methyl 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a solution of methyl 4-bromo-2-furancarboxylate (500 mg, 2.439 mmol) in THF (5 mL) was added aqueous Na_2CO_3 (2N, 3.6 mL, 7.2 mmol), $PdCl_2$(dppf) (160 mg, 0.22 mmol), and 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (700 mg, 2.96 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (460 mg, 76 %) as a light yellow solid: LC-MS (ES) m/z 235 $(M+H)^+$.

b) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

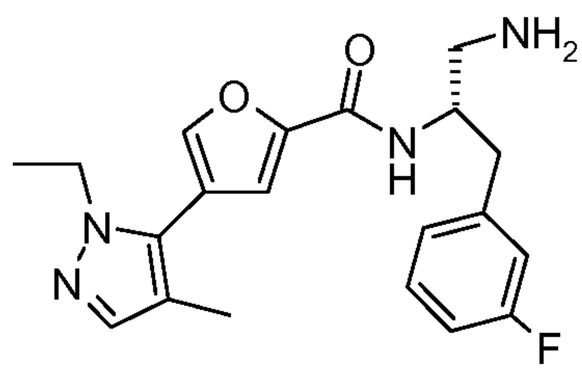


To a solution of methyl 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (210 mg, 0.90 mmol) in THF/H_2O (5mL/0.5 mL) was added KOH (200 mg, 3.56 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 221 $(M+H)^+$.

To the crude 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid in DCM (5 mL) at 25 °C was added PyBrOP (370 mg, 0.79 mmol) in one portion, followed by the addition of DIPEA (0.8 mL, 4.58 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (220 mg, 0.74 mmol) was added to the reaction solution. After 2h, the reaction mixture was concentrated

and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (164 mg, 54%) as a white solid: LC-MS (ES) m/z 501 $(M+H)^+$.

c) *N*-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

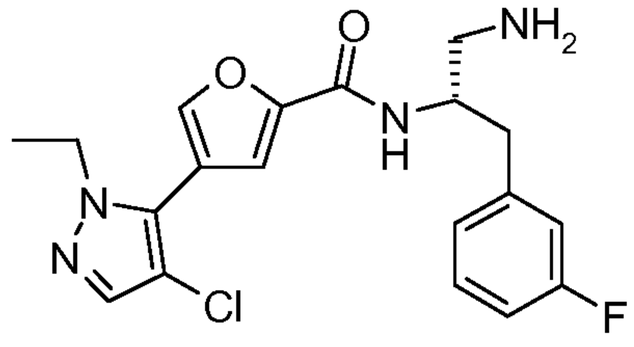


At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to a solution of N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (150 mg, 0.3 mmol) in MeOH (5 mL). After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (10 mL) and washed with H_2O (10 mL x 3).

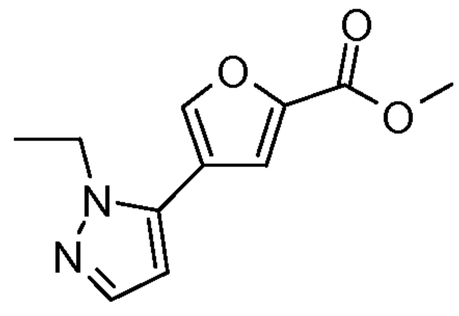
To the DCM solution was added HCl (36%, 1 mL, 12 mmol). After 1h, the aqueous phase was separated, and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (80 mg, 57%) as an off-white solid: LC-MS (ES) m/z 371 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 8.19 (s, 1H), 8.05 (s, 1H), 7.44 (s, 1H), 7.32 (m, 1H), 7.16-7.08 (m, 2H), 6.97 (m, 1H), 4.62 (m, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.38-3.18 (m, 2H), 3.10-2.99 (m, 2H), 2.15 (s, 3H), and 1.46 (t, J = 7.1 Hz, 3H).

Example 253

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

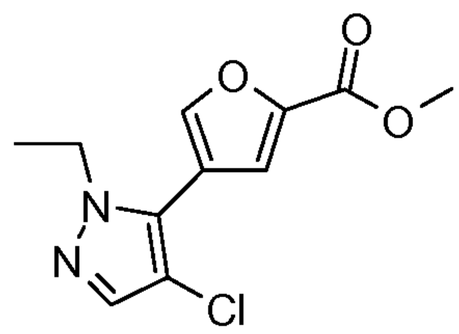


a) methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



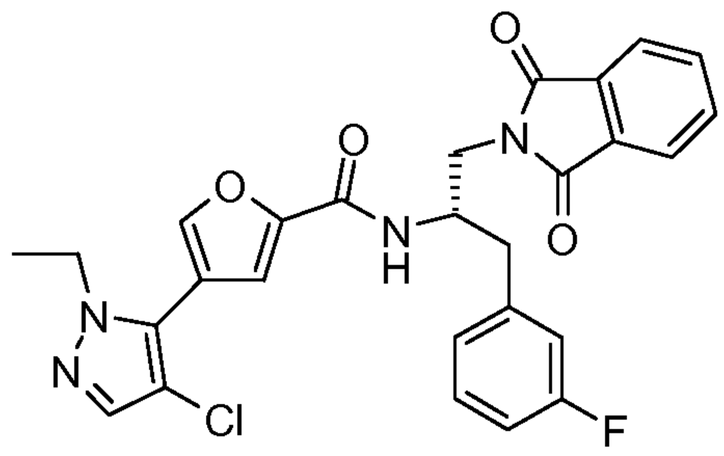
To a solution of methyl 4-bromo-2-furancarboxylate (1.0 g, 4.88 mmol) in THF (20 mL) was added aqueous Na_2CO_3 (2N, 8 mL, 16 mmoL), $PdCl_2$(dppf) (0.35 g, 0.49 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.3 g, 5.85 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (0.8 g, 74.5%) as a light yellow solid: LC-MS (ES) m/z = 221 $(M+H)^+$.

b) methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



A mixture of methyl 4-(1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.36 mmol) and NCS (218 mg, 1.63 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 5h, the reaction mixture was concentrated and purified via column chromatography (silica, 10-20% EtOAc/Hexane) affording the title compound (260 mg, 75%) as a white solid: LC-MS (ES) m/z 255 $(M+H)^+$.

c) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-furancarboxamide

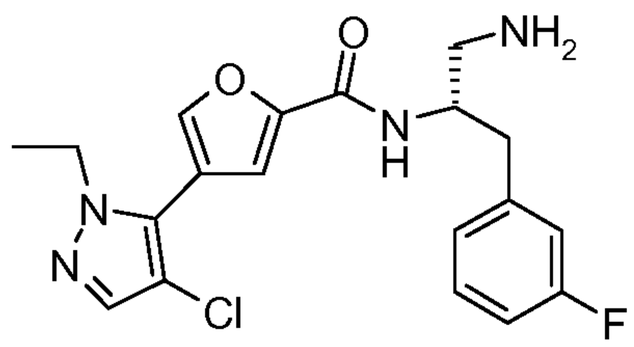


To a solution of methyl 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (250 mg, 0.98 mmol) in THF/H_2O (5mL/0.5 mL) was added KOH (200 mg, 3.56 mmol). The reaction mixture was heated to 50° C for 4 h. After the

mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (5mL x3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without further purification: LC-MS (ES) m/z 241 $(M+H)^+$.

To the above crude acid in DCM (5 mL) at 25 °C was added PyBrOP (550 mg, 1.18 mmol) in one portion, followed by the addition of DIPEA (0.7 mL, 4.01 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (322 mg, 1.08 mmol) was added to the reaction solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (360 mg, 70 %) as a white solid: LC-MS (ES) m/z 521 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

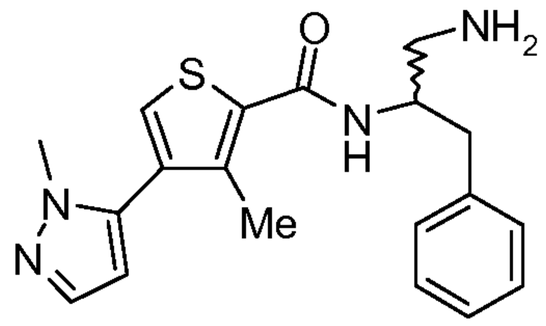


At RT, NH_2NH_2 (0.15 mL, 4.78 mmol) was added to a solution of 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-furancarboxamide (350 mg, 0.67 mmol) in MeOH (5 mL) . After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (15 mL) and washed with H_2O (10 mL x 3).

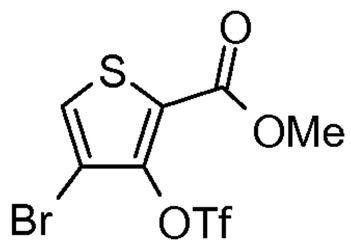
To the above DCM solution was added HCl (36%, 2 mL, 23.7 mmol)). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (260 mg, 78%) as an off-white solid: LC-MS (ES) m/z 391 $(M+H)^+$. NMR (d_6-DMSO, 400 MHz) δ ppm 8.70 (m, 1H), 8.29 (s, 1H), 8.02 (m, 2H), 7.70 (s, 1H), 7.50-7.45 (m, 1H), 7.36-7.30 (m, 1H), 7.14-7.08 (m, 2H), 7.06-7.01 (m, 1H), 4.43 (m, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.04-2.88 (m, 4H), and 1.30 (t, J = 7.3 Hz, 3H).

