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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 August 2010 (05.08.2010)

PCT

(10) International Publication Number
WO 2010/088177 A1

(51) International Patent Classification:
*C07D 471/02* (2006.01)

(21) International Application Number:
PCT/US2010/021945

(22) International Filing Date:
25 January 2010 (25.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/149,115 2 February 2009 (02.02.2009) US

(71) Applicants *(for all designated States except US)*: **MERCK SHARP & DOHME CORP.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **BANYU PHARMACEUTICAL CO., LTD.** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARMSTRONG, Donna, J.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **GOTO, Yasuhiro** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP). **HASHIHAYATA, Takashi** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP). **KATO, Tetsuya** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP). **KELLY, Michael, J., III** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LAYTON, Mark, E.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LINDSLEY, Craig, W.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **OGINO, Yoshio** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP). **ONOZAKI, Yu** [JP/JP]; Kitanomaru Square, 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667 (JP). **RODZINAK, Kevin, J.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **ROSSI, Michael, A.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **SANDERSON, Philip, E.** [GB/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **WANG, Jiabing** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **YAROSCHAK, Melissa, M.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK SHARP & DOHME CORP.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (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, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, 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, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, 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))*

**Published**:

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

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: INHIBITORS OF AKT ACTIVITY

(57) **Abstract**: The instant invention provides for compounds that inhibit Akt activity. In particular, the compounds disclosed selectively inhibit one or two of the Akt isoforms. The invention also provides for compositions comprising such inhibitory compounds and methods of inhibiting Akt activity by administering the compound to a patient in need of treatment of cancer.

WO 2010/088177 A1

TITLE OF THE INVENTION

INHIBITORS OF AKT ACTIVITY

BACKGROUND OF THE INVENTION

The present invention relates to compounds which are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB; hereinafter referred to as "Akt"). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer.

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-xL, 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 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-1), 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 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 by upstream kinases. In addition, introduction of constitutively active PI3K or Akt mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Three members of the Akt subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ (hereinafter referred to as "Akt1", "Akt2" and "Akt3"), respectively. The isoforms

are homologous, particularly in regions encoding the catalytic domains. Akts 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. The current model of Akt activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt 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 occurs on two regulatory sites, Thr308 in the catalytic domain activation loop and on Ser473 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 and Akt3. The upstream kinase, which phosphorylates Akt at the activation loop site has been cloned and termed 3'-phosphoinositide - dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt, 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 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.

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheng et al. Proc. Natl. Acad. Sci. U.S.A. 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheng 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).

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. Natl. 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.

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. No specific PDK1 inhibitors have been disclosed. 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).

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

It is also an object of the present invention to provide pharmaceutical compositions that comprise the novel compounds that are inhibitors of Akt.

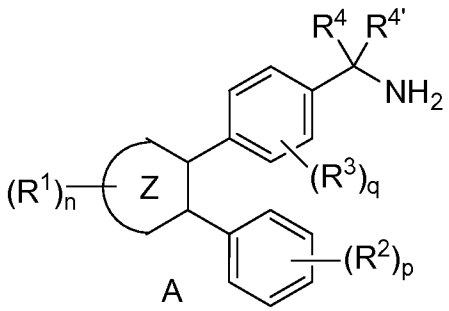
It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt activity.

## SUMMARY OF THE INVENTION

The instant invention provides for compounds that inhibit Akt activity. In particular, the compounds disclosed selectively inhibit one or two of the Akt isoforms. The invention also provides for compositions comprising such inhibitory compounds and methods of inhibiting Akt activity by administering the compound to a patient in need of treatment of cancer.

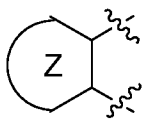
## DETAILED DESCRIPTION OF THE INVENTION

The compounds of the instant invention are useful in the inhibition of the activity of the serine/threonine kinase Akt. In a first embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula A:

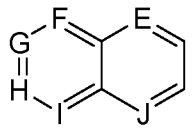



A

wherein:




is selected from:




and wherein E, F, G, H, I and J are independently selected from CH or N;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; n is 0, 1, 2, 3, 4, 5 or 6; p is 0, 1, 2, 3, 4 or 5 and q is 0, 1, 2, 3 or 4;

$R^1$ can be found on either ring of the bicyclic moiety and is independently selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^2$ is independently selected from: $(C_1\text{-}C_6)$alkyl, halo and OH, wherein said alkyl is optionally substituted with halo;

$R^3$ is independently selected from: $(C_1\text{-}C_6)$alkyl, halo and OH, wherein said alkyl is optionally substituted with halo;

$R^4$ and $R^{4'}$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)NR^7R^8$, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$, or $R^4$ and $R^{4'}$ can be taken together to form a $(C_3\text{-}C_8)$cycloalkyl or a monocyclic heterocycle optionally containing one to four heteroatoms selected from N, O and S, said cycloalkyl and monocyclic heterocycle optionally substituted with one or more substituents selected from $R^6$, wherein the $R^6$ substituent is optionally a spirocyclic moiety;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one to three substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

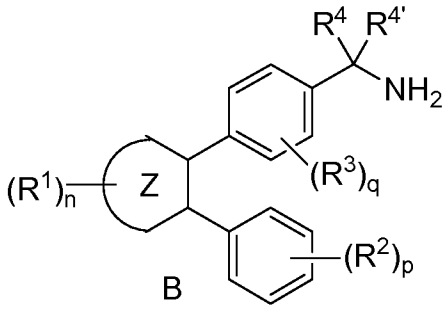
$R^7$ and $R^8$ are independently selected from: H, $(C=O)O_bC_1$-$C_{10}$ alkyl, $(C=O)O_bC_3$-$C_8$ cycloalkyl, $(C=O)O_b$aryl, $(C=O)O_b$heterocyclyl, $C_1$-$C_{10}$ alkyl, aryl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, heterocyclyl, $C_3$-$C_8$ cycloalkyl, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one to three substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one to three substituents selected from $R^{6a}$;

$R^a$ is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

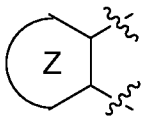
$R^b$ is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)_aO_b(C_1$-$C_6)$alkyl, or $S(O)_2R^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

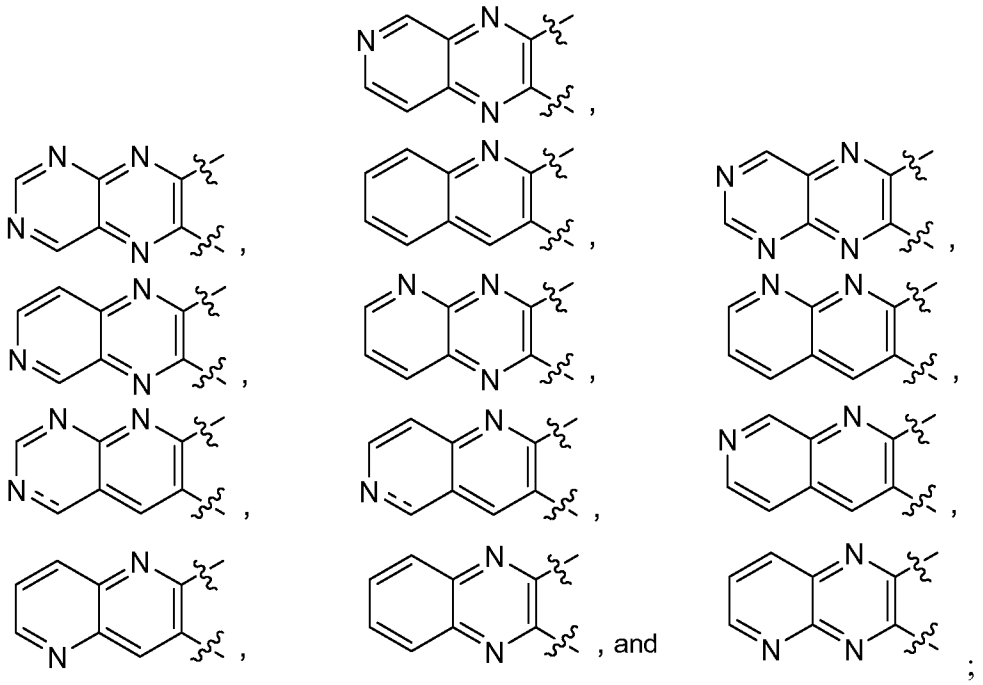
In a second embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula B:




wherein:



is selected from:

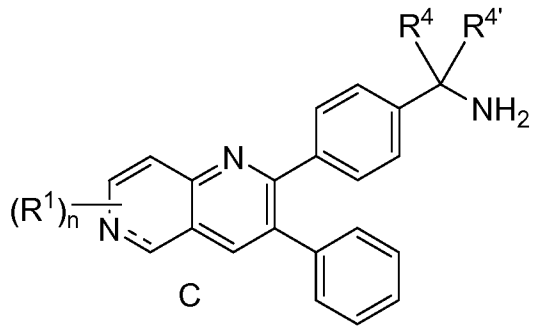


and wherein the dashed line is an optional double bond,

and all other substituents and variables are as defined in the first embodiment,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a third embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula C:



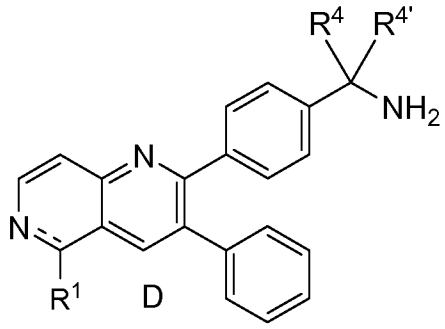
C

wherein the dashed line is an optional double bond,

and wherein all other substituents and variables are as defined in the first embodiment,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a fourth embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula D:




wherein the dashed line is an optional double bond,

and wherein all other substituents and variables are as defined in the first embodiment,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

A specific compound of the instant invention is:

2-[4-(1-amino-1-methylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**1-8**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine (**2-4**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine (**2-5**);

2-methyl-1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine (**2-6**);

2-[4-(1-amino-2-phenylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6*H*)-one (**2-7**);

2-[4-(1,2-diammonioethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine (**3-5**);

2-[4-(1-ammonio-2-fluoroethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine (**4-6**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopropanamine (**5-1**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**6-5**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopentanamine (**6-6**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclohexanamine (**6-7**);

[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**7-2**);

[4-(6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**8-2**);

[4-(6-benzyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**8-3**);

[4-(5-oxo-3-phenyl-6-propyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**8-4**);

[4-(6-ethyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**8-5**);

2-[4-(1-aminocyclobutyl)phenyl]-6-(difluoromethyl)-3-phenyl-1,6-naphthyridin-5(6H)-one (**9-1**);

{4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**10-3**);

{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-2**);

{4-[5-hydroxy-8-(2-methoxy-1,3-thiazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-3**);

{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-4**);

{4-[8-(3-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-5**);

{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-6**);

{4-[8-(1-benzofuran-2-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin -2-yl]phenyl}methanamine (**11-7**);
{4-[5-hydroxy-8-(5-methyl-2-furyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-8**);
{4-[5-hydroxy-8-(4-methylthien-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-9**);
{4-[8-(1-benzothien-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-10**);
{4-[8-(1-benzothien-7-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-11**);
{4-[8-(1-benzofuran-5-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-12**);
[4-(5-hydroxy-3-phenyl-8-thien-3-yl-1,6-naphthyridin-2-yl)phenyl] methanamine (**11-13**);
{4-[5-hydroxy-8-(3-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanamine (**11-14**);
{4-[5-hydroxy-8-(2-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-15**);
{4-[8-(2-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-16**);
{4-[8-(2-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-17**);
{4-[5-hydroxy-8-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-18**);
{4-[8-(3-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-19**);
{4-[5-hydroxy-8-(3-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-20**);
(4-{5-hydroxy-3-phenyl-8-[3-(trifluoromethyl)phenyl]-1,6-naphthyridin-2-yl}phenyl) methanamine (**11-21**);
{4-[5-hydroxy-8-(3-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-22**);
{4-[8-(3-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-23**);
{4-[5-hydroxy-8-(4-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-24**);
{4-[8-(4-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-25**);
{4-[8-(4-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-26**);

{4-[5-hydroxy-8-(4-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-27**);
{4-[8-(3,5-dimethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-28**);
{4-[8-(3,5-dichlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-29**);
{4-[8-(3-ethoxyphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-30**);
[4-(8-cyclohex-1-en-1-yl-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**11-31**);
{4-[5-hydroxy-8-(3-mercaptophenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-32**);
{4-[5-hydroxy-8-(2-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-33**);
(4-{5-hydroxy-8-[3-(hydroxymethyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) (**11-34**);
{4-[8-(3-cyanophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-35**);
{4-[5-hydroxy-8-(3-isopropylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-36**);
{4-[8-(1,1'-biphenyl-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-37**);
2-[4-(ammoniomethyl)phenyl]-8-[3-(dimethylamino)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridine (**11-38**);
{4-[8-(3-acetylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-39**);
(4-{5-hydroxy-8-[3-(methoxycarbonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**11-40**);
8-(3-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridine (**11-41**);
[4-(5-hydroxy-8-{3-[(methylamino)carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-42**);
(4-{5-hydroxy-8-[3-(methylsulfonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**11-43**);
{4-[8-(3-ethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-44**);
{4-[5-hydroxy-8-(3-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-45**);
6-[4-(ammoniomethyl)phenyl]-1-hydroxy-4-isobutyl-7-phenylisoquinoline(**11-46**);
{4-[5-oxo-3-phenyl-8-(1-propyl-1*H*-pyrazol-4-yl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-47**);
{4-[8-(4-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-48**);

{4-[5-oxo-3-phenyl-8-(2-thienyl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-49**);
[4-(5-oxo-3-phenyl-8-pyridin-3-yl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-50**);
[4-(5-oxo-3,8-diphenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-51**);
{4-[8-(2-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-52**);
{4-[8-(6-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-53**);
{4-[8-(3-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-54**);
{4-[8-(4-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-55**);
{4-[8-(2-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine (**11-56**);
{4-[6-methyl-8-(4-methyl-2-thienyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-57**);
{4-[8-(4-fluoro-3-methylphenyl)-6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine (**11-58**);
[4-(8-cyano-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-59**);
[4-(8-chloro-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-60**);
[4-(8-bromo-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**11-61**);
1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**12-5**);
1-[4-(8-cyano-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**12-6**);
[3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine (**13-6**);
[5-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)pyridin-2-yl] methanamine (**13-7**);
[2,3-difluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanamine (**13-8**);
[2-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanamine (**13-9**);
{4-[3-(4-chlorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine (**14-4**);
1-{4-[3-(4-fluorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**15-3**);
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-4**);
2-[4-(aminomethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine-4-carbonitrile (**17-7**);
(1*R*)-1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**18-4**);
1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropanamine (**19-5**);
1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-2**);

1-{4-[5-(2-oxopyrrolidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-7**);
1-(4-{3-phenyl-5-[(2-pyridin-4-ylethyl)thio]-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine (**20-8**);
2-[4-(1-ammoniocyclobutyl) phenyl]-5-diazan-2-iumyl-3-phenyl-1,6-naphthyridine (**20-9**);
1-(4-{5-[2,2-difluoro-2-(pyridin-4-yl)ethoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine (**20-10**);
1-(4-{5-[2-methyl-2-(pyridin-4-yl)propoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine (**20-11**);
1-(4-{5-[(2-fluoropyridin-4-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine (**20-12**);
1-{4-[3-phenyl-5-(pyridin-3-yloxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-13**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(1,3,4-thiadiazol-2-yl)-1,6-naphthyridin-5-amine (**20-14**);
2-[4-(1-aminocyclobutyl)phenyl]-N-(3-methyl-1H-pyrazol-5-yl)-3-phenyl-1,6-naphthyridin-5-amine (**20-15**);
1-{4-[3-phenyl-5-(piperidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-16**);
1-{4-[5-(3,3-difluoroazetidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-17**);
1-{4-[5-(3,3-difluoropiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-18**);
1-{4-[5-(4-hydroxypiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-19**);
2-[4-(1-aminocyclobutyl)phenyl]-N-(benzyloxy)-3-phenyl-1,6-naphthyridin-5-amine (**20-20**);
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine(**21-3**);
5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridine (**22-3**);
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-2-ylethyl)amino]-3-phenyl-1,6-naphthyridine (**22-4**);
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-4-ylethyl)amino]-3-phenyl-1,6-naphthyridine (**22-5**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(2- pyridine-2-ylethyl) amino]-1,6-naphthyridine (**22-6**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-piperidin-1-yl-1,6-naphthyridine (**22-7**);
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine (**22-8**);
2-[4-(ammoniomethyl) phenyl]-5-(benzylamino) -3-phenyl-1,6-naphthyridine (**22-9**);
2-({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}amino) ethanamine (**22-10**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrrolidin-1-yl-1,6-naphthyridine (**22-11**);
2-[4-(ammoniomethyl) phenyl]-5-(diethylamino) -3-phenyl-1,6-naphthyridine (**22-12**);
2-[4-(ammoniomethyl) phenyl]-5-(methylamino) -3-phenyl-1,6-naphthyridine (**22-13**);
2-[4-(ammoniomethyl) phenyl]-5-[bis(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine

(**22-14**);
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)(methyl) amino]-3-phenyl-1,6-naphthyridine (**22-15**);
2-[4-(ammoniomethyl) phenyl]-5-[ethyl(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine (**22-16**);
5-[4-(aminocarbonyl)piperidin-1-yl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridine (**22-17**);
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(2-pyridin-4-ylethyl)amino]-1,6-naphthyridine (**22-18**);
2-[4-(ammoniomethyl) phenyl]-5-morpholin-4-yl-3-phenyl-1,6-naphthyridine (**22-19**);
2-[4-(ammoniomethyl )phenyl]-5-[2-(hydroxymethyl) morpholin-4-yl]-3-phenyl-1,6-naphthyridine (**22-20**);
2-[4-(aminomethyl)phenyl]-N-ethyl-3-phenyl-1,6-naphthyridin-5-amine (**22-21**);
{4-[3-phenyl-5-(4H-1,2,4-triazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine (**22-22**);
[4-(3-phenyl-5-piperazin-1-yl-1,6-naphthyridin-2-yl)phenyl]methanamine (**22-23**);
4-[5-(ethylthio)-3-phenyl-1,6-naphthyridin-2-yl]benzylamine (**22-24**);
[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**22-25**);
[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**22-26**);
1-{4-[3-phenyl-5-(2-piperidin-1-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine (**23-1**);
2-[4-(ammoniomethyl) phenyl]-5-phenoxy-3-phenyl-1,6-naphthyridine (**23-2**);
(4-{5-[4-(aminocarbonyl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**23-3**);
{4-[5-(4-nitrophenoxy)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**23-4**);
(4-{5-[4-(1H-imidazol-1-yl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**23-5**);
(4-{3-phenyl-5-[4-(1H-1,2,4-triazol-1-yl)phenoxy]-1,6-naphthyridin-2-yl}phenyl) methanamine (**23-6**);
(4-{5-[4-(methoxycarbonyl) phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**23-7**);
2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)acetamide (**23-8**);
1-(4-{5-[(1-methylpiperidin-3-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**23-9**);
tert-butyl 2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethylcarbamate (**23-10**);
tert-butyl 4-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)butylcarbamate (**23-11**);
2-[3-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)propyl]pyridine (**23-12**);
2-[2-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethyl]pyridine (**23-13**);

2-[({2-[4-(ammoniomethyl )phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) methyl]morpholine (**23-14**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridine (**23-15**);
1-{4-[5-(2-morpholin-4-ylethoxy)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanamine (**23-16**);
1-{4-[3-phenyl-5-(2-piperidin-4-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine (**23-17**);
3-[2-({2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) ethyl]piperidine (**23-18**);
1-(4-{3-phenyl-5-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]-1,6-naphthyridin-2-yl}phenyl) methanamine (**23-19**);
4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl) benzylamine (**23-20**);
2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridine (**24-2**);
{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-3**);
[(3,3'-diphenyl-5,5'-bi-1,6-naphthyridine-2,2'-diyl)di-4,1-phenylene] dimethanamine (**24-4**);
4-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}benzyl)morpholine (**24-5**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(1H-pyrazol-1-ium-3-yl)-1,6-naphthyridine (**24-6**);
1-{4-[3-phenyl-5-(1H-pyrrol-2-yl)-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-7**);
3-{2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}aniline (**24-8**);
[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene] dimethanamine (**24-9**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrimidin-5-yl-1,6-naphthyridine (**24-10**);
3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridine (**24-11**);
4-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} pyridine (**24-12**);
1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl }methanamine (**24-13**);
5-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}isoquinoline (**24-14**);
{4-[3-phenyl-5-(3-thienyl)-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-15**);
1-{4-[5-(3,5-dimethylisoxazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-16**);
{4-[5-(3,5-dimethyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-17**);
1-(4-{5-[3-(benzyloxy) phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**24-18**);
1-(4-{5-[3-(benzyloxy)phenyl] -3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**24-19**);
{4-[5-(2-naphthyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-20**);
5-(4-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridine (**24-21**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(E)-2-phenylvinyl]-1,6-naphthyridine (**24-22**);
(4-{5-[4-(benzyloxy)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**24-23**);
{4-[5-(4-{[(2-hydroxyethyl) amino] carbonyl}phenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-24**);
3-[(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} benzoyl)amino]-N,N-dimethylpropan-1-amine (**24-25**);

[4-(5-{4-[(cyclopropylamino) carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**24-26**);

1-{4-[5-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**24-27**);

(1*R*)-1-{4-[3-phenyl-5-(1*H*-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-1**);

{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**25-2**);

(1R)-1-{4-[3-phenyl-5-(thiophen-3-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-3**);

(1R)-1-{4-[3-phenyl-5-(thiophen-2-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-4**);

(1R)-1-{4-[5-(5-chlorothiophen-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-5**);

1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclopropanamine (**26-1**);

1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**27-1**);

1,1'-[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene]dicyclobutanamine (**27-2**);

1-{4-[5-(3-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**27-3**);

1-{4-[5-(4-methyl-1,3-thiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**27-4**);

1-{4-[3-phenyl-5-(1,3-thiazol-2-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**27-5**);

2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro[3.4]octan-2amine (**28-9**);

2-{4-[3-phenyl-5-(pyridin-3-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2 amine (**28-10**);

2-{4-[3-phenyl-5-(pyridin-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine (**28-11**);

2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro [3.4]octan-2-amine (**29-1**);

trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**30-4**);

trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-3-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**31-1**);

2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridine (**32-2**);

1-[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**33-1**);

1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanamine (**34-2**);

1-[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-1-amine (**35-1**);

[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-2**);

[4-(5-isobutyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-3**);

[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-4**);

[4-(3-phenyl-5-propyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-5**);

[4-(5-benzyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-6**);