Example 254

N-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

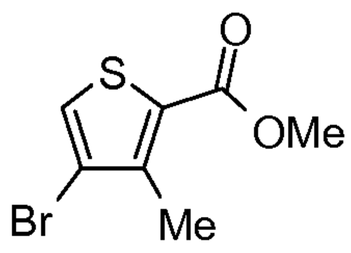


a) methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate



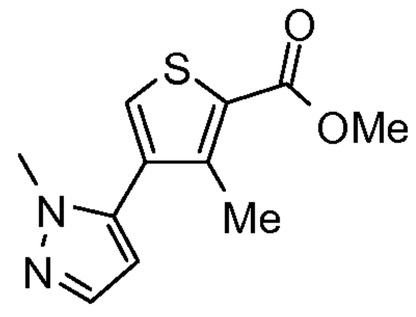
To a solution of methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate (0.948 g, 4.0 mmol) in CH_2Cl_2 (5 mL) and pyridine (1 mL) at 0 ^oC was added Tf_2O (1.0 mL, 6.0 mmol). The mixture was stirred for 1 h, poured onto ice water (10 mL) and extracted with CH_2Cl_2 (5 mL x 3). The collected organic layers were dried (Na_2SO_4) and concentrated to give a red syrup which was used directly in the next step without further purification: LC-MS (ES) m/z 370 $(M+H)^+$.

b) methyl 4-bromo-3-methyl-2-thiophenecarboxylate



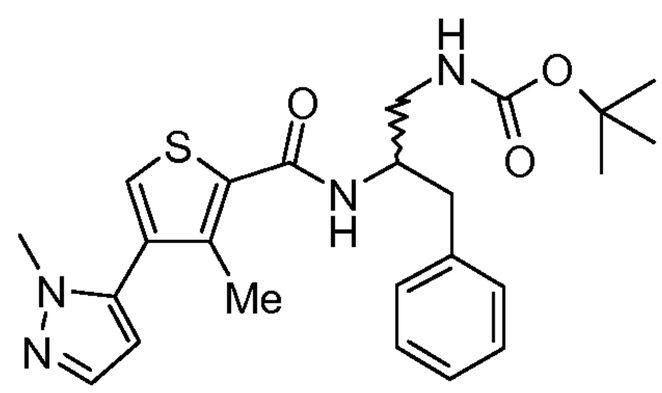
To a solution of methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate (825 mg, 2.25 mmol) in dioxane/H_2O (5 mL/1 mL) was added K_2CO_3 (930 mg, 6.75 mmol), tetrakistriphenylphosphine Pd(0) (260 mg, 0.22 mmol), and methylboronic acid (175 mg, 2.91 mmol). The reaction mixture was heated to 70° C in a sealed tube for 12h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 9:1) to give the title compound (441 mg, 84%) as a brown solid: LC-MS (ES) m/z 236 $(M+H)^+$.

c) methyl 4-[1-(dimethylamino)ethenyl]-3-methyl-2-thiophenecarboxylate



To a solution of methyl 4-bromo-3-methyl-2-thiophenecarboxylate (300 mg, 1.27 mmol) in dioxane/H_2O (5 mL/1 mL) was added K_2CO_3 (525 mg, 3.80 mmol), tetrakistriphenylphosphine Pd(0) (15 mg, 0.01 mmol), and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (345 mg,1.7 mmol). The reaction mixture was heated to 70 °C in a sealed tube for 2h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 9:1 to 4:1) to give the title compound (270mg, 90%): LC-MS (ES) m/z 237 $(M+H)^+$.

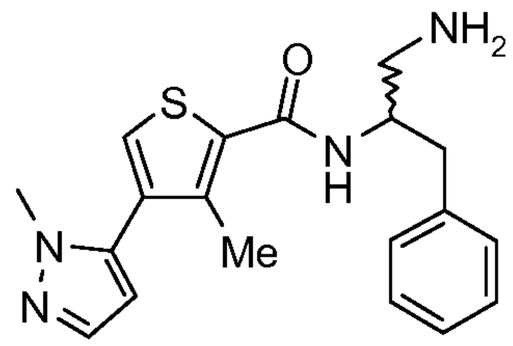
d) 1,1-dimethylethyl [2-({[3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of methyl 4-[1-(dimethylamino)ethenyl]-3-methyl-2-thiophenecarboxylate (50 mg, 0.21 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (122 mg, 2.1 mmol). The resulting mixture was heated to 50 °C for 2h. The THF was removed under vacuum and the aqueous layer was acidified with 6 N HCl to pH 3 and extracted with CH_2Cl_2 (5 mL x 3). The organic fractions was dried over Na_2SO_4 and concentrated to give the crude 3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly in the next step.

To a solution of the crude 3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid in DCM (2 mL) was added PyBrop (0.14 g, 0.3 mmol) and DIPEA (0.1 mL, 0.57 mmol). After 15 min, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate was added to the reaction in one portion and stirred for 2h at RT. The reaction solution was concentrated under vacuum and purified on silica gel (EtOAc /Hexane, 20-50%) to give the title compound (51 mg, 49 % for two steps) as a solid: LC-MS (ES) m/z 455 $(M+H)^+$.

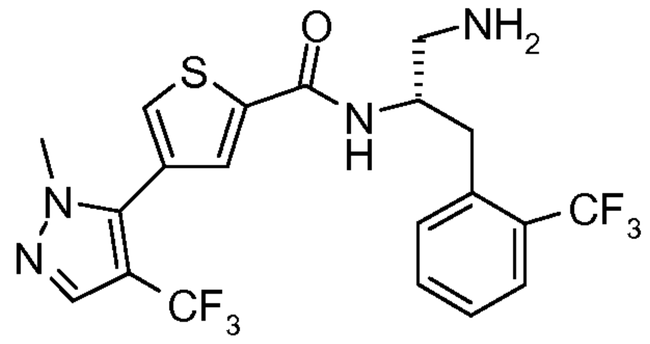
e) *N*-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



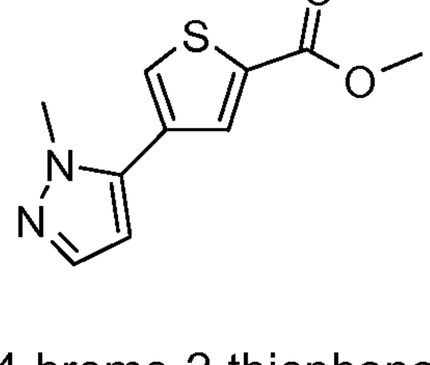
To a solution of 1,1-dimethylethyl [2-({[3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (51 mg, 0.11 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction was stirred over 5h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10 %) to afford the bis-TFA salt of the title compound. (16 mg, 41%): LC-MS (ES) m/z 355 $(M+H)^+$. NMR (d_4-MeOD, 400 MHz) δ ppm 7.64 (s, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.28-7.21 (m, 1H), 6.30 (d, J = 2.0 Hz, 1H), 4.58 (m, 1H), 3.69 (s, 3H), 3.27-3.13 (m, 2H), 3.07-2.93 (m, 2H), and 2.13 (s, 3H).

Example 255

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide



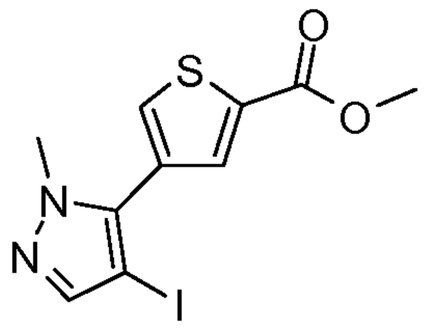
a) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1.0 g, 4.5 mmol) in dioxane/H_2O (5:1, 12 mL) was added K_2CO_3 (1.86 mg, 13.5 mmol), tetrakistriphenylphosphine Pd(0) (300 mg, 0.25 mmol), and 1-methyl-5-(4,4,5,5-

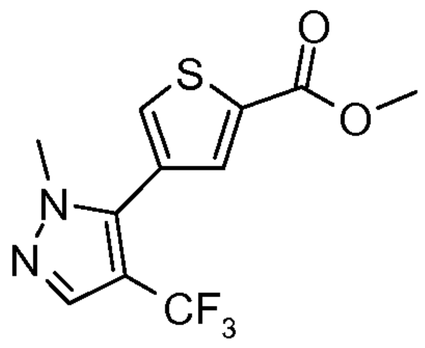
tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.23 g, 5.9 mmol). The reaction mixture was heated to 75° C in a sealed tube for 2h. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-40%) to give the title compound (701 mg, 70%) as a white solid: LC-MS (ES) m/z 223 $(M+H)^+$.

b) methyl 4-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



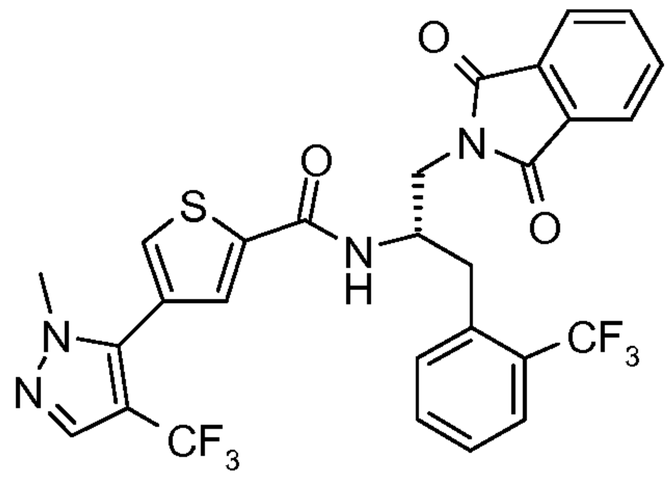
To a solution of methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (700 m g, 3.15 mmol) in THF (5 mL) was added NIS (922 mg, 4.09 mmol) in one portion. The reaction mixture was stirred at 75 °C for 10 h, and then cooled to room temperature. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-20%) to give the title compound (470 mg, 43%) as an off white solid: LC-MS (ES) m/z 350 $(M+H)^+$.

c) methyl 4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxylate



To a solution of methyl 4-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (470 mg, 1.35 mmol), copper (I) iodide (256 mg, 1.35 mmol) and potassium fluoride (78 mg, 1.35 mmol) in anhydrous DMF/HMPA (2 ml/2 mL) was added triethyl(trifluoromethyl)silane (745 mg, 4.04 mmol). The mixture was heated to 70 °C under N_2 in a sealed tube. After 10h, the reaction was quenched with NH_4Cl (sat'd) (2 mL), extracted with ether (5 mL x 5) and washed with distilled water (5 mL x 5). The combined organic phase was dried over Mg_2SO_4 and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.29 g, 74%) as a yellow syrup: LC-MS (ES) m/z 291 $(M+H)^+$.