[4-(5-isopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**36-7**);
[4-(5-cyclohexyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**36-8**);
[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**36-9**);
[4-(5-butyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**36-10**);
{4-[5-(3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**36-11**);
trans-3-amino-1-cyclopropyl-3-{4-[3-phenyl-5-methyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol (**37-3**);
trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-methyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol (**38-2**);
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[( pyridine-4-ylmethoxy)methyl]-1,6-naphthyridine (**39-4**);
{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**40-1**);
{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**41-3**);
trans-3-amino-1-cyclopropyl-3-{4-[5-(fluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol (**42-4**);
trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol (**43-3**);
1-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**44-1**);
trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-(2-fluorophenyl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**45-1**);
1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutanamine (**46-2**);
1-[4-(5-{[(2-methoxypyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutanamine (**47-1**);
4-[({2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methoxy)methyl]pyridin-2(1H)-one (**48-1**);
1-[4-(5-{[(3-hydroxy[1,2,4]triazolo[4,3-a]pyridin-7-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**49-1**);
1-[4-(5-ethenyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**50-1**);
2-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}ethanol (**50-2**);
{4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**51-3**);
{4-[5-(4-hydroxybutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**51-4**);
{4-[5-(4-morpholin-4-ylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**51-5**);
{4-[5-(3-morpholin-4-ylpropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**51-6**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethyl)-1,6-naphthyridine (**51-7**);
2-[4-(ammoniomethyl) phenyl]-5-[2-(1-methyl-1H-imidazol-5-yl)ethyl]-3-phenyl-1,6-naphthyridine (**51-8**);
(4-{5-[2-(3-aminophenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl )methanamine (**51-9**);
(4-{5-[2-(3-hydroxyphenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine

(**51-10**);
N-(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}propyl)-4-oxo-5-phenyl-4,5-dihydro-1,3-oxazol-2-amine (**51-11**);
2-[4-(ammoniomethyl) phenyl]-5-(3-hydroxy-3-phenylpropyl)-3-phenyl-1,6-naphthyridine (**51-12**);
5-[2-(4-aminophenyl)ethyl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridine (**51-13**);
[4-(5-{3-[2-(hydroxymethyl) phenoxy]propyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine (**51-14**);
benzyl 4-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2,2-dimethylbut-3-ynoate (**51-15**);
{4-[5-(3-carboxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**51-16**);
{4-[5-(3-carboxy-3-methylbut-1-yn-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**51-17**);
{4-[5-(3-hydroxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**51-18**);
4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-methylbut-3-yn-2-ol (**52-2**);
4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-3-chloro-2-methylbut-3-en-2-ol (**52-3**);
(4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**53-2**);
(4-{5-[5-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**54-1**);
{4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**55-2**);
2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide (**56-2**);
[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**57-2**);
{4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**58-3**);
[4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**59-1**);
2-[4-(1-aminocyclobutyl)phenyl]-3-(2-fluorophenyl)-1,6-naphthyridine-5-carbonitrile (**60-3**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**61-2**);
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-7**);
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**63-1**);
2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**64-4**);
1-[4-(5-carboxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**65-2**);

{4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**66-2**);
{4-[5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**66-3**);
{4-[3-phenyl-5-(3-phenyl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine (**66-4**);
{4-[3-phenyl-5-(1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine (**66-5**);
(4-{5-[3-(1H-indol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**66-6**);
(4-{5-[3-(2,3-dihydro-1H-inden-2-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**66-7**);
{4-[3-phenyl-5-(3-pyrimidin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl} methanamine (**66-8**);
{4-[5-(3-biphenyl-4-yl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine (**66-9**);
2-(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl) pyrrolidinium (**66-10**);
(4-{5-[3-(4-methylmorpholin-3-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**66-11**);
(4-{5-[3-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**66-12**);
4-[(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)methyl]morpholin-4-ium (**66-13**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-4-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine (**66-14**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-3-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine (**66-15**);
(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) methanamine (**66-16**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[3-(1H-pyrazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridine (**66-17**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine (**66-18**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine (**66-19**);
{4-[5-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl} methanamine (**67-1**);
1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine (**68-2**);

1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine (**68-3**);
3-(5-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)-4-methylmorpholine (**68-4**);
1-(4-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**69-3**);
(4-{5-[(E)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**69-4**);
2-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1,2,4-oxadiazol-5-yl)ethanamine (**69-5**);
(4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine (**70-3**);
{4-[5-(ammoniomethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**70-4**);
(4-{5-[(benzoylamino) methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**70-5**);
[4-(3-phenyl-5-{[(phenylacetyl )amino]methyl}-1,6-naphthyridin-2-yl)phenyl]methanamine (**70-6**);
(4-{5-[(glycoloylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**70-7**);
2-[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)amino]-2-oxoethanamine (**70-8**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(pyrazin-2-ylcarbonyl)amino]methyl}-1,6-naphthyridine (**70-9**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-({[(5-phenyl-4H-1,2,4-triazol-3-yl)acetyl]amino} methyl)-1,6-naphthyridine (**70-10**);
7-{[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) amino]carbonyl}-1,2,3,4-tetrahydro-1,8-naphthyridine (**70-11**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(quinoxalin-6-ylcarbonyl)amino]methyl}-1,6-naphthyridine (**70-12**);
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-1-ylacetyl)amino]methyl}-3-phenyl-1,6-naphthyridine (**70-13**);
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-2-ylcarbonyl)amino]methyl}-3-phenyl-1,6-naphthyridine (**70-14**);
{4-[5-({[4-(ammoniomethyl) benzoyl]amino}methyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine (**70-15**);
2-[4-(ammoniomethyl) phenyl]-5-[(isonicotinoylamino)methyl]-3-phenyl-1,6-naphthyridine (**70-16**);
4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl} pyridine (**71-2**);
N-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)-2-hydroxy-N-(2-hydroxyethyl)ethanamine (**71-3**);

2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[( pyridine-4-ylcarbonyl)( pyridine-4-ylmethyl)amino]methyl}-1,6-naphthyridine (**72-2**);
2-[4-(1-ammoniocyclobutyl)phenyl]-5-{[isonicotinoyl(pyridin-4-ylmethyl) amino]methyl}-3-phenyl-1,6-naphthyridine (**73-3**);
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridine (**74-5**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(6-methoxypyridin-3-yl)-3-phenyl-1,7-naphthyridine (**74-6**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-imidazol-4-yl)-3-phenyl-1,7-naphthyridine (**74-7**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1-propyl-1H-pyrazol-4-yl)-1,7-naphthyridine (**74-8**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1H-pyrazol-4-yl)-1,7-naphthyridine (**74-9**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-pyrimidin-5-yl-1,7-naphthyridine (**74-10**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3,6-diphenyl-1,7-naphthyridine (**74-11**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridine (**74-12**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-1,7-naphthyridine (**74-13**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-benzyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridine (**74-14**);
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,7-naphthyridine (**75-6**);
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,5-naphthyridine (**75-7**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile (**76-3**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(2-phenylethyl)-1,7-naphthyridin-8-amine (**77-1**);
1-[4-(3-phenyl-1,5-naphthyridin-2-yl)phenyl]methanamine (**78-5**);
1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl} cyclobutanamine (**79-9**);
6-[4-(1-aminocyclobutyl)phenyl]-7-phenyl-1,5-naphthyridin-2(1H)-one (**80-2**);
6-[4-(1-aminocyclobutyl)phenyl]-1-methyl-7-phenyl-1,5-naphthyridin-2(1H)-one (**81-1**);
6-trans-3-cyclopropyl-3-hydroxy-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanamine (**82-1**);
trans-3-hydroxy-3-methyl-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanamine (**82-2**);
trans-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy-3-methyl cyclobutanamine (**82-3**);
trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy cyclobutanamine (**82-4**);
1-[4-(6-morpholin-4-yl-3-phenyl-1,5-naphthyridin-2-yl)phenyl] cyclobutanamine (**83-2**);
1-{4-[6-(diethylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanamine (**83-3**);
1-{4-[6-(butylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanamine (**83-4**);

[4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanamine (**84-2**);
2-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-3-phenylquinoxalin-5-ol (**85-4a**);
3-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-2-phenylquinoxalin-5-ol (**85-4b**);
(4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanamine (**86-3a**);
(4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanamine (**86-3b**);
1-{4-[3-phenyl-6-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-3**);
1-{4-[3-phenyl-7-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-4**);
1-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanamine (**88-3a**);
1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanamine (**88-3b**);
1-(4-{3-phenyl-5-[2-(pyridin-4-yl)ethoxy]quinoxalin-2-yl}phenyl) cyclobutanamine (**89-2a**);
1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl} cyclobutanamine (**89-2b**);
1-{4-[3-phenyl-5-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl}cyclobutanamine (**90-3**);
1-{4-[3-phenyl-8-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl}cyclobutanamine (**90-4**);
(4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanamine (**91-3a**);
(4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanamine (**91-3b**);
[4-(6-hydroxy-3-phenylpyrido[2,3-b] pyrazin-2-yl)phenyl] methanamine (**91-4a**);
[4-(6-hydroxy-2-phenylpyrido[2,3-b] pyrazin-3-yl)phenyl] methanamine (**91-4b**);
4-{2-[4-(ammonio methyl) phenyl]-3-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazine (**91-5a**);
4-{3-[4-(ammoniomethyl) phenyl]-2-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazine (**91-5b**);
1-{4-[3-phenyl-6-(2-pyridin-4-ylethoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine (**91-6a**);
1-(4-{2-phenyl-6-[2-(pyridin-4-yl)ethoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine (**91-6b**);
1-{4-[3-phenyl-6-(3-pyridin-4-ylpropoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine (**91-7a**);
1-(4-{2-phenyl-6-[3-(pyridin-4-yl)propoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine (**91-7b**);
{4-[3-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine (**92-1a**);
{4-[2-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanamine (**92-1b**);
1-{4-[3-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine (**92-2a**);
1-{4-[2-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanamine (**92-2b**);
{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine (**93-2a**);

{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine (**93-2b**);
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine (**94-1a**);
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine (**94-1b**);
{4-[3-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine (**94-2a**);
{4-[2-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine (**94-2b**);
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-4**);
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-5**);
2-[4-(aminomethyl)phenyl]-3-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2a**);
3-[4-(aminomethyl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2b**);
1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)phenyl]methanamine (**97-1a**);
1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)phenyl]methanamine (**97-1b**);
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazine (**98-6a**);
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-(dimethylamino)ethyl]piperazine (**98-6b**);
4-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(methylamino)ethyl]piperazine (**99-2a**);
4-{3-[4-(1-ammoniocyclobutyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazine (**99-2b**);
7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-4**);
7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**101-3**);
[4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanamine (**102-4**);
1-[4-(4-hydroxy-6-phenylpteridin-7-yl)phenyl]cyclobutanamine (**103-3a**);
1-[4-(4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanamine (**103-3b**);
1-[4-(3-phenylquinoxalin-2-yl)phenyl] cyclobutanamine (**103-4**);
1-[4-(2-amino-4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanamine (**103-5b**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(4-methylpiperazin-4-ium-1-yl)-6-phenylpyrido[2,3-d]pyrimidine (**106-8**);
7-[4-(1-ammonio cyclobutyl)phenyl]-2-[(2-hydroxyethyl)amino]-6-phenylpyrido[2,3-d] pyrimidine (**106-9**);
2-[4-(aminocarbonyl) piperidin-1-yl]-7-[4-(1-ammoniocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidine (**106-10**);

2-(4-acetylpiperazin-1-yl)-7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidine (**106-11**);
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-piperazin-4-ium-1-ylpyrido[2,3-d]pyrimidine (**106-12**);
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-(4-pyrazin-2-ylpiperazin-1-yl) pyrido [2,3-d]pyrimidine (**106-13**);
7-[4-(1-ammonio cyclobutyl)phenyl]-2-(4-benzoylpiperazin-1-yl)-6-phenylpyrido[2,3-d] pyrimidine (**106-14**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(methylamino)-6-phenylpyrido[2,3-d]pyrimide (**106-15**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(dimethylamino)-6-phenylpyrido[2,3-d]pyrimide (**106-16**);
1-{4-[2-(4-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}cyclobutanamine (**106-17**);
1-{4-[2-(3-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}cyclobutanamine (**106-18**);
(2R)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol (**106-19**);
(2S)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol (**106-20**);
4-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)butan-1-ol (**106-21**);
5-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)pentan-1-ol (**106-22**);
3-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)-2,2-dimethylpropan-1-ol (**106-23**);
6-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)hexan-1-ol (**106-24**);
1-{4-[2-(3-hydroxypyrrolidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanamine (**106-25**);
1-(4-{2-[(2-ammonioethyl)(2-methoxy-2-oxoethyl)amino]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) cyclobutanamine (**106-26**);
1-[4-(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanamine (**106-27**);
1-[4-(2-{[2-(acetylamino) ethyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanamine (**106-28**);
[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine (**107-3**);
7-[4-(ammoniomethyl) phenyl]-2-(ethylthio)-6-phenylpyrido[2,3-d]pyrimidine (**107-4**);
{4-[2-(4-acetylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine (**107-5**);

(4-{2-[4-(2-hydroxy ethyl) piperazin-1-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl} phenyl) methanamine (**107-6**);
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperazin-1-yl)-N,N-dimethylethanamine (**107-7**);
4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-1-methylpiperazin-1-ium (**107-8**);
[4-(2-hydroxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine (**107-9**);
[4-(2-amino-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine (**107-10**);
{4-[2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine (**107-11**);
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}piperazin-1-yl)-N,N-diethylethanamine (**107-12**);
(4-{2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) methanamine (**107-13**);
{4-[2-(1H-imidazol-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine (**107-14**);
1-(1-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperidin-4-yl) pyrrolidinium (**107-15**);
{4-[2-(2,5-dimethylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine (**107-16**);
(2S)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium (**107-17**); and
(2R)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium (**107-18**);
or a pharmaceutically acceptable salt or stereoisomer thereof.