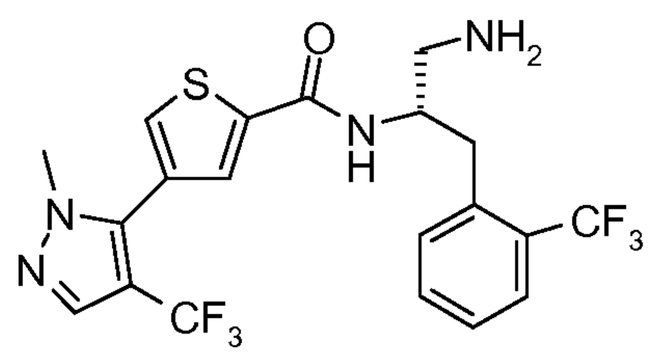
d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide



To a solution of methyl 4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxylate (150 mg, 0.52 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (116 mg, 2.0 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 277 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (279 mg, 0.59 mmol) in one portion, followed by the addition of DIPEA (0.5 mL, 2.87 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (174 mg, 0.5 mmol). After 2h, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (0.21 g, 67% for 2 steps): LC-MS (ES) m/z 607 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide

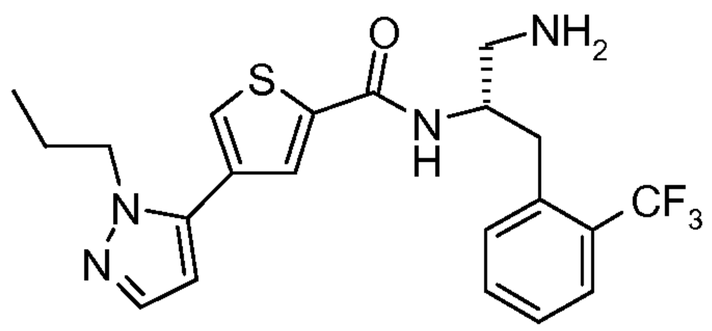


N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide (210 mg, 0.35 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.9 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-

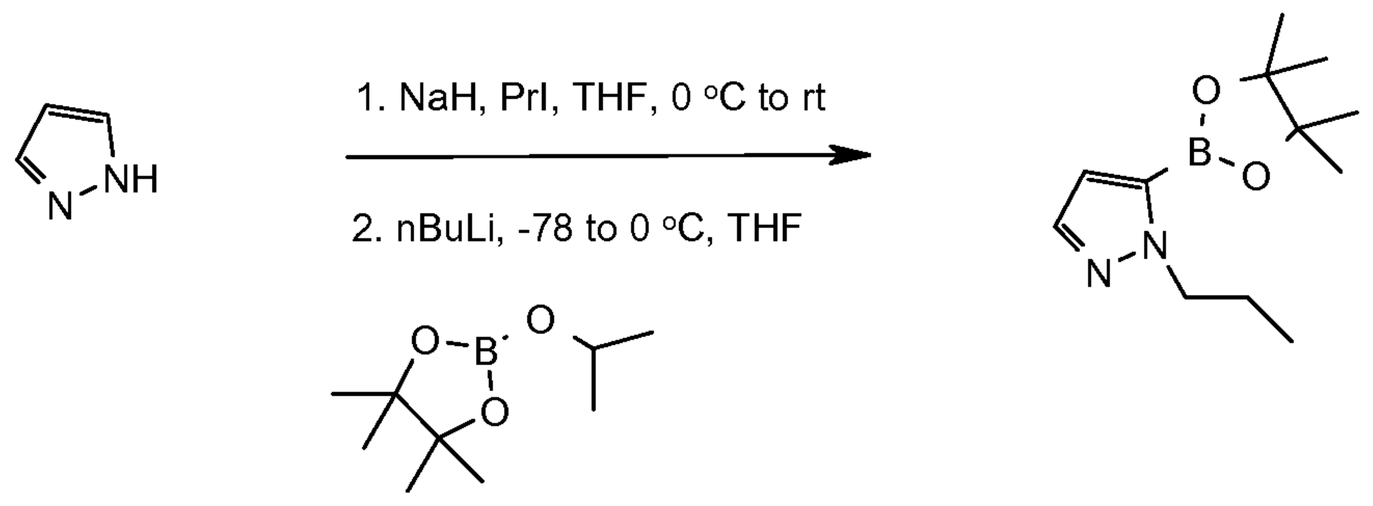
10%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water, and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH and treated with HCl (aq). After stirring overnight, the reaction was concentrated to give the title compound (95 mg, 57%) as a white solid. LC-MS: LC-MS (ES) m/z 477 $(M+H)^+$. NMR (d_6-DMSO, 400 MHz): δ ppm 8.92 (d, J = 9.1 Hz, 1H), 8.06 (m, 4H), 7.99 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.53 (m, 1H), 7.43 (m, 1H), 4.49 (m, 1H), 3.83 (s, 3H), and 3.14-2.99 (m, 4H).

Example 256

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



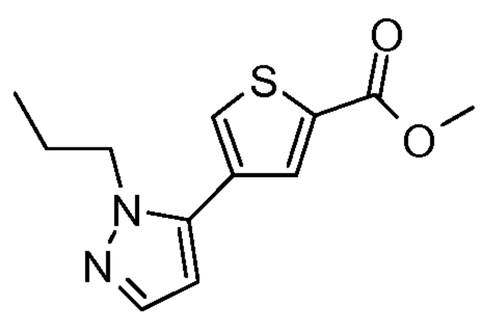
a) 1-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



To a suspension of NaH (60% in mineral oil, 4.0 g, 100 mmol) in THF (200 mL) was added 1H-pyrazole (6.8 g, 100 mmol) at 0 °C portionwise. After stirring at RT for 1h, PrI (17.85 g, 105 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 10h and monitored by LC-MS: m/e = 111 $(M+H)^+$. After the reaction was complete, NaI was removed by filtration. The resulting 1-propyl-1*H*-pyrazole containing THF solution was used directly in the next step.

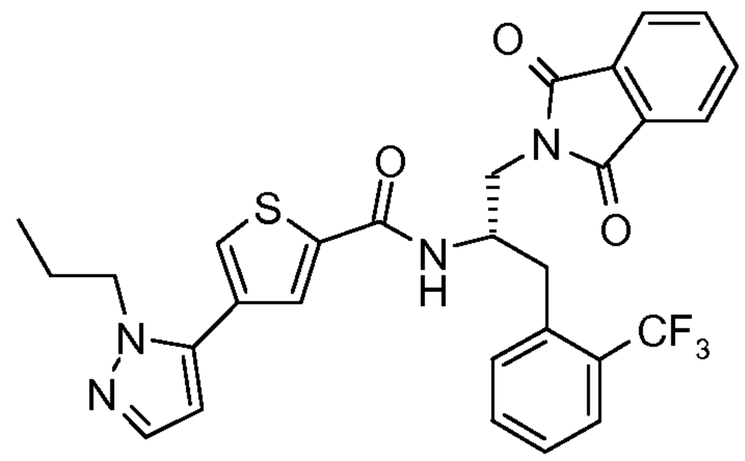
To the above THF solution of 1-propyl-1*H*-pyrazole was added n-BuLi (2.5M in Hexane, 40 mL, 100 mmol) at -78°C,. The reaction solution was stirred for 2 hours at RT and then re-cooled to -78°C [*J. Heterocyclic Chem*. **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.6 g, 100 mmol). After 30 min at -78°C, the reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown solid which was used directly without further purification: LC-MS (ES) m/z 154 $(M+H)^+$ for [RB(OH)2].

b) methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (221 mg, 1.0 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (414 mg, 3.0 mmol), tetrakistriphenylphosphine Pd(0) (60 mg, 0.05 mmol), and 1-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (404 mg, 1.5 mmol). The reaction mixture was heated to 70° C in a sealed tube for 2h. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-40%) to give the title compound (176 mg, 70%) as a white solid: LC-MS (ES) m/z 251 $(M+H)^+$.

c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

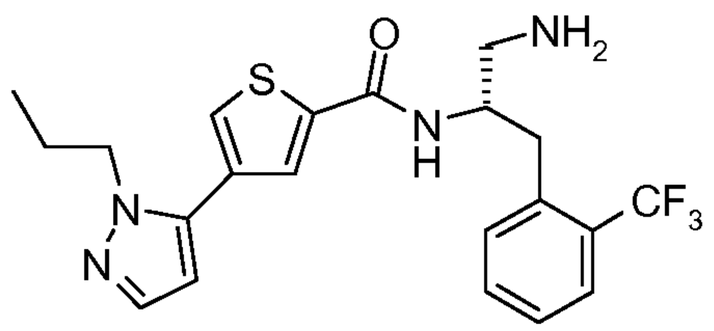


To a solution of methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate

(160 mg, 0.64 mmol) in THF/H_2O (2 mL/1 mL) was added KOH (151 mg, 2.56 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification. LCMS (ES) m/z = 237 $(M+H)^+$.