A specific salt of a compound of the instant invention is selected from:
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate (**2-4**);
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate (**2-5**);
2-methyl-1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate (**2-6**);
2-[4-(1,2-diammonioethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-1-ium trichloride (**3-5**);
2-[4-(1-ammonio-2-fluoroethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-1-ium dichloride (**4-6**);
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopropanaminium chloride (**5-1**);
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium chloride (**6-5**);

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopentanaminium chloride (**6-6**);
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclohexanaminium chloride (**6-7**);
[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**7-2**);
[4-(6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-2**);
[4-(6-benzyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-3**);
[4-(5-oxo-3-phenyl-6-propyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-4**);
[4-(6-ethyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-5**);
{4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**10-3**);
{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-2**);
{4-[5-hydroxy-8-(2-methoxy-1,3-thiazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-3**);
{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-4**);
{4-[8-(3-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-5**);
{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-6**);
{4-[8-(1-benzofuran-2-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin -2-yl]phenyl}methanaminium chloride (**11-7**);
{4-[5-hydroxy-8-(5-methyl-2-furyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-8**);
{4-[5-hydroxy-8-(4-methylthien-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-9**);
{4-[8-(1-benzothien-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-10**);
{4-[8-(1-benzothien-7-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-11**);
{4-[8-(1-benzofuran-5-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-12**);
[4-(5-hydroxy-3-phenyl-8-thien-3-yl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate (**11-13**);

{4-[5-hydroxy-8-(3-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanaminium trifluoroacetate (**11-14**);
{4-[5-hydroxy-8-(2-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-15**);
{4-[8-(2-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-16**);
{4-[8-(2-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-17**);
{4-[5-hydroxy-8-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-18**);
{4-[8-(3-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-19**);
{4-[5-hydroxy-8-(3-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-20**);
(4-{5-hydroxy-3-phenyl-8-[3-(trifluoromethyl)phenyl]-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**11-21**);
{4-[5-hydroxy-8-(3-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-22**);
{4-[8-(3-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-23**);
{4-[5-hydroxy-8-(4-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-24**);
{4-[8-(4-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-25**);
{4-[8-(4-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-26**);
{4-[5-hydroxy-8-(4-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-27**);
{4-[8-(3,5-dimethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**11-28**);
{4-[8-(3,5-dichlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**11-29**);
{4-[8-(3-ethoxyphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**11-30**);
[4-(8-cyclohex-1-en-1-yl-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate (**11-31**);
{4-[5-hydroxy-8-(3-mercaptophenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-32**);

{4-[5-hydroxy-8-(2-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-33**);
(4-{5-hydroxy-8-[3-(hydroxymethyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**11-34**);
{4-[8-(3-cyanophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-35**);
{4-[5-hydroxy-8-(3-isopropylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**11-36**);
{4-[8-(1,1'-biphenyl-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**11-37**);
2-[4-(ammoniomethyl)phenyl]-8-[3-(dimethylamino)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridin-1-ium bis(trifluoroacetate) (**11-38**);
{4-[8-(3-acetylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-39**);
(4-{5-hydroxy-8-[3-(methoxycarbonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**11-40**);
8-(3-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridin-1-ium dichloride (**11-41**);
[4-(5-hydroxy-8-{3-[(methylamino)carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-42**);
(4-{5-hydroxy-8-[3-(methylsulfonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**11-43**);
{4-[8-(3-ethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**11-44**);
{4-[5-hydroxy-8-(3-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**11-45**);
6-[4-(ammoniomethyl)phenyl]-1-hydroxy-4-isobutyl-7-phenylisoquinolinium dichloride (**11-46**);
{4-[5-oxo-3-phenyl-8-(1-propyl-1*H*-pyrazol-4-yl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-47**);
{4-[8-(4-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-48**);
{4-[5-oxo-3-phenyl-8-(2-thienyl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**11-49**);
[4-(5-oxo-3-phenyl-8-pyridin-3-yl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-50**);
[4-(5-oxo-3,8-diphenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-51**);
{4-[8-(2-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-52**);

{4-[8-(6-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-53**);
{4-[8-(3-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-54**);
{4-[8-(4-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-55**);
{4-[8-(2-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-56**);
{4-[6-methyl-8-(4-methyl-2-thienyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**11-57**);
{4-[8-(4-fluoro-3-methylphenyl)-6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**11-58**);
[4-(8-cyano-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-59**);
[4-(8-chloro-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-60**);
[4-(8-bromo-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**11-61**);
1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanaminium chloride (**12-5**);
1-[4-(8-cyano-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium trifluoroacetate (**12-6**);
[3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**13-6**);
[5-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)pyridin-2-yl] methanaminium chloride (**13-7**);
[2,3-difluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**13-8**);
[2-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**13-9**);
{4-[3-(4-chlorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**14-4**);
1-{4-[3-(4-fluorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium trifluoroacetate (**15-3**);
1-{4-[5-(2-oxopyrrolidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate (**20-7**);
2-[4-(1-ammoniocyclobutyl) phenyl]-5-diazan-2-iumyl-3-phenyl-1,6-naphthyridin-6-ium trichloride (**20-9**);
1-{4-[3-phenyl-5-(piperidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate

(**20-16**);
1-{4-[5-(3,3-difluoroazetidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate (**20-17**);
1-{4-[5-(3,3-difluoropiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate (**20-18**);
1-{4-[5-(4-hydroxypiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate (**20-19**);
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**21-3**);
5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**22-3**);
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-2-ylethyl)amino]-3-phenyl-1,6-naphthyridin-1-ium dichloride (**22-4**);
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-4-ylethyl)amino]-3-phenyl-1,6-naphthyridin-1-ium dichloride (**22-5**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(2-pyridinium-2-ylethyl) amino]-1,6-naphthyridin-6-ium trichloride (**22-6**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-piperidin-1-yl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**22-7**);
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-8**);
2-[4-(ammoniomethyl) phenyl]-5-(benzylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-9**);
2-({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}amino) ethanaminium dichloride (**22-10**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrrolidin-1-yl-1,6-naphthyridin-6-ium dichloride (**22-11**);
2-[4-(ammoniomethyl) phenyl]-5-(diethylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-12**);
2-[4-(ammoniomethyl) phenyl]-5-(methylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-13**);
2-[4-(ammoniomethyl) phenyl]-5-[bis(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-14**);
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)(methyl) amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-15**);
2-[4-(ammoniomethyl) phenyl]-5-[ethyl(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-16**);
5-[4-(aminocarbonyl)piperidin-1-yl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-17**);

2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(2-pyridin-4-ylethyl)amino]-1,6-naphthyridin -1-ium dichloride (**22-18**);
2-[4-(ammoniomethyl) phenyl]-5-morpholin-4-yl-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-19**);
2-[4-(ammoniomethyl )phenyl]-5-[2-(hydroxymethyl) morpholin-4-yl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**22-20**);
{4-[3-phenyl-5-(4H-1,2,4-triazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**22-22**);
[4-(3-phenyl-5-piperazin-1-yl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**22-23**);
[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**22-25**);
[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**22-26**)
2-[4-(ammoniomethyl) phenyl]-5-phenoxy-3-phenyl-1,6-naphthyridin-1-ium bis(trifluoroacetate) (**23-2**);
(4-{5-[4-(aminocarbonyl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**23-3**);
{4-[5-(4-nitrophenoxy)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**23-4**);
(4-{5-[4-(1H-imidazol-1-yl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**23-5**);
(4-{3-phenyl-5-[4-(1H-1,2,4-triazol-1-yl)phenoxy]-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**23-6**);
(4-{5-[4-(methoxycarbonyl) phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**23-7**);
2-[3-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)propyl]pyridinium dichloride (**23-12**);
2-[2-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethyl]pyridinium dichloride (**23-13**);
2-[({2-[4-(ammoniomethyl )phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) methyl]morpholin-4-ium dichloride (**23-14**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-6-ium dichloride (**23-15**);
3-[2-({2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) ethyl]piperidinium (**23-18**);
2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridin-6-ium dichloride (**24-2**);
{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**24-3**);
[(3,3'-diphenyl-5,5'-bi-1,6-naphthyridine-2,2'-diyl)di-4,1-phenylene] dimethanaminium dichloride (**24-4**);
4-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}benzyl)morpholin-4-ium dichloride (**24-5**);

2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(1H-pyrazol-1-ium-3-yl)-1,6-naphthyridin-6-ium trichloride (**24-6**);

[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene] dimethanaminium dichloride (**24-9**);

2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrimidin-5-yl-1,6-naphthyridin-6-ium dichloride (**24-10**);

3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridinium dichloride (**24-11**);

4-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridinium dichloride (**24-12**);

5-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}isoquinolinium dichloride (**24-14**);

{4-[3-phenyl-5-(3-thienyl)-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**24-15**);

{4-[5-(3,5-dimethyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**24-17**);

{4-[5-(2-naphthyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**24-20**);

5-(4-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**24-21**);

2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(E)-2-phenylvinyl]-1,6-naphthyridin-6-ium dichloride (**24-22**);

(4-{5-[4-(benzyloxy)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**24-23**);

{4-[5-(4-{[(2-hydroxyethyl) amino] carbonyl}phenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**24-24**);

3-[(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} benzoyl)amino]-N,N-dimethylpropan-1-aminium bis(trifluoroacetate) (**24-25**);

[4-(5-{4-[(cyclopropylamino) carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate (**24-26**);

{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**25-2**);

1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclopropanaminium trifluoroacetate (**26-1**);

1,1'-[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene]dicyclobutanaminium dichloride (**27-2**);

2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridin-1-ium dichloride (**32-2**);

1-[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium formate (**33-1**);

1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanaminium chloride (**34-2**);

1-[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium chloride (**35-1**);

[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-2**);
[4-(5-isobutyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium trifluoroacetate (**36-3**);
[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium trifluoroacetate (**36-4**);
[4-(3-phenyl-5-propyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-5**);
[4-(5-benzyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-6**);
[4-(5-isopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-7**);
[4-(5-cyclohexyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**36-8**);
[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**36-9**);
[4-(5-butyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride (**36-10**);
{4-[5-(3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**36-11**);
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(pyridinium-4-ylmethoxy)methyl]-1,6-naphthyridin-6-ium trichloride (**39-4**);
{4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-3**);
{4-[5-(4-hydroxybutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-4**);
{4-[5-(4-morpholin-4-ylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-5**);
{4-[5-(3-morpholin-4-ylpropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-6**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethyl)-1,6-naphthyridin-6-ium dichloride (**51-7**);
2-[4-(ammoniomethyl) phenyl]-5-[2-(1-methyl-1H-imidazol-5-yl)ethyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**51-8**);
(4-{5-[2-(3-aminophenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl )methanaminium chloride (**51-9**);
(4-{5-[2-(3-hydroxyphenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**51-10**);
N-(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}propyl)-4-oxo-5-phenyl-4,5-dihydro-1,3-oxazol-2-aminium dichloride (**51-11**);
2-[4-(ammoniomethyl) phenyl]-5-(3-hydroxy-3-phenylpropyl)-3-phenyl-1,6-naphthyridin-6-ium dichloride (**51-12**);
5-[2-(4-aminophenyl)ethyl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**51-13**);
[4-(5-{3-[2-(hydroxymethyl) phenoxy]propyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate (**51-14**);
benzyl 4-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2,2-dimethylbut-3-ynoate (**51-15**);

{4-[5-(3-carboxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**51-16**);
{4-[5-(3-carboxy-3-methylbut-1-yn-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**51-17**);
{4-[5-(3-hydroxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**51-18**);
(4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**53-2**);
(4-{5-[5-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**54-1**);
{4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride (**55-2**);
2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide (**56-2**);
[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**57-2**);
{4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**58-3**);
[4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**59-1**);
2-[4-(1-aminocyclobutyl)phenyl]-3-(2-fluorophenyl)-1,6-naphthyridine-5-carbonitrile (**60-3**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**61-2**);
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-7**);
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**63-1**);
2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**64-4**);
{4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-2**);
{4-[5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-3**);
{4-[3-phenyl-5-(3-phenyl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-4**);
{4-[3-phenyl-5-(1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-5**);
(4-{5-[3-(1H-indol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**66-6**);
(4-{5-[3-(2,3-dihydro-1H-inden-2-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate (**66-7**);
{4-[3-phenyl-5-(3-pyrimidin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**66-8**);

{4-[5-(3-biphenyl-4-yl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**66-9**);
2-(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl) pyrrolidinium bis(trifluoroacetate) (**66-10**);
(4-{5-[3-(4-methylmorpholin-3-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**66-11**);
(4-{5-[3-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate (**66-12**);
4-[(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)methyl]morpholin-4-ium bis(trifluoroacetate) (**66-13**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-4-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**66-14**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-3-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**66-15**);
(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate (**66-16**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[3-(1H-pyrazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**66-17**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**66-18**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**66-19**);
{4-[5-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl} methanaminium chloride (**67-1**);
1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanaminium trifluoroacetate (**68-2**);
1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanaminium trifluoroacetate (**68-3**);
3-(5-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)-4-methylmorpholin-4-ium dichloride (**68-4**);

(4-{5-[(E)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**69-4**);
2-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1,2,4-oxadiazol-5-yl)ethanaminium dichloride (**69-5**);
(4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**70-3**);
{4-[5-(ammoniomethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium dichloride (**70-4**);

(4-{5-[(benzoylamino) methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**70-5**);
[4-(3-phenyl-5-{[(phenylacetyl )amino]methyl}-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**70-6**);
(4-{5-[(glycoloylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**70-7**);
2-[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)amino]-2-oxoethanaminium dichloride (**70-8**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(pyrazin-2-ylcarbonyl)amino]methyl}-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**70-9**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-({[(5-phenyl-4H-1,2,4-triazol-3-yl)acetyl]amino} methyl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**70-10**);
7-{[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) amino]carbonyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-1-ium bis(trifluoroacetate) (**70-11**);
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(quinoxalin-6-ylcarbonyl)amino]methyl}-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**70-12**);
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-1-ylacetyl)amino]methyl}-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**70-13**);
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-2-ylcarbonyl)amino]methyl}-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**70-14**);
{4-[5-({[4-(ammoniomethyl) benzoyl]amino}methyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium bis(trifluoroacetate) (**70-15**);
2-[4-(ammoniomethyl) phenyl]-5-[(isonicotinoylamino)methyl]-3-phenyl-1,6-naphthyridinediium trichloride (**70-16**);
4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl} pyridinium trichloride (**71-2**);
N-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)-2-hydroxy-N-(2-hydroxyethyl)ethanaminium dichloride (**71-3**);
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[(pyridinium-4- ylcarbonyl)(pyridinium-4-ylmethyl)amino]methyl}-1,6-naphthyridin-6-ium tetrachloride (**72-2**);
2-[4-(1-ammoniocyclobutyl)phenyl]-5-{[isonicotinoyl(pyridin-4-ylmethyl) amino]methyl}-3-phenyl-1,6-naphthyridinediium trichloride (**73-3**);
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridin-1-ium dichloride (**74-5**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(6-methoxypyridin-3-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride (**74-6**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-imidazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride (**74-7**);

2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1-propyl-1H-pyrazol-4-yl)-1,7-naphthyridin-1-ium dichloride (**74-8**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1H-pyrazol-4-yl)-1,7-naphthyridin-1-ium dichloride (**74-9**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-pyrimidin-5-yl-1,7-naphthyridin-1-ium dichloride (**74-10**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3,6-diphenyl-1,7-naphthyridin-1-ium dichloride (**74-11**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride (**74-12**);
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-1,7-naphthyridin-1-ium dichloride (**74-13**);
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-benzyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride (**74-14**);
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,7-naphthyridin-7-ium dichloride (**75-6**);
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,5-naphthyridin-1-ium dichloride (**75-7**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile (**76-3**);
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(2-phenylethyl)-1,7-naphthyridin-8-amine (**77-1**);
6-trans-3-cyclopropyl-3-hydroxy-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanaminium chloride (**82-1**);
trans-3-hydroxy-3-methyl-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanaminium formate (**82-2**);
trans-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy-3-methyl cyclobutanaminium chloride (**82-3**);
trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy cyclobutanaminium chloride (**82-4**);
1-[4-(6-morpholin-4-yl-3-phenyl-1,5-naphthyridin-2-yl)phenyl] cyclobutanaminium chloride (**83-2**);
1-{4-[6-(diethylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride (**83-3**);
1-{4-[6-(butylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride (**83-4**);
[4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanaminium chloride (**84-2**);
(4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3a**);
(4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3b**);
1-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3a**);

1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3b**);
1-(4-{3-phenyl-5-[2-(pyridin-4-yl)ethoxy]quinoxalin-2-yl}phenyl) cyclobutanaminium chloride (**89-2a**);
1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**89-2b**);
1-{4-[3-phenyl-5-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**90-3**);
1-{4-[3-phenyl-8-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**90-4**);
(4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanaminium chloride (**91-3a**);
(4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanaminium chloride (**91-3b**);
[4-(6-hydroxy-3-phenylpyrido[2,3-b] pyrazin-2-yl)phenyl] methanaminium trifluoroacetate (**91-4a**);
[4-(6-hydroxy-2-phenylpyrido[2,3-b] pyrazin-3-yl)phenyl] methanaminium trifluoroacetate (**91-4b**);
4-{2-[4-(ammonio methyl) phenyl]-3-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazin-1-ium bis(trifluoroacetate) (**91-5a**);
4-{3-[4-(ammoniomethyl) phenyl]-2-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazin-1-ium bis(trifluoroacetate) (**91-5b**);
{4-[3-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**92-1a**);
{4-[2-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**92-1b**);
{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**93-2a**);
{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanaminium trifluoroacetate (**93-2b**);
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**94-1a**);
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanaminium trifluoroacetate (**94-1b**);
{4-[3-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**94-2a**);
{4-[2-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl} methanaminium trifluoroacetate (**94-2b**);
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6a**);

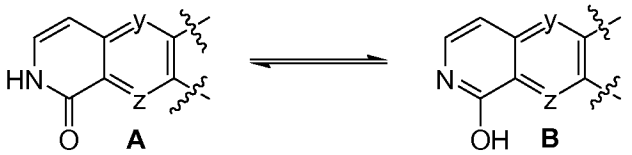
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6b**);
4-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(methylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**99-2a**);
4-{3-[4-(1-ammoniocyclobutyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**99-2b**);
[4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanaminium chloride (**102-4**);
1-[4-(4-hydroxy-6-phenylpteridin-7-yl)phenyl]cyclobutanaminium chloride (**103-3a**);
1-[4-(4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanaminium chloride (**103-3b**);
1-[4-(3-phenylquinoxalin-2-yl)phenyl] cyclobutanaminium chloride (**103-4**);
1-[4-(2-amino-4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanaminium chloride (**103-5b**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(4-methylpiperazin-4-ium-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-8-ium trichloride (**106-8**);
7-[4-(1-ammonio cyclobutyl)phenyl]-2-[(2-hydroxyethyl)amino]-6-phenylpyrido[2,3-d] pyrimidin-8-ium dichloride (**106-9**);
2-[4-(aminocarbonyl) piperidin-1-yl]-7-[4-(1-ammoniocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride (**106-10**);
2-(4-acetylpiperazin-1-yl)-7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride (**106-11**);
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-piperazin-4-ium-1-ylpyrido[2,3-d]pyrimidin-8-ium trichloride (**106-12**);
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-(4-pyrazin-2-ylpiperazin-1-yl) pyrido [2,3-d]pyrimidine-1,8-diium trichloride (**106-13**);
7-[4-(1-ammonio cyclobutyl)phenyl]-2-(4-benzoylpiperazin-1-yl)-6-phenylpyrido[2,3-d] pyrimidin-8-ium dichloride (**106-14**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride (**106-15**);
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(dimethylamino)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride (**106-16**);
1-{4-[2-(4-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanaminium chloride (**106-17**);
1-{4-[2-(3-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanaminium chloride (**106-18**);
1-{4-[2-(3-hydroxypyrrolidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanaminium chloride (**106-25**);
1-(4-{2-[(2-ammonioethyl)(2-methoxy-2-oxoethyl)amino]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) cyclobutanaminium dichloride (**106-26**);
1-[4-(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanaminium chloride (**106-27**);

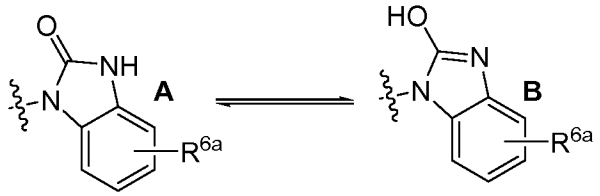
1-[4-(2-{[2-(acetylamino) ethyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanaminium chloride (**106-28**);
[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-3**);
7-[4-(ammoniomethyl) phenyl]-2-(ethylthio)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride (**107-4**);
{4-[2-(4-acetylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate (**107-5**);
(4-{2-[4-(2-hydroxy ethyl) piperazin-1-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl} phenyl) methanaminium trifluoroacetate (**107-6**);
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperazin-1-yl)-N,N-dimethylethanaminium bis(trifluoroacetate) (**107-7**);
[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl] methanaminium trifluoroacetate (**107-8**);
4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-1-methylpiperazin-1-ium bis(trifluoroacetate) (**107-9**);
[4-(2-hydroxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-10**);
[4-(2-amino-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-11**);
{4-[2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate (**107-12**);
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}piperazin-1-yl)-N,N-diethylethanaminium bis(trifluoroacetate) (**107-13**);
(4-{2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) methanaminium trifluoroacetate (**107-14**);
{4-[2-(1H-imidazol-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate (**107-15**);
1-(1-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperidin-4-yl) pyrrolidinium bis(trifluoroacetate) (**107-16**);
{4-[2-(2,5-dimethylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate (**107-17**);
(2S)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium bis(trifluoroacetate) (**107-18**); and
(2R)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium bis(trifluoroacetate) (**107-19**);
or a pharmaceutically acceptable stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon*

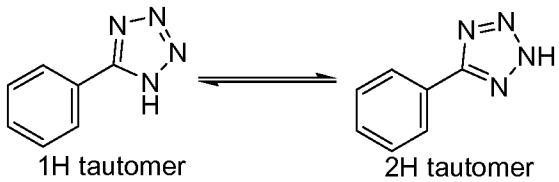
*Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention.