To the above acid in DCM (2 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (298 mg, 0.64 mmol) in one portion, followed by the addition of DIPEA (0.2 mL, 1.15 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (208 mg, 0.6 mmol). After 1h, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (0.22 g, 61% for 2 steps): LC-MS (ES) m/z 567 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

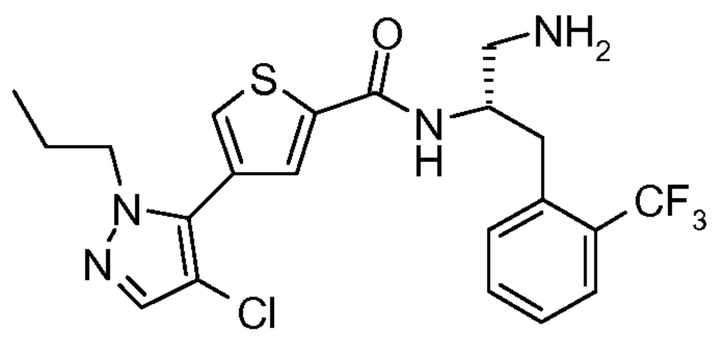


N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (220 mg, 0.36 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.3 mL, 9.56 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (4M in dioxane). After stirring overnight, the reaction solution was concentrated to give the title compound (112 mg, 57%) as an off white solid: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz): δ ppm 9.06-8.99 (m, 1H), 8.23-8.02 (m, 4H), 7.92 (br s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.62-7.49 (m, 3H), 7.42 (m,

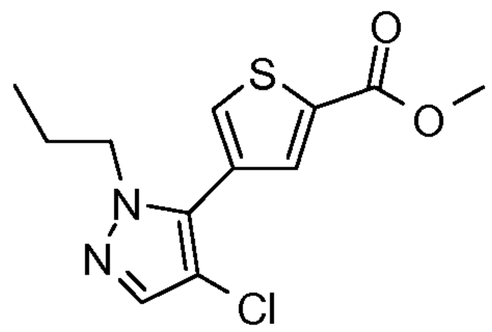
1H), 4.50 (m, 1H), 4.20 (m, 2H), 3.15-2.99 (m, 4H), 1.74 (m, 2H), and 0.80 (t, J = 7.3 Hz, 3H).

Example 257

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

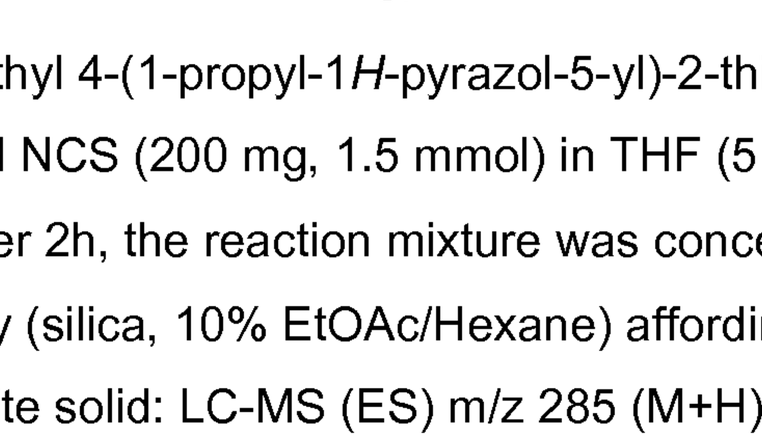


a) methyl 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.0 mmol) and NCS (200 mg, 1.5 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 10% EtOAc/Hexane) affording the title compound (199 mg, 70%) as a white solid: LC-MS (ES) m/z 285 $(M+H)^+$.

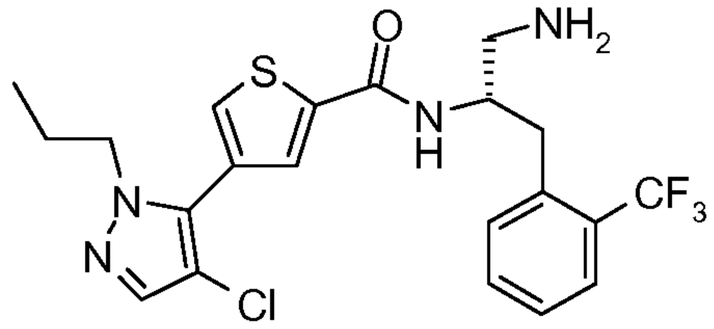
b) 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of methyl 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (199 mg, 0.7 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (100 mg, 1.7 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 271 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (326 mg, 0.7 mmol) in one portion, followed by the addition of DIPEA (0.3 mL, 1.15 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (232 mg, 0.7 mmol). After 10 min, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (312 mg, 74% for 2 steps): LC-MS (ES) m/z 601 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

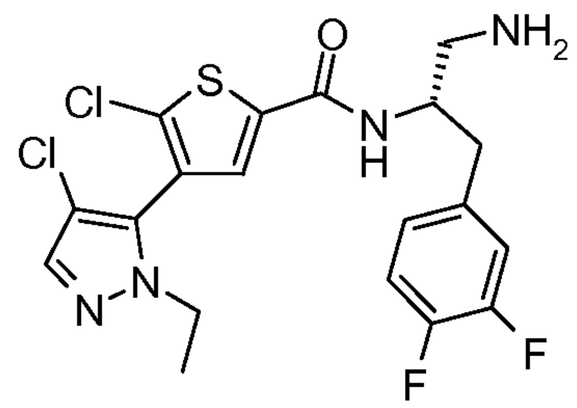


4-(4-Chloro-1-propyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (312 mg, 0.52 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.9 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the tile compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (aq). After stirring overnight, the reaction was concentrated to give the title compound (185 mg, 66%) as an off white solid: LC-MS (ES) m/z 471 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.92 (m, 2H), 7.74-7.68 (m, 1H), 7.60 (s, 1H), 7.58-7.51 (m, 2H), 7.45-7.41 (m,

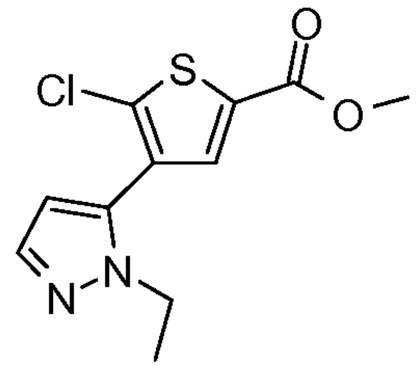
1H), 4.67 (m, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.37-3.09 (m, 4H), 1.77 (m, 2H), and 0.82 (t, J = 7.6 Hz, 3H).

Example 258

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

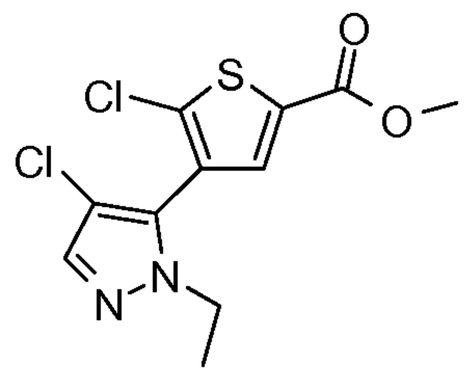


a) methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



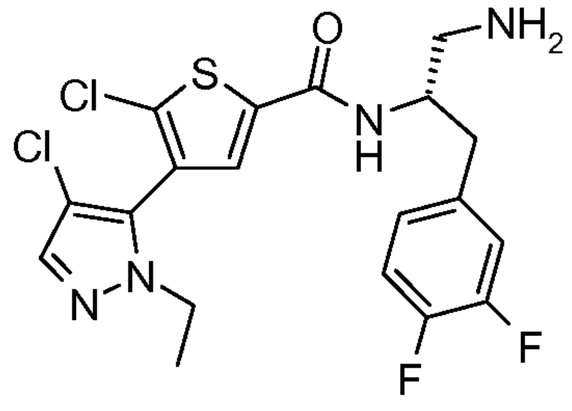
To a 100 mL sealed flask was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.61 g, 11.74 mmol), potassium carbonate (3.25 g, 23.48 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (2 g, 7.83 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.4 g, 0.78 mmol) in 1,2-dimethoxyethane (DME) (50 mL) and H_2O (10 ml). After stirring for 3h at 70 ºC, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [EtOAc/hexanes, 10-30%] to give the product [1.8 g, 85%] as an off white solid: LC-MS (ES) m/z 271 $(M+H)^+$.

b) methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



Methyl 5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.8 g, 6.65 mmol) and NCS (1.3 g, 9.74 mmol) in THF (10 mL) were heated to 70 °C under N_2 for 2 h. The reaction solution was concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (1.5 g, 74%) as a syrup: LC-MS (ES) m/z 305 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

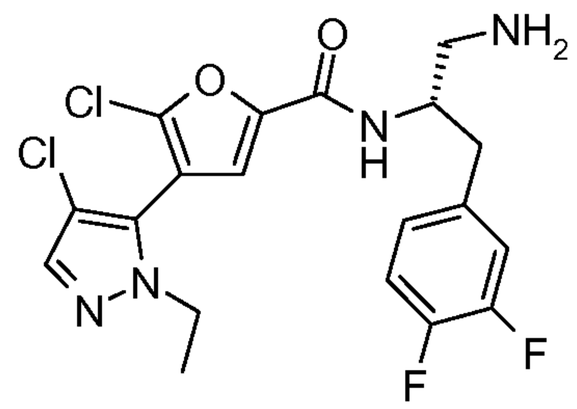


The title compound (290 mg, 58.4 %) was prepared as an off-white solid according to the procedure of Example 236, except substituting 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (526 mg, 1.662 mmol) for 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide: LC-MS (ES) m/z 459 $(M+H)^+$,

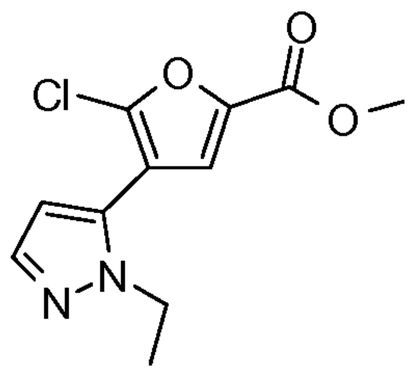
NMR (d_4-MeOD, 400 MHz) δ ppm 7.76 (m, 1H), 7.62 (s, 1H), 7.28-7.22 (m, 1H), 7.20-7.10 (m, 2H), 4.52 (m, 1H), 4.07 (m, 2H), 3.27-3.16 (m 2H), 3.05-2.94 (m, 2H), and 1.34 (m, 3H).

Example 259

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

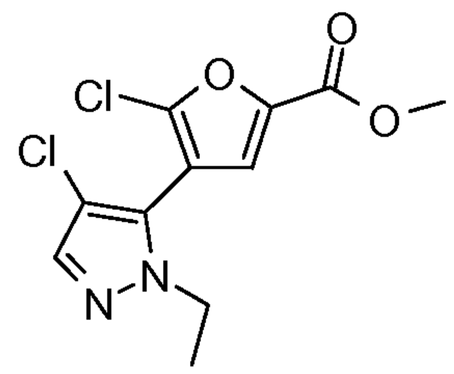


a) methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a 100 mL sealed flask was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.61 g, 11.74 mmol), potassium carbonate (3.25 g, 23.48 mmol), methyl 4-bromo-5-chloro-2-furancarboxylate (1.85 g, 8.33 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.16 g, 0.31 mmol) in 1,2-Dimethoxyethane (DME) (30 mL) and H_2O (5 mL). After stirring for 2h at 75 ºC, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [EtOAc/hexanes, 10-30%] to give the product (0.8 g, 50.1%) as an off-white solid: LC-MS (ES) m/z 255 $(M+H)^+$.

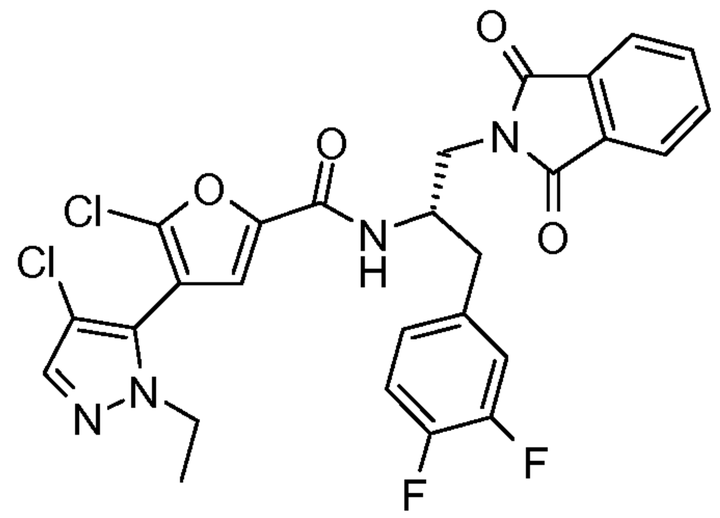
b) methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



A mixture of methyl 5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (800 mg, 3.14 mmol) and NCS (600 mg, 4.49 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 2h, the reaction mixture was concentrated and purified

via column chromatography (silica, 10-20% EtOAc/Hexane) affording the title compound (710 mg, 78%) as a white solid: LC-MS (ES) m/z 289 $(M+H)^+$.

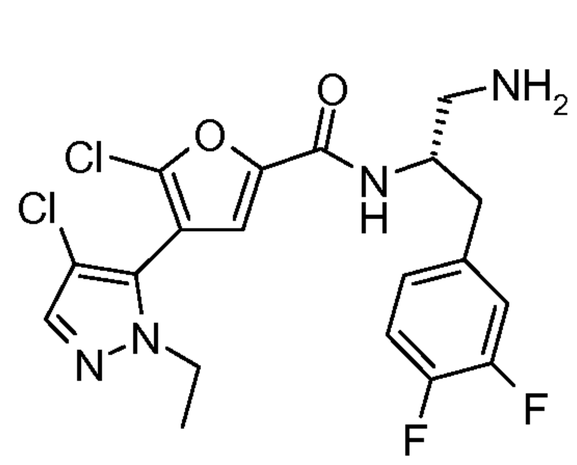
c) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide



To a solution of methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate (480 mg, 1.66 mmol) in THF/H_2O (5mL/1 mL) was added KOH (460 mg, 8.20 mmol). The reaction mixture was heated to 50° C for 4 h. After the mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (10 mL x3). The collected organic layers were concentrated under vacuum to give a crude acid (420 mg, 92%), which was used directly without further purification: LC-MS (ES) m/z 275 $(M+H)^+$.

To the above acid (400 mg) in DCM (5 mL) at 25 °C was added PyBrOP (881 mg, 1.89 mmol) in one portion, followed by the addition of DIPEA (1.5 mL, 8.59 mmol). After 10 min, 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (506 mg, 1.60 mmol) was added. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 30-50 % EtOAc/Hexane) affording the title compound (655 mg, 79%) as a white solid: LC-MS (ES) m/z 573 $(M+H)^+$.

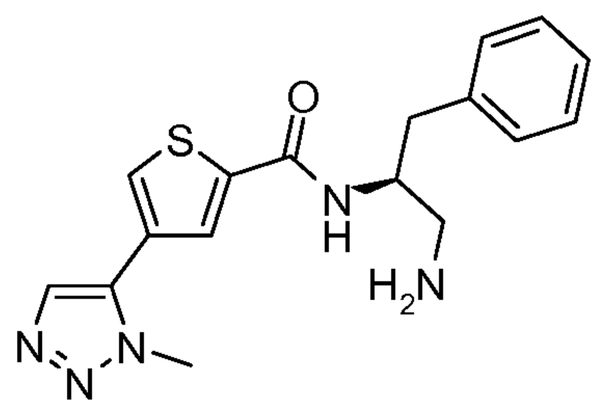
c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide



At RT, NH_2NH_2 (0.5 mL, 15.93 mmol) was added to a solution of 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide (610 mg, 1.06 mmol) in MeOH (5 mL). After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (20 mL) and washed with H_2O (20 mL x 3).

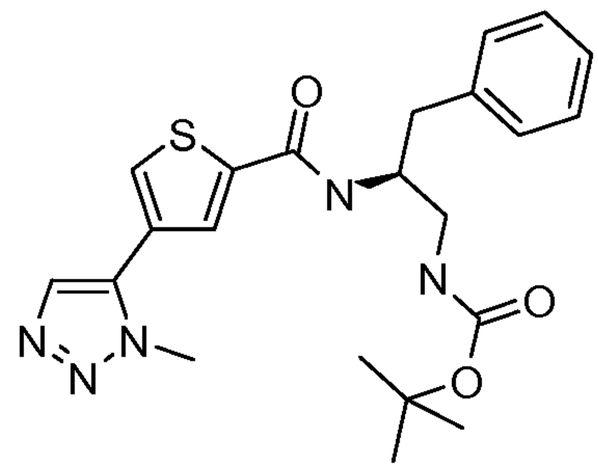
To the DCM solution was added HCl (36%, 10 mL, 120 mmol). After 1h, the aqueous phase was separated and washed with DCM (30 ml x 3). Water was removed under high vacuum to give the tilte compound (410 mg, 87%) as an off-white solid: LC-MS (ES) m/z 443 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.61 (s, 1H), 7.36 (s, 1H), 7.29-7.10 (m, 3H), 4.57 (m, 1H), 4.09 (q, J = 7.3 Hz, 2H), 3.27-3.23 (m, 1H), 3.20-3.14 (m, 1H), 3.06-3.01 (m, 1H), 2.97-2.92 (m, 1H), and 1.36 (t, J = 7.3 Hz, 3H).

Example 260



Preparation of N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



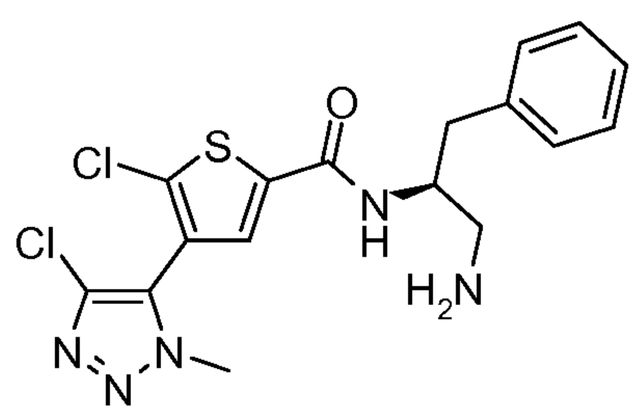
A mixture of 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (prepared according to Preparation 22 except substituting

2-[(2S)-2-amino-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione for 2-[(2S)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione) (236 mg, 0.537 mmol), 1-methyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole (200 mg, 0.537 mmol) (prepared according to patent IPN WO97/01553), $Pd(PPh_3)_2Cl_2$ (37.7 mg, 0.054 mmol), TRIETHYLAMINE (74.9 µl, 0.537 mmol) and toluene (3 ml) was degassed by N_2 and sealed. The reaction mixture was heated at 110 °C for 4 hr. LC/MS showed the reaction was completed. The reaction mixture was concentrated and purified *via* column chromatography (silica, 70% EtOAc in hexane) to give the title product (120 mg, 51%) LCMS (ES) m/z = 442.2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

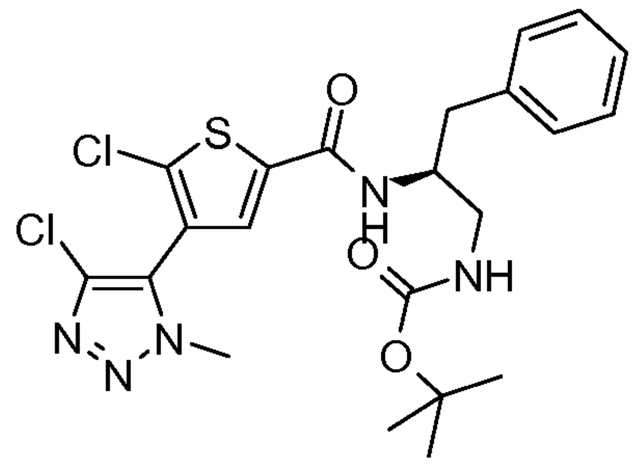
A solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (60 mg, 0.14 mmol) in TFA-DCM (4ml, 1:3) was stirred at rt for 1h. LCMS showed the reaction was completed. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (5%-65% acetonitrile in water with 0.1% TFA) to give 42.2 mg (67%) of the TFA salt as a white solid. LCMS (ES) m/z 342.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.52 Hz, 1H), 7.87-7.91 (m, 2H), 7.34-7.21 (m, 5H), 4.55 (m, 1H), 4.19 (s, 3H), 3.30-3.21 (m, 1H), 3.09-3.18 (m, 1H), 3.01 (d, J=7.6Hz, 2H)