In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof. The two tautomeric forms of the benzimidazolonyl moiety are also within the scope of the instant invention.




Tetrazoles exist as a mixture of 1H/2H tautomers. The tautomeric forms of the tetrazol moiety are also within the scope of the instant invention.




When any variable (e.g. $R^2$, $R^{6a}$, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is bicyclic or tricyclic, it is intended that the bond be attached to any of the suitable atoms on any ring of the cyclic moiety.

It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences lead to subtle changes

in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or dramatic changes in potency, solubility, lack of off target activity, packaging properties, and so on. (Diass, J. O. *et al.* Organometallics (2006) 5:1188-1198; Showell, G.A. et al. Bioorganic & Medicinal Chemistry Letters (2006) 16:2555-2558).

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to four substituents, and the more preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, $C_1$-$C_{10}$, as in "($C_1$-$C_{10}$)alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrange-ment. For example, "($C_1$-$C_{10}$)alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "($C_2$-$C_{10}$)alkenyl" means an alkenyl radical having from 2 to 10 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "($C_2$-$C_{10}$)alkynyl" means an alkynyl radical having from 2 to 10 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-

methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as ($C_0$-$C_6$)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -$CH_2$Ph, -$CH_2CH_2$Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. Such heteraoaryl moieties for substituent Q include but are not limited to: 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl and 4-isoquinolinyl.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl,

dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

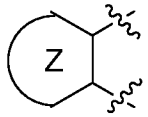
As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

A spirocyclic moiety refers to an aryl, heterocyclyl, or ($C_3$-$C_6$)cycloalkyl, that is attached to a ($C_3$-$C_6$)cycloalkyl, for example cyclobutyl. The spirocyclic moiety may be optionally substituted with one to three substituents selected from $R^6$. Preferred examples of substituents attached to the spirocyclic moieties include: ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

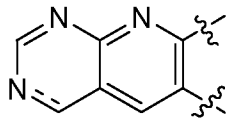
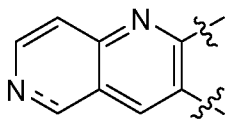
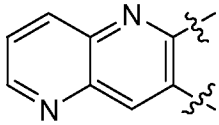
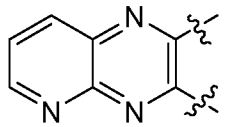
In an embodiment of Formula A, E, F, G, H, I and J are independently selected from CH and N wherein at least two of E, F, G, H, I and J are CH.

In an embodiment of Formula A, n is 1, 2, 3, 4, 5 or 6.

In another embodiment of Formula A, n is 1, 2 or 3.

In an embodiment of Formula B 

is selected from:


,

,

, and

;

In an embodiment of Formulas A and B, n is 0, 1, 2 or 3; p is 0, 1 or 2; and q is 0, 1 or 2.

In another embodiment of Formulas A and B, n is 0, 1, 2 or 3; p is 0 and q is 0.

In another embodiment of Formulas A, B and C, n is 1, 2 or 3; p is 0, 1 or 2; and q is 0, 1 or 2.

In another embodiment of Formulas A, B, C and D, n is 1, 2 or 3; p is 0 and q is 0.

In an embodiment of Formulas C and D, n is 1, 2 or 3.

In an embodiment of Formulas A, B, C and D, $R^2$ is ($C_1$-$C_6$)alkyl, $CF_3$, halo and OH, wherein said alkyl is optionally substituted with one to three halo.

In an embodiment of Formulas A, B, C and D, $R^2$ is halo.

In an embodiment of Formulas A and B, $R^3$ is halo.

In another embodiment of Formulas A, B, C and D, $R^1$ is independently selected from: H, OH, halo, oxo, ($C_1$-$C_6$)alkyl, cycloalkyl, ($C_2$-$C_6$)alkenyl, O($C_1$-$C_6$)alkyl, S($C_1$-

$C_6$)alkyl, $NR^zR^{z'}$, NH(C=O), aryl, heteroaryl, heterocyclyl, (O)heterocyclyl, phenyl, (O)phenyl, cycloalkene, and CN,

wherein said alkyl, cycloalkyl, alkenyl, phenyl, $NR^zR^{z'}$, NH(C=O), cycloalkene, aryl, heteroaryl and heterocyclyl are optionally substituted with one to three substituents selected from: phenyl, (O)phenyl, heterocyclyl, halo, oxo, OH, O($C_1$-$C_6$)alkyl, C=O($C_1$-$C_6$)alkyl, (C=O)O($C_1$-$C_6$)alkyl, $CF_3$, ($C_1$-$C_6$)alkyl, SH, CN, $NH_2$, $CO_2H$, $(C=O)NR^zR^{z'}$, $NR^zR^{z'}$, NH(C=O), S(O)$_2$($C_1$-$C_6$)alkyl, and $NO_2$,

wherein said alkyl, $R^zR^{z'}$, NH(C=O), phenyl and heterocyclyl are optionally substituted with one to three substituents selcted from: halo, oxo, OH, ($C_1$-$C_6$)alkyl, cycloalkyl, phenyl, heterocyclyl, and $NR^zR^{z'}$,

wherein said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from: OH, halo, phenyl, $NH_2$, and O($C_1$-$C_6$)alkyl, and

wherein $R^z$ and $R^{z'}$ are independently selected from: H, ($C_1$-$C_6$)alkyl, cycloalkyl, O($C_1$-$C_6$)alkyl, $NH_2$, and heterocyclyl.

In another embodiment of Formulas A, B, C and D, $R^1$ is independently selected from: oxo and O($C_1$-$C_6$)alkyl;

wherein said alkyl is optionally substituted with one to three substituents selected from: phenyl, (O)phenyl, heterocyclyl, halo, oxo, OH, O($C_1$-$C_6$)alkyl, C=O($C_1$-$C_6$)alkyl, (C=O)O($C_1$-$C_6$)alkyl, $CF_3$, ($C_1$-$C_6$)alkyl, SH, CN, $NH_2$, $CO_2H$, $(C=O)NR^zR^{z'}$, $NR^zR^{z'}$, NH(C=O), S(O)$_2$($C_1$-$C_6$)alkyl and $NO_2$,

wherein said alkyl, $R^zR^{z'}$, NH(C=O), phenyl and heterocyclyl are optionally substituted with one to three substituents selcted from: halo, oxo, OH, ($C_1$-$C_6$)alkyl, cycloalkyl, phenyl, heterocyclyl and $NR^zR^{z'}$,

wherein said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from: OH, halo, $NH_2$, and O($C_1$-$C_6$)alkyl, and

wherein $R^z$ and $R^{z'}$ are independently selected from: H, ($C_1$-$C_6$)alkyl, cycloalkyl, O($C_1$-$C_6$)alkyl, $NH_2$ and heterocyclyl.

In another embodiment of Formulas A, B, C and D, $R^4$ and $R^{4'}$ are independently selected from: H, ($C_1$-$C_6$)alkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, said alkyl, alkenyl and alkynyl are optionally substituted with one to three substituents selected from OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen, or $R^4$ and $R^{4'}$ can be taken together to form a ($C_3$-$C_6$)cycloalkyl optionally containing a heteroatom selected from N, O and S, said cycloalkyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In another embodiment of Formulas A, B, C and D, $R^4$ and $R^{4'}$ are taken together to form a ($C_3$-$C_6$)cycloalkyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In another embodiment of Formulas A, B, C and D, $R^4$ and $R^{4'}$ are taken together to form cyclobutyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In another embodiment of Formulas A, B, C and D, $R^1$ is selected from: OH, oxo, ($C_1$-$C_6$)alkyl, O($C_1$-$C_6$)alkyl and heterocyclyl, said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from $R^6$; and $R^4$ and $R^{4'}$ are taken together to form a ($C_3$-$C_6$)cycloalkyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In another embodiment of Formulas A, B, C and D, n is 1; $R^1$ is selected from: OH, oxo, ($C_1$-$C_6$)alkyl, O($C_1$-$C_6$)alkyl and heterocyclyl, said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from $R^6$; and $R^4$ and $R^{4'}$ are taken together to form a ($C_3$-$C_6$)cycloalkyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In an embodiment of Formula D, $R^1$ is selected from: OH, oxo, ($C_1$-$C_3$)alkyl, O($C_1$-$C_3$)alkyl and heterocyclyl, said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from heterocyclyl, O($C_1$-$C_3$)alkyl and $NR^zR^{z'}$, wherein said heterocyclyl, alkyl and $R^zR^{z'}$ are optionally substituted with one to three substituents selected from: H, ($C_1$-$C_3$)alkyl, cycloalkyl, (C=O)heterocyclyl, O($C_1$-$C_3$)alkyl, $NH_2$ and heterocyclyl.

In another embodiment of Formula D, $R^1$ is selected from: OH, oxo, ($C_1$-$C_3$)alkyl, O($C_1$-$C_3$)alkyl and heterocyclyl, said alkyl and heterocyclyl are optionally substituted with one to three substituents selected from heterocyclyl, O($C_1$-$C_3$)alkyl and $NR^zR^{z'}$, wherein said heterocyclyl, alkyl and $R^zR^{z'}$ are optionally substituted with one to three substituents selected from: H, ($C_1$-$C_6$)alkyl, cycloalkyl, (C=O)heterocyclyl, O($C_1$-$C_6$)alkyl, $NH_2$ and heterocyclyl; and $R^4$ and $R^{4'}$ are taken together to form a ($C_3$-$C_6$)cycloalkyl optionally substituted with one or more substituents selected from ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, OH, oxo, $CF_3$, $NH_2$, CHO, $CO_2H$ and halogen.

In another embodiment, $R^z$ and $R^{z'}$ are independently selected from: H, ($C_1$-$C_6$)alkyl, cycloalkyl, O($C_1$-$C_6$)alkyl, $NH_2$ and heterocyclyl.

Included in the instant invention is the free form of compounds of Formula A, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the isolated specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the isolated salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula A. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar

solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic (TFA) and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N$^1$-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.,* 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then

be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

UTILITY

The compounds of the instant invention are inhibitors of the activity of Akt and are thus useful in the treatment or prevention of cancer, in particular cancers associated with irregularities in the activity of Akt and downstream cellular targets of Akt. Such cancers include, but are not limited to, ovarian, pancreatic, breast and prostate cancer, as well as cancers (including glioblastoma) where the tumor suppressor PTEN is mutated (Cheng et al., *Proc. Natl. Acad. Sci.* (1992) 89:9267-9271; Cheng et al., *Proc. Natl. Acad. Sci.* (1996) 93:3636-3641; Bellacosa et al., *Int. J. Cancer* (1995) 64:280-285; Nakatani et al., *J. Biol. Chem.* (1999) 274:21528-21532; Graff, *Expert. Opin. Ther. Targets* (2002) 6(1):103-113; and Yamada and Araki, *J. Cell Science*. (2001) 114:2375-2382; Mischel and Cloughesy, *Brain Pathol.* (2003) 13(1):52-61).

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment or prevention of cancer. Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: non small cell, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colorectal, rectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform,

oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: breast, prostate, colon, colorectal, lung, non small cell lung, brain, testicular, stomach, pancrease, skin, small intestine, large intestine, throat, head and neck, oral, bone, liver, bladder, kidney, thyroid and blood.

Cancers that may be treated by the compounds, compositions and methods of the invention include: breast, prostate, colon, ovarian, colorectal and lung (non small cell).

Cancers that may be treated by the compounds, compositions and methods of the invention include: breast, colon, (colorectal) and lung (non small cell).

Cancers that may be treated by the compounds, compositions and methods of the invention include: lymphoma and leukemia.