Example 261



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-Dimethylethyl [(2*S*)-2-({[5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol- 5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

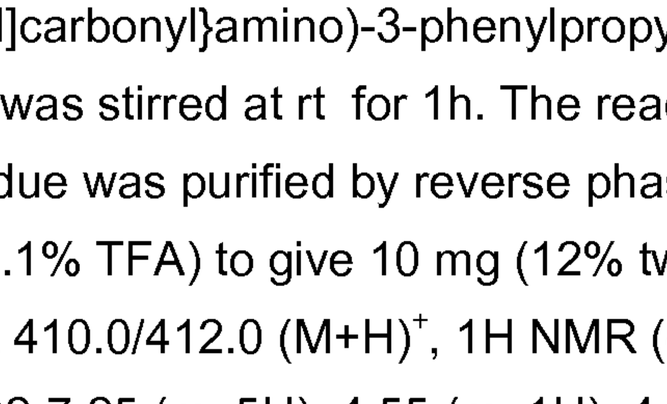


To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (70 mg, 0.16 mmol) in 2 ml of DMF was added NCS (42.3 mg, 0.32 mmol). The reaction mixture was heated at 50 °C for 2 hr and then diluted with 50 ml of EtOAc. The organic layer was washed with H_2O and concentrated to give the title product as a crude mixture, which was used in next step without purification. LCMS (ES) m/z = 510.2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from a) in TFA-DCM (4ml, 1:3) was stirred at rt for 1h. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (5%-65% acetonitrile in water with 0.1% TFA) to give 10 mg (12% two steps) of white solid as TFA salt. LCMS (ES) m/z 410.0/412.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.62 (s, 1H), 7.32-7.25 (m, 5H), 4.55 (m, 1H), 4.02 (s, 3H), 3.21 (m, 1H), 3.10 (m, 1H), 2.98 (d, 2H).

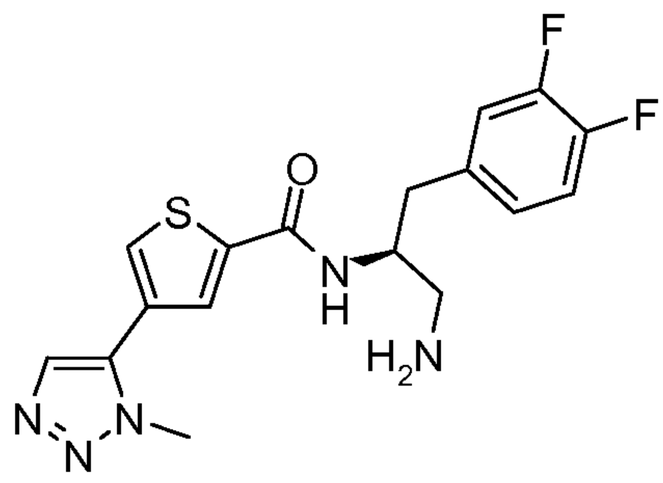
Example 262



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

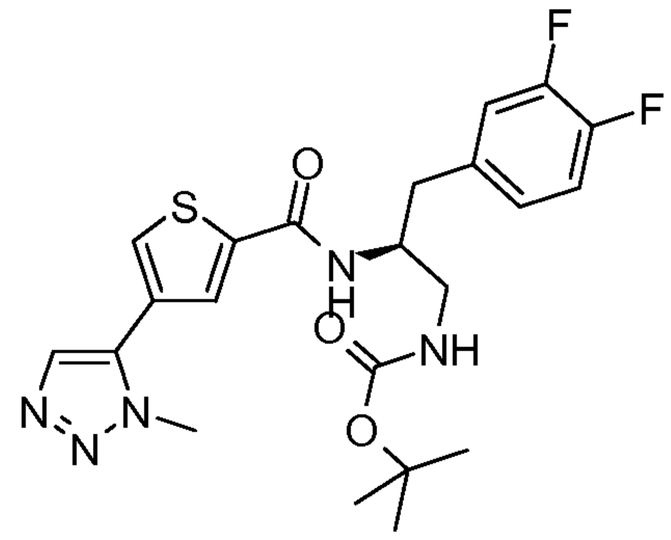
The title compound was prepared as a white solid according to the procedure of Example 260, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-fluorophenyl)propyl]carbamate (123mg, 0.27mmol) for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LCMS (ES) m/z 360.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.05 (d, J=1.6 Hz, 1H), 7.89-7.91 (m, 2H), 7.33-7.30 (m, 2H, 7.06-7.02 (m, 2H), 4.55 (m, 1H), 4.20 (s, 3H), 3.23 (m, 1H), 3.17 (m, 1H), 2.99 (m, 2H).

Example 263



Preparation of N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-Dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate



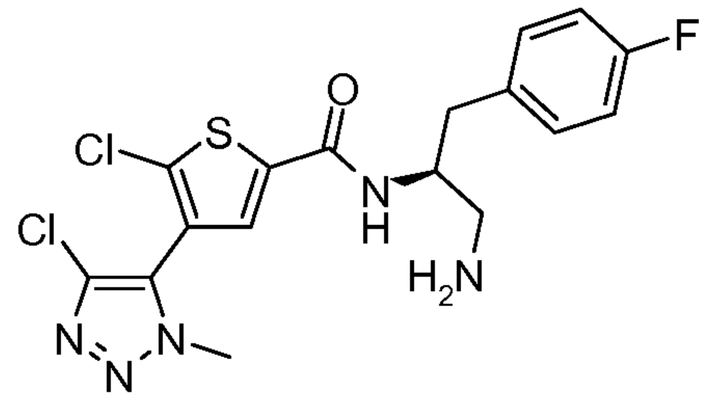
A solution of 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-di-fluorophenyl)propyl]carbamate (50 mg, 0.11 mmol), 1-methyl-5-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-1,2,3-triazole (44 mg, 0.21 mmol) , Na_2CO_3 (2N, 0.1ml) and $PddppfCl_2$ (8.6 mg, 0.01 mmol) in 3 ml of 1,4-dioxane was irridiated in MW reactor at 150 °C for 20 min. The crude reaction mixture was purified by column chromatography (silica, 70% EtOAc in hexane) to give the title product (29 mg, 46%): LCMS (ES) m/z = 478.2 (M+H).

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared according to Example 260 b) except substituting 1,1-dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate (29mg, 0.06mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 378.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.07 (d, J=1.6 Hz, 1H), 7.88-7.91 (m, 2H), 7.23-7.09 (m, 3H), 4.55 (m, 1H), 4.20 (s, 3H), 3.24 (m, 1H), 3.15 (m, 1H), 2.98 (m, 2H).

Example 264

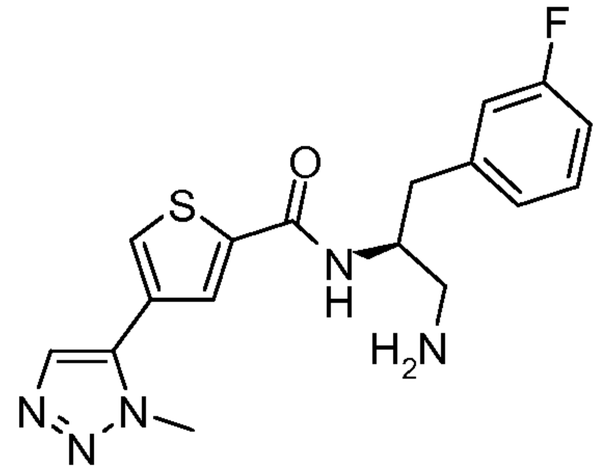


Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-(4-fluorophenyl)propyl]carbamate (68 mg, 0.15 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 428.0/430.0 $(M+H)^+$, 1H NMR (400 MHz,

METHANOL-*d*4) δppm 7.66 (s, 1H), 7.30 (m, 2H), 7.04 (m, 2H), 4.55 (m, 1H), 4.02 (s, 3H, 3.21-3.10 (m, 2H), 2.98 (m, 2H).

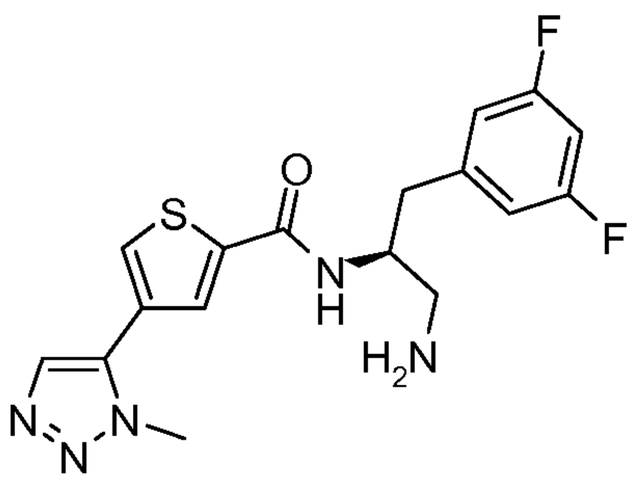
Example 265



Preparation *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-fluorophenyl)propyl]carbamate (300mg, 0.66mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 360.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.6 Hz, 1H), 7.90 (m, 2H), 7.33-7.30 (m, 1H), 7.13-7.09 (m, 2H), 6.98-6.95 (m, 1H), 4.55 (m, 1H), 4.19 (s, 3H), 3.24 (m, 1H), 3.17 (m, 1H), 3.04-2.99 (m, 2H).