Akt signaling regulates multiple critical steps in angiogenesis. Shiojima and Walsh, *Circ. Res.* (2002) 90:1243-1250. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. *Cancer Research*, 55:4575-4580, 1995 and Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi et al., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); bladder carcinomas (A.J. Dickinson et al., *Br. J. Urol.*, 1994, 74:762-766); colon carcinomas (L.M. Ellis et al., *Surgery*, 1996, 120(5):871-878); and oral cavity tumors (J.K. Williams et al., *Am. J. Surg.*, 1994, 168:373-380). Other cancers include, advanced tumors, hairy cell leukemia, melanoma, advanced head and neck, metastatic renal cell, non-Hodgkin's lymphoma, metastatic breast, breast adenocarcinoma, advanced melanoma, pancreatic, gastric, glioblastoma, lung, ovarian, non-small cell lung, prostate, small cell lung, renal cell carcinoma, various solid tumors, multiple myeloma, metastatic prostate, malignant glioma, renal cancer, lymphoma, refractory metastatic disease, refractory multiple myeloma, cervical cancer, Kaposi's sarcoma, recurrent anaplastic glioma, and metastatic colon

cancer (Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). Thus, the Akt inhibitors disclosed in the instant application are also useful in the treatment of these angiogenesis related cancers.

Tumors which have undergone neovascularization show an increased potential for metastasis. In fact, angiogenesis is essential for tumor growth and metastasis. (S.P. Cunningham, et al., *Can. Research*, 61: 3206-3211 (2001)). The Akt inhibitors disclosed in the present application are therefore also useful to prevent or decrease tumor cell metastasis.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 June 2000). The undesireable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Further included within the scope of the invention is a method of treating or preventing a non-malignant disease in which angiogenesis is implicated, including but not limited to: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis, psoriasis, obesity and Alzheimer's disease (Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). In another embodiment, a method of treating or preventing a disease in which angiogenesis is implicated includes: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis and psoriasis.

Further included within the scope of the invention is a method of treating hyperproliferative disorders such as restenosis, inflammation, autoimmune diseases and allergy/asthma.

Further included within the scope of the instant invention is the use of the instant compounds to coat stents and therefore the use of the instant compounds on coated stents for the treatment and/or prevention of restenosis (WO03/032809).

Further included within the scope of the instant invention is the use of the instant compounds for the treatment and/or prevention of osteoarthritis (WO03/035048).

Further included within the scope of the invention is a method of treating hyperinsulinism.

The compounds of the invention are also useful in preparing a medicament that is useful in treating the diseases described above, in particular cancer.

In an embodiment of the invention, the instant compound is a selective inhibitor whose inhibitory efficacy is dependent on the PH domain. In this embodiment, the compound exhibits a decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt proteins lacking the PH domain.

In a further embodiment, the instant compound is selected from the group of a selective inhibitor of Akt1, a selective inhibitor of Akt2 and a selective inhibitor of both Akt1 and Akt2.

In another embodiment, the instant compound is selected from the group of a selective inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3 and a selective inhibitor of two of the three Akt isoforms.

In another embodiment, the instant compound is a selective inhibitor of all three Akt isoforms, but is not an inhibitor of one, two or all of such Akt isoforms that have been modified to delete the PH domain, the hinge region or both the PH domain and the hinge region.

The present invention is further directed to a method of inhibiting Akt activity which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound.

The compounds of this invention may be administered to mammals, including humans, either alone or, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For

example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

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

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying

agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula A may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

The dosage regimen utilizing the compounds of the instant invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the cancer to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease. For example, compounds of the instant invention can be administered in a total daily dose of up to 10,000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 10,000 mg, e.g., 2,000 mg, 3,000 mg, 4,000 mg, 6,000 mg, 8,000 mg or 10,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

For example, compounds of the instant invention can be administered in a total daily dose of up to 1,000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 1,000 mg, e.g., 200 mg, 300 mg, 400 mg, 600 mg, 800 mg or 1,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms “intermittent” or “intermittently” as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound of the instant invention may be administration one to six days per week or it may mean administration in cycles (e.g. daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

In addition, the compounds of the instant invention may be administered according to any of the schedules described above, consecutively for a few weeks, followed by a rest period. For example, the compounds of the instant invention may be administered according to any one of the schedules described above from two to eight weeks, followed by a rest period of one week, or twice daily at a dose of 100 - 500 mg for three to five days a week. In another particular embodiment, the compounds of the instant invention may be administered three times daily for two consecutive weeks, followed by one week of rest.

Any one or more of the specific dosages and dosage schedules of the compounds of the instant invention, may also be applicable to any one or more of the therapeutic agents to be used in the combination treatment (hereinafter refered to as the "second therapeutic agent").

Moreover, the specific dosage and dosage schedule of this second therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific second therapeutic agent that is being used.

Of course, the route of administration of the compounds of the instant invention is independent of the route of administration of the second therapeutic agent. In an embodiment, the administration for a compound of the instant invention is oral administration. In another embodiment, the administration for a compound of the instant invention is intravenous administration. Thus, in accordance with these embodiments, a compound of the instant invention is administered orally or intravenously, and the second therapeutic agent can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

In addition, a compound of the instant invention and second therapeutic agent may be administered by the same mode of administration, i.e. both agents administered e.g. orally, by IV. However, it is also within the scope of the present invention to administer a compound of the instant invention by one mode of administration, e.g. oral, and to administer the second therapeutic agent by another mode of administration, e.g. IV or any other ones of the administration modes described hereinabove.

The first treatment procedure, administration of a compound of the instant invention, can take place prior to the second treatment procedure, i.e., the second therapeutic agent, after the treatment with the second therapeutic agent, at the same time as the treatment with the second therapeutic agent, or a combination thereof. For example, a total treatment period can be decided for a compound of the instant invention. The second therapeutic agent can be administered prior to onset of treatment with a compound of the instant invention or following treatment with a compound of the instant invention. In addition, anti-cancer treatment can be administered during the period of administration of a compound of the instant invention but does not need to occur over the entire treatment period of a compound of the instant invention.

The instant compounds are also useful in combination with therapeutic, chemotherapeutic and anti-cancer agents. Combinations of the presently disclosed compounds with therapeutic, chemotherapeutic and anti-cancer agents are within the scope of the 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. Such agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, histone deacetylase inhibitors, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents,

topoisomerase inhibitors, proteosome inhibitors, ubiquitin ligase inhibitors, and aurora kinase inhibitors.

Examples of cytotoxic/cytostatic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032), Raf kinase inhibitors (such as Bay43-9006) and mTOR inhibitors (such as Wyeth's CCI-779).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-

[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in Publications WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98 and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-5116 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938,

4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or

platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the CHK11 and CHK12 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO

2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibitors of Raf kinase (for example BAY-43-9006 ), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an $IC_{50}$ for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of $IC_{50}$ for COX-2 over $IC_{50}$ for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, U.S. Patent 5,861,419, U.S. Patent 6,001,843, U.S. Patent 6,020,343, U.S. Patent 5,409,944, U.S. Patent 5,436,265, U.S. Patent 5,536,752, U.S. Patent 5,550,142, U.S. Patent 5,604,260, U.S. 5,698,584, U.S. Patent 5,710,140, WO 94/15932, U.S. Patent 5,344,991, U.S. Patent 5,134,142, U.S. Patent 5,380,738, U.S. Patent 5,393,790, U.S. Patent 5,466,823, U.S. Patent 5,633,272 and U.S. Patent 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_V\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_V\beta_3$ integrin and the $\alpha_V\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_V\beta_6$, $\alpha_V\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$,

$\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of

a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886,

95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with P450 inhibitors including: xenobiotics, quinidine, tyramine, ketoconazole, testosterone, quinine, methyrapone, caffeine, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafyline, cimetidine, dextromethorphan, ritonavir, indinavir, amprenavir, diltiazem, terfenadine, verapamil, cortisol, itraconazole, mibefradil, nefazodone and nelfinavir.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with Pgp and/or BCRP inhibitors including: cyclosporin A, PSC833, GF120918, cremophorEL, fumitremorgin C, Ko132, Ko134, Iressa, Imatnib mesylate, EKI-785, Cl1033, novobiocin, diethylstilbestrol, tamoxifen, resperpine, VX-710, tryprostatin A, flavonoids, ritonavir, saquinavir, nelfinavir, omeprazole, quinidine, verapamil, terfenadine, ketoconazole, nifidepine, FK506, amiodarone, XR9576, indinavir, amprenavir, cortisol, testosterone, LY335979, OC144-093, erythromycin, vincristine, digoxin and talinolol.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include

bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

The compounds of the instant invention may also be administered in combination with γ-secretase inhibitors and/or inhibitors of NOTCH signaling. Such inhibitors include compounds described in WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957,251, WO 2004/089911, WO 02/081435, WO 02/081433, WO 03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 and WO 02/47671 (including LY-450139).

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with potassium salts, magnesium salts, beta-blockers (such as atenolol) and endothelin-a (ETa)antagonists with the goal of maintaining cardiovascular homeostasis.

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with insulin, insulin secretagogues, PPAR-gamma agonists, metformin, somatostatin receptor agonists such as octreotide, DPP4 inhibitors, sulfonylureas and alpha-glucosidase inhibitors with the goal of maintaining glucose homeostasis.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with PARP inhibitors.

A compound of the instant invention may also be useful for treating cancer in combination with the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin

(Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (dromostanolone®); dromostanolone propionate (masterone injection®); Elliott's B Solution (Elliott's B Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®);

Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); zoledronate (Zometa®) and vorinostat (Zolinza®).

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term “treating cancer” or “treatment of cancer” refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of the instant invention and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and in the Examples that follow are: Ac (acetyl); AcOH (acetic acid); AEBSF (p-aminoethylbenzenesulfonyl fluoride); BF3 $OEt_2$ (borontrifluoride etherate); Boc (t-butoxycarbonyl); $Boc_2O$ (di-tert-butyl dicarbonate); Bu (butyl); BSA (bovine serum albumin); BuLi (n-Butyl lithium); Cal (calculated); Calc'd (calculated); $CDCl_3$ (chloroform-d); CDI (carbonyldiimidazole); $CHCl_3$ (chloroform); CuI (copper iodide); $CuSO_4$ (copper sulfate); DCE (dichloroethane); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DIBAL-H (diisobutylaluminum hydride); DIEA (diisopropylethylamine); DIPEA (diisopropylethylamine); DMAP (4-dimethylaminopyridine); DMF (N,N-dimethylformamide); DMI (1,3-dimethyl-2-imidazolidinone); DMSO (dimethyl sulfoxide); DPPA (diphenylphosphoryl azide); dppf (1,1'-bis(diphenylphosphino)ferrocene; DTT (dithiothreitol); EDC (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide); EDTA (ethylene-diamine-tetra-acetic acid); EGTA (ethylene-glycol-tetra-acetic acid); Eq (equivalents); Et (ethyl); $Et_3N$ (triethylamine); EtOAc (ethyl acetate); EtOH (ethanol); $H_2SO_4$ (sulfuric acid); HCl (hydrochloric acid); HOAc (acetic acid); HOBT (hydroxybenzotriazole); HPLC (high-performance liquid chromatography); HRMS (high resolution mass spectrum); IPA (isopropanol); LAH (lithium aluminum hydride); LC/MS (liquid chromatograph-mass spectrometer); LCMS (liquid chromatograph-mass spectrometer); LDA (lithium diisopropylamide); LHMDS (lithium bis(trimethylsilyl)amide); LRMS (low resolution mass spectrum); mCPBA (meta-chloroperbenzoic acid); Me (methyl); MeCN (acetonitrile); MeOH (methanol); $MgSO_4$ (magnesium sulfate); min (minutes); MP-$B(CN)H_3$ (Macroporous cyanoborohydride); MS (mass spectrometer); n-BuLi (n-Butyl lithium); n-BuOH (1-butanol); $N_2$ (nitrogen); $Na_2CO_3$ (sodium carbonate); $NaHCO_3$ (sodium bicarbonate); $Na_2SO_4$ (sodium sulfate); $Na(OAc)_3BH$ (sodium triacetoxyborohydride); NaH (sodium hydride); NaHMDS (sodium bis(trimethylsilyl)amide); NaOH (sodium hydroxide); NaOMe (sodium methoxide); NBS (N-bromosuccinamide); $NH_4OAc$ (ammonium acetate); $NH_3$ (ammonia); NIS (N-iodosuccinamide); NMP (N-methylpyrrolidinone); NMR (nuclear magnetic resonance); $O_3$ (ozone); PBS (phosphate buffered saline); PCR (polymerase chain reaction); Pd/C (palladium on carbon); $PdCl_2$(dppf)-$CH_2Cl_2$ adduct (Dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct); Pd(dppf) ([1,1'-bis(diphenylphosphino)ferrocene] palladium); $Pd(Ph_3)_4$ (palladium(0) tetrakis-triphenylphosphine); $Pd(Ph_3P)_2Cl_2$ (trans-dichlorobis(triphenylphosphine)palladium (II)); $Pd_2(dba)_3$ (bis(dibenzylideneacetone)palladium (0)); $POCl_3$ (phosphorous oxychloride); Pr (propyl); PS-DIEA (polystyrene diisopropylethylamine); PS-$PPh_3$ (polystyrene-triphenyl phosphine); Pyr (pyridine); TBAF (tetrabutylammonium fluoride); tetrakis (palladium(0) tetrakis-triphenylphosphine); TFA

(trifluoroacteic acid); THF (tetrahydrofuran); $Ti(OEt)_4$ (titanium (IV) ethoxide); $TMSCH_2N_2$ (trimethylsilyldiazomethane); TMSCN (trimethylsilylcyanide); Tosyl-Cl (para-toluenesulfonyl chloride); Zn (zinc); $Zn(CN)_2$ (zinc cyanide); Sat (saturated) and Tosic (p-toluenesulfonic acid).