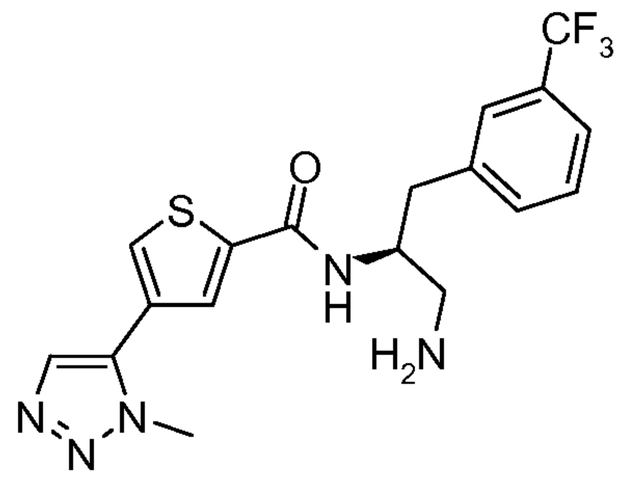
Example 266



Preparation *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,5-difluorophenyl)propyl]carbamate (300mg, 0.66mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 378.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.6 Hz, 1H), 7.91 (m, 2H), 6.96-6.93 (m, 2H), 6.84-6.83 (m, 1H), 4.55 (m, 1H), 4.19 (s, 3H), 3.24 (m, 1H), 3.19 (m, 1H), 3.05-2.98 (m, 2H).

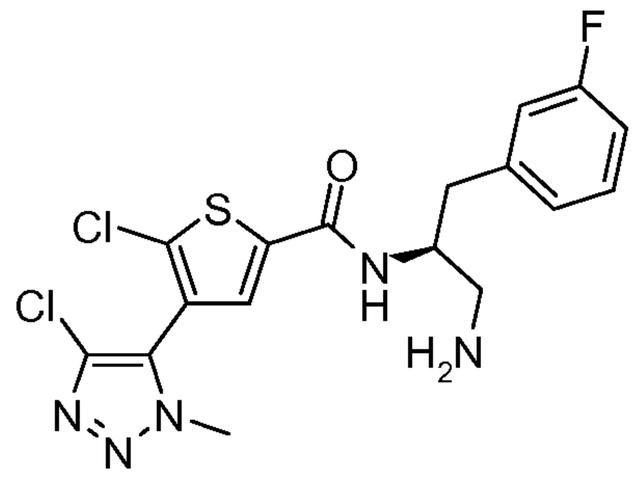
Example 267



Preparation *N*-{(1*S*)-2-amino-1-[(3-trifluoromethylphenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-(trifluoromethyl)phenyl)propyl]carbamate (500 mg, 0.99 mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 410.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.2 Hz, 1H), 7.97 (s, 1H), 7.91 (s, 1H), 7.72 (d, J=1.2Hz, 1H) 7.54 (m, 2H), 7.44 (m, 1H), 4.55 (m, 1H), 4.21 (s, 3H), 3.30-3.10 (m, 4H).

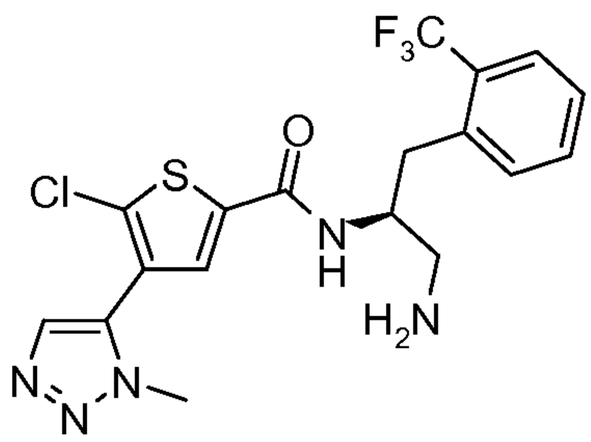
Example 268



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

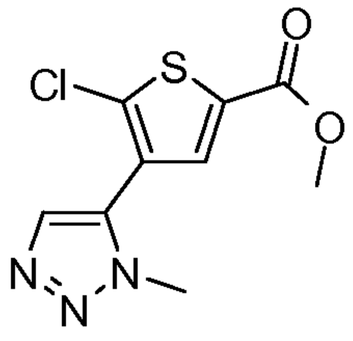
The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-(3-fluorophenyl)propyl]carbamate (50mg, 0.11mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 428.0/430.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.63 (s, 1H), 7.33 (m, 1H), 7.12-7.07 (m, 3H), 4.55 (m, 1H), 4.02 (s, 3H), 3.23-2.98 (m, 4H).

Example 269



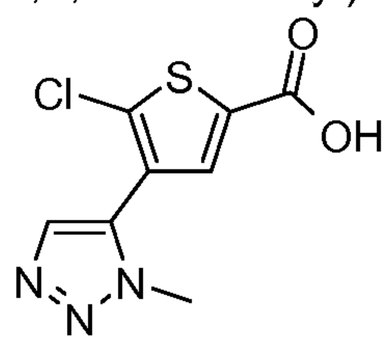
Preparation of N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate



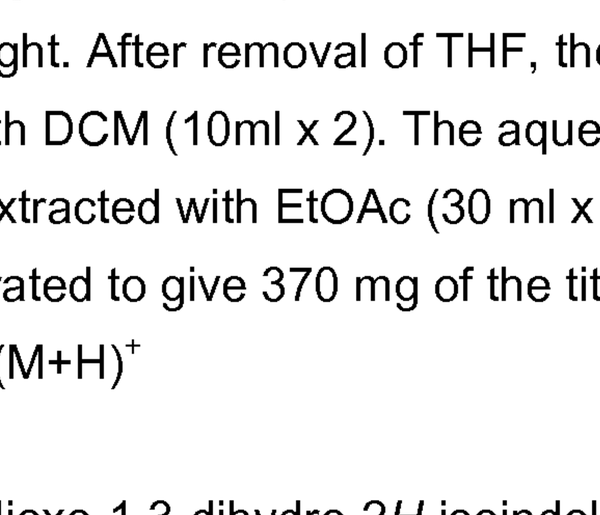
A mixture of 1-methyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole (2.0 g, 5.37 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (1.25 g, 4.9 mmol), $Pd(PPh_3)_2Cl_2$ (171 mg, 0.244 mmol), TRIETHYLAMINE (0.68 ml, 4.89 mmol) and toluene (3 ml) was heated at 110 °C for 4hr under N_2. The reaction mixture was purified *via* column chromatography (silica, 50%-70% EtOAc in hexane) to give the title compound as a white solid (400 mg, 32%): LCMS (ES) m/z 258.2 $(M+H)^+$.

b) 5-Chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate (400 mg, 1.55 mmol) and 1N LiOH (2.0 ml, 2.0 mmol) in THF (6 ml) was stirred at rt overnight. After removal of THF, the residue was diluted with 10 ml of H_2O and washed with DCM (10ml x 2). The aqueous layer was acidified to pH 3 with 1N HCl and then extracted with EtOAc (30 ml x 4). The organic layers were combined and concentrated to give 370 mg of the title compound as a white solid. LCMS (ES) m/z 244.0 $(M+H)^+$

c) 5-Chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

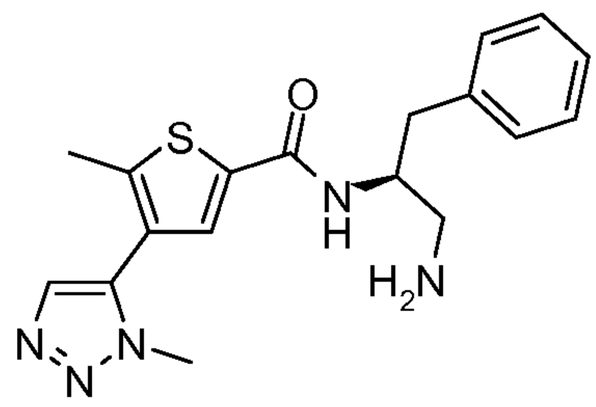


A solution of 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid (370mg, 1.52mmol), 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (from Preparation 6, 529mg, 1.52 mmol), PyBrop (708 mg, 1.52 mmol) and DIPEA (2.65 ml, 15.2 mmol) in 20 ml of DCM was stirred at rt for 2hr. The reaction mixture was diluted with 50 ml of DCM and washed with H_2O, 0.1N HCl and brine. The organic layer was concentrated and the residue was purified *via* column chromatography (silica, 50%-70% EtOAc in hexane) to give the title compound as a white solid (700mg, 80%): LCMS (ES) m/z 574.0 $(M+H)^+$.

d) N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

A solution of 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide (700 mg, 1.22 mmol) and hydrazine (0.19 mL, 6.1 mmol) in 5 mL of MeOH was stirred at rt overnight, diluted with 200 ml of H_2O and extracted with DCM (100 ml x2). The combined organic layers were concentrated and the resulting solid was dissolved in 6N HCl (50 ml). The aqueous layer was washed with DCM (50 ml x2). The organic layers were discarded and the remaining aqueous solution was concentrated to give the product as an HCl salt (490mg, 75%): LCMS (ES) m/z 444.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.10(m, 1H), 7.92 (m, 1H), 7.73 (m, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 4.65 (m, 1H), 4.17 (s, 3H), 3.25-3.11 (m, 4H).

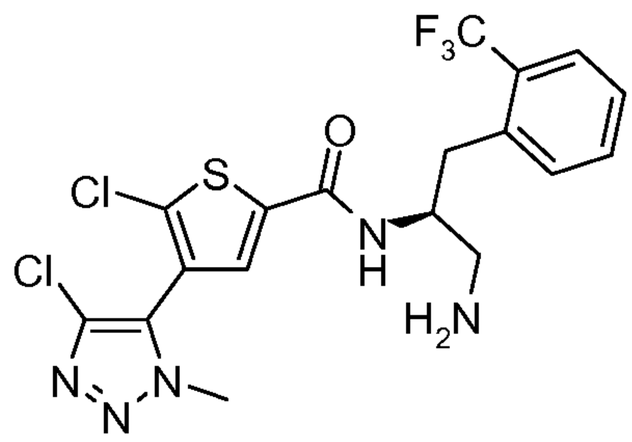
Example 270



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 269, except substituting methyl 4-bromo-5-methyl-2-thiophenecarboxylate (from Preparation 10) for methyl 4-bromo-5-chloro-2-thiophenecarboxylate and 2-{(2*S*)-2-amino-3-phenylpropyl}-1*H*-isoindole-1,3(2*H*)-dione (preparation 5) for 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 356.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.60 (s, 1H), 8.01(s, 1H), 7.34-7.21 (m, 5H), 4.55 (m, 1H), 4.26 (s, 3H), 3.25 (m, 2H), 3.03 (m, 2H), 2.21 (s, 3H).

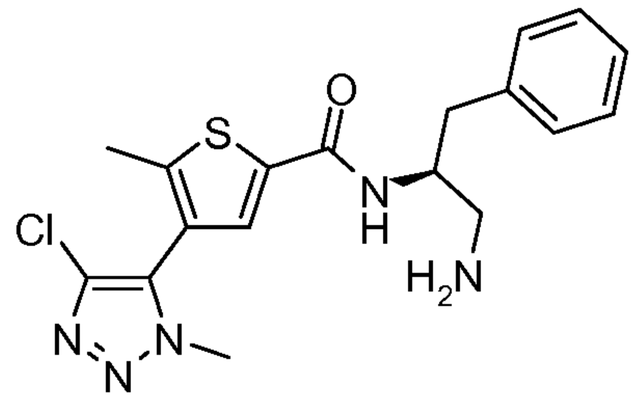
Example 271



Preparation of N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl) methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide (120 mg, 0.27 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 478.0/ 480.0$(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.79 (s, 1H), 7.73(d, J=7.6Hz, 1H), 7.56 (m, 2H), 7.45 (m, 1H), 4.65 (m, 1H), 4.05 (s, 3H), 3.29-3.10 (m, 4H).

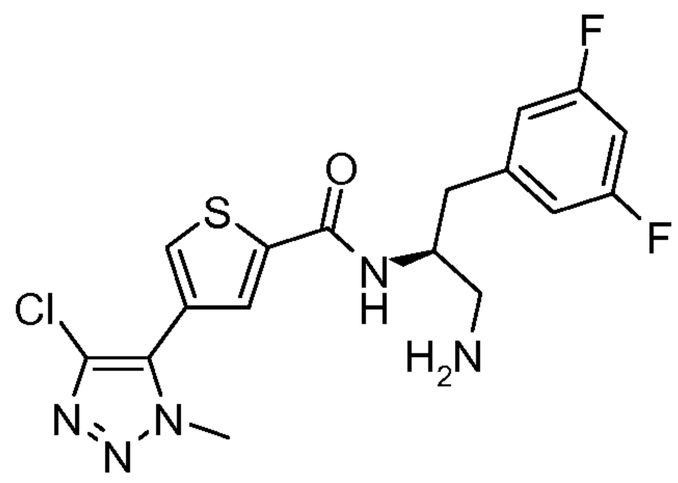
Example 272



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (prepared in Example 270) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 390.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.72(s, 1H), 7.31-7.22 (m, 5H), 4.55 (m, 1H), 3.99 (s, 3H), 3.19 (m, 2H), 3.02 (m, 2H), 2.41 (s, 3H).

Example 273



Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) Methyl 4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	457

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	457

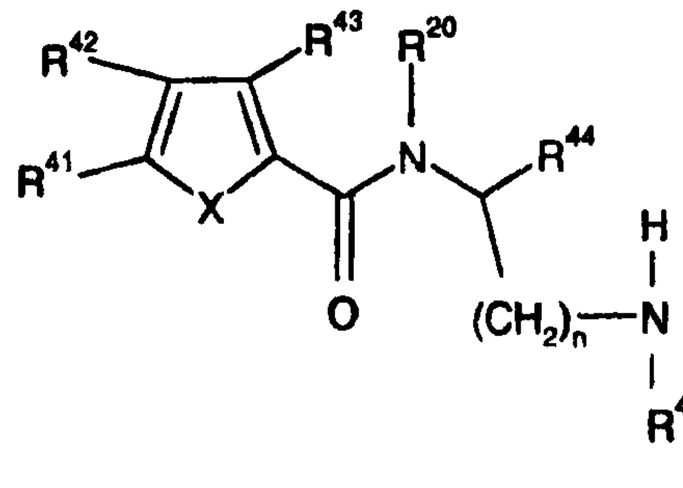
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

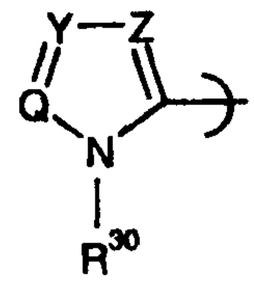
1. A compound of Formula (I),



(I)

wherein:

R^{41} is chlorine, ethyl, methyl or methoxy;

R^{42} is  ,

where Q is nitrogen, Y is –CH- and Z is $-C(R^{48})-$, and R^{30} is methyl or ethyl, where R^{48} is hydrogen, methyl, chlorine or bromine;

R^{43} is hydrogen;

R^{44} is $-CH_2$-phenyl wherein the phenyl is substituted by one or two substituents, wherein said substituents are fluorine or trifluoromethyl;

R^{45} is hydrogen;

R^{20} is hydrogen;

X is O or S; and

n is 1;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 which is:

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;
N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide; or
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;
or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 which is:
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide; or
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 which is:
N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;
or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 which is:
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;
or a pharmaceutically acceptable salt thereof.

6. Use of a compound defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or lessening the severity of a disease or condition, wherein the disease or condition is cancer or arthritis.

7. Use of a compound defined in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, for treating or lessening the severity of a disease or condition, wherein the disease or condition is cancer or arthritis.

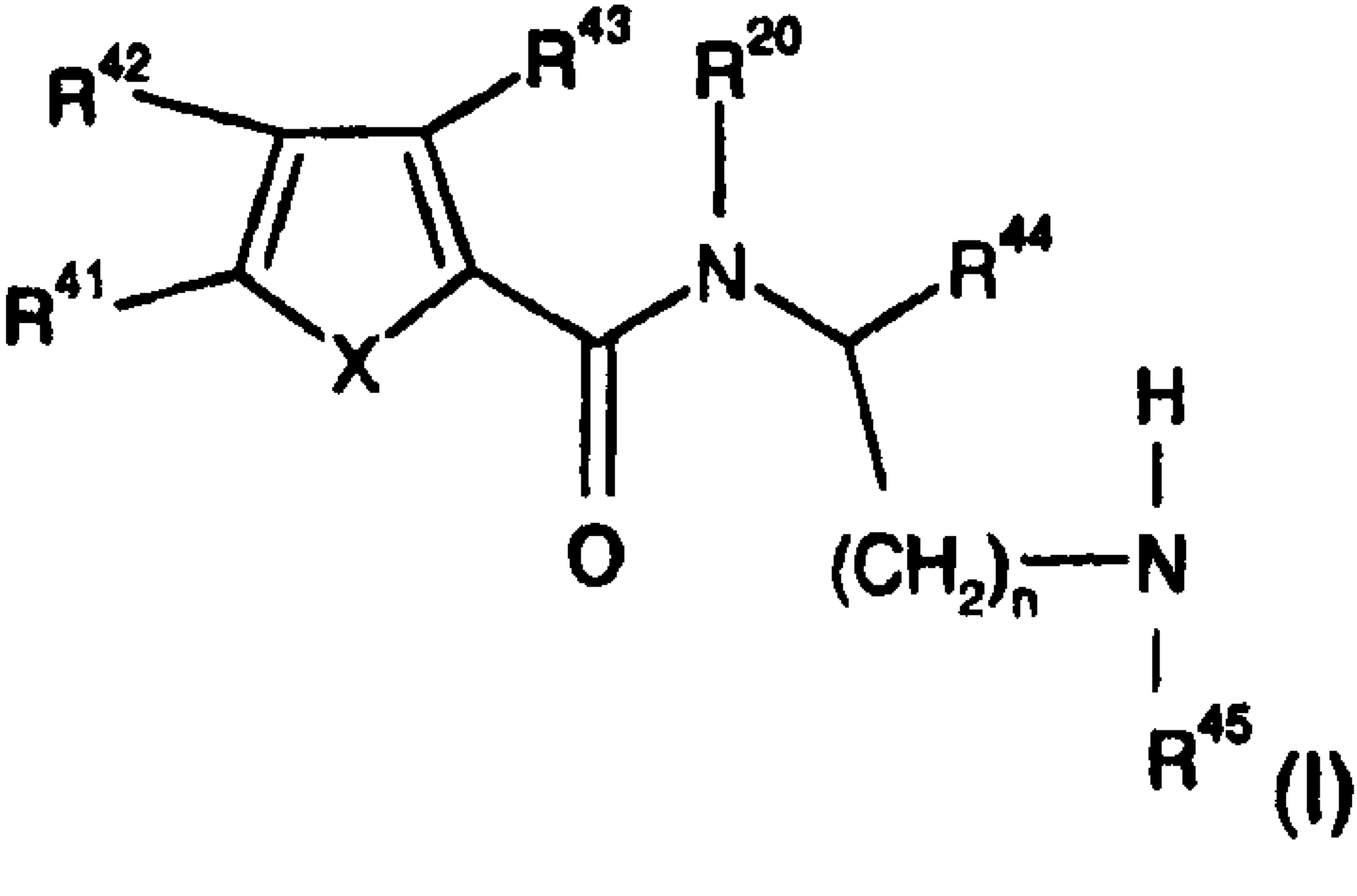
8. The use according to claim 6 or 7, wherein said cancer is brain cancer, glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid, Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, cancer of the mouth, gastrointestinal stromal tumor (GIST) or testicular cancer.

9. The use according to claim 8 wherein said cancer is brain cancer, glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma or thyroid.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition according to claim 10 which further comprises at least one anti-neoplastic agent.

12. The pharmaceutical composition according to claim 11 wherein the at least one anti-neoplastic agent is an anti-microtubule agent, a platinum coordination complex, an alkylating agent, an antibiotic agent, a topoisomerase II inhibitor, an antimetabolite, a topoisomerase I inhibitor, a hormone or hormonal analogue, a signal transduction pathway inhibitor; a non-receptor tyrosine kinase angiogenesis inhibitor; an immunotherapeutic agent; a proapoptotic agent; or a cell cycle signaling inhibitor.



(I)