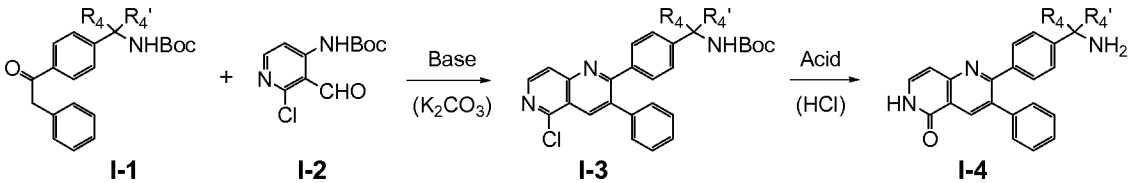
The compounds of this invention may be prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the Reaction Schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions of Formula A herein above.

Synopsis of Reaction Schemes

Utilizing the following general Reaction Schemes, Reaction Schemes I - VI, one of ordinary skill in the art would be able to synthesize the substituted bicyclic molecules (see Formula A) of the instant invention. The requisite intermediates are in some cases commercially available or can be prepared according to literature procedures.

As illustrated in Reaction Scheme I, a ketone derivative **I-1** is condensed with aldehyde **I-2** under basic conditions, such as potassium carbonate, sodium methoxide or aqueous potassium hydroxide, to give the substituted bicycle, in this case chloronaphthyridine **I-3**. Deprotection of the amine with an acid such as hydrochloric acid or trifluoroacetic acid, and in this case hydrolysis of the chloride, generates **I-4**. The aldehyde precursor, such as aldehyde **I-2**, is readily available from formylation of the corresponding protected amine under basic conditions or oxidation of an aromatic methyl group. The ketone derivative **I-1** is available from the corresponding aryl-halide via cyanation and reaction with a nucleophilic benzyl Grignard reagent or aryl lithium addition to a phenyl acetate derivative.

Reaction Scheme I

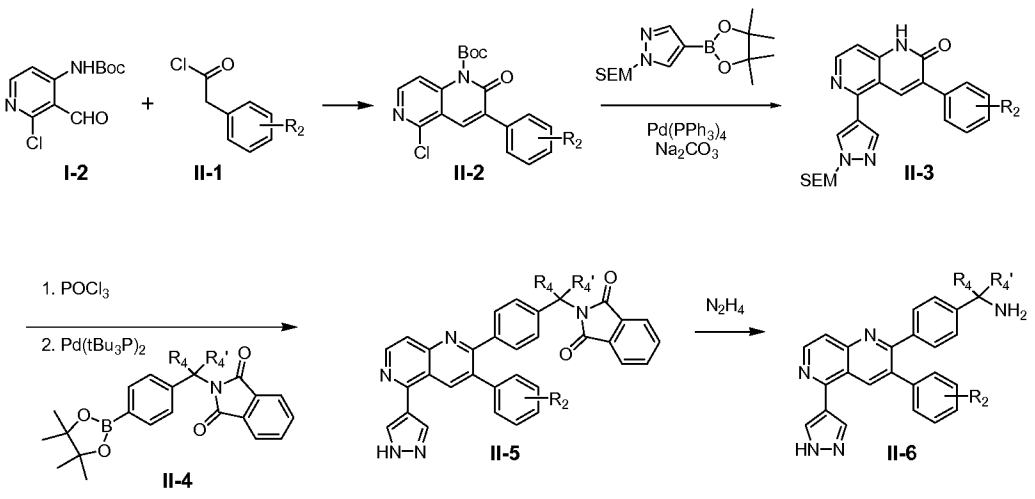



**I-1** **I-2** **I-3** **I-4**

As illustrated in Reaction Scheme II, condensation between aldehyde **I-2** and a phenyl acetic acid derivative under basic conditions, such as acid chloride **II-1**, gives the substituted bicycle, in this case chloro-naphthyidinone **II-2**. Chloride **II-2** can be further functionalized using methods familiar to one of ordinary skill in the art, in this case with a heteroaryl ring using a palladium-catalyzed coupling reaction, to give naphthyridinone **II-3**.

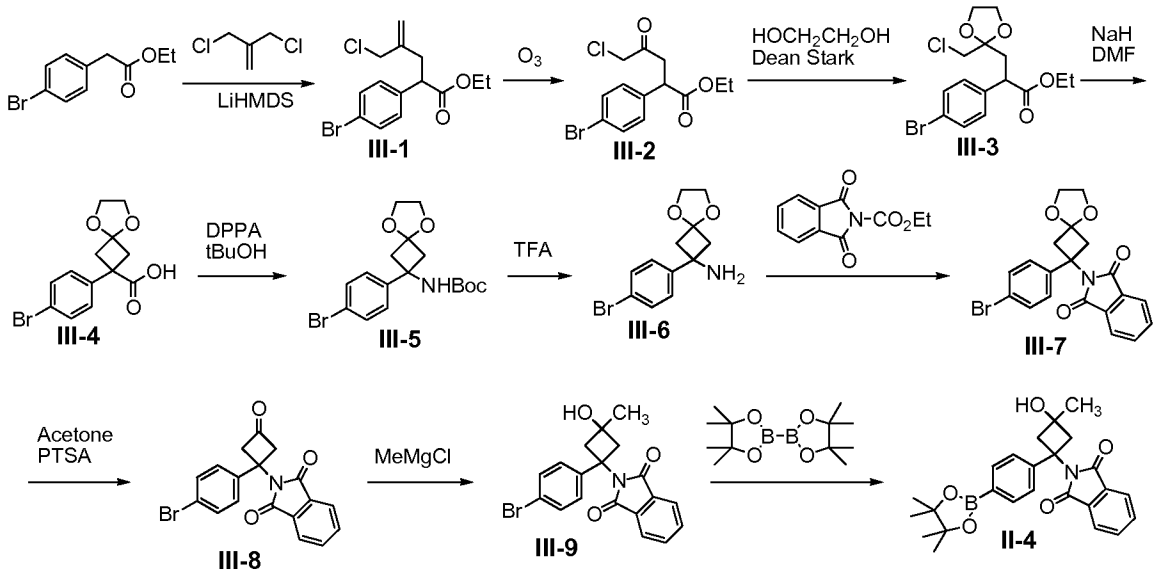
Naphthyridinone **II-3** is activated to a halide or triflate suitable for palladium-catalyzed reaction with boronate ester **II-4** to give **II-5**. Deprotection of the amine, in this case with hydrazine, generates **II-6**.

Reaction Scheme II



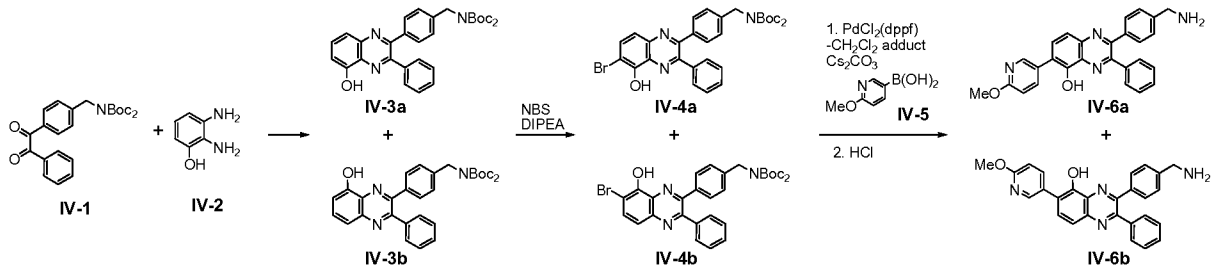

Boronate esters of the structure **II-4** can be prepared according to the reactions outlined in Reaction Scheme III. A phenyl acetic acid derivative is first alkylated with 3-chloro-2-chloromethyl-1-propene using a base such as LHMDS to give **III-1**. The olefin is then oxidatively cleaved, for example with ozone, to give ketone **III-2** which is reacted with a diol such as ethylene glycol to give **III-3**. Cyclization under basic conditions and a hydrolytic work-up then gives the cycloalkyl compound **III-4**. Generation of the acyl azide followed by rearrangement and trapping of the resulting isocyanate with the appropriate alcohol gives carbamate **III-5**. Deprotection with acid under anhydrous conditions gives **III-6**, and protection with a phthalamido group give **III-7**. Ketal hydrolysis under acidic conditions gives **III-8**. Nucleophilic addition with a Grignard reagent gives alcohol **III-9**, and borylation catalyzed by palladium gives boronate ester **II-4**.

Reaction Scheme III



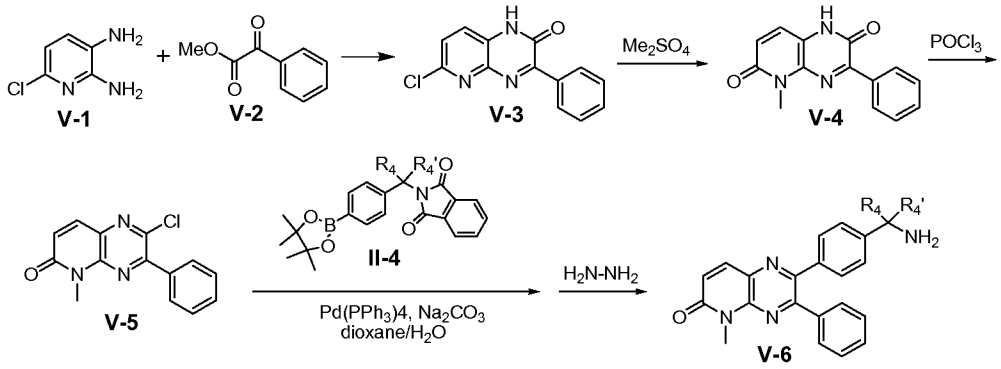

As illustrated in Reaction Scheme IV, a diketone derivative **IV-1** is condensed with diamine **IV-2** under acidic conditions to give the substituted bicycle, in this case a mixture of regioisomeric hydroxy-quinoxalines **IV-3a** and **IV-3b**. The bicyclic ring can be functionalized in using methods familiar to one of ordinary skill in the art such as alkylation and halogenation. In this case, treatment of **IV-3a** and **IV-3b** with an electrophilic halogenating reagent, NBS, gives bromides **IV-4a** and **IV-4b**, which are coupled to boronic acid **IV-5** under palladium-catalyzed conditions. Deprotection of the amine with an acid such as hydrochloric acid generates **IV-6a** and **IV-6b**. The diketone **IV-1** is available from oxidation of either an acetylene or ketone **I-1**.

Reaction Scheme IV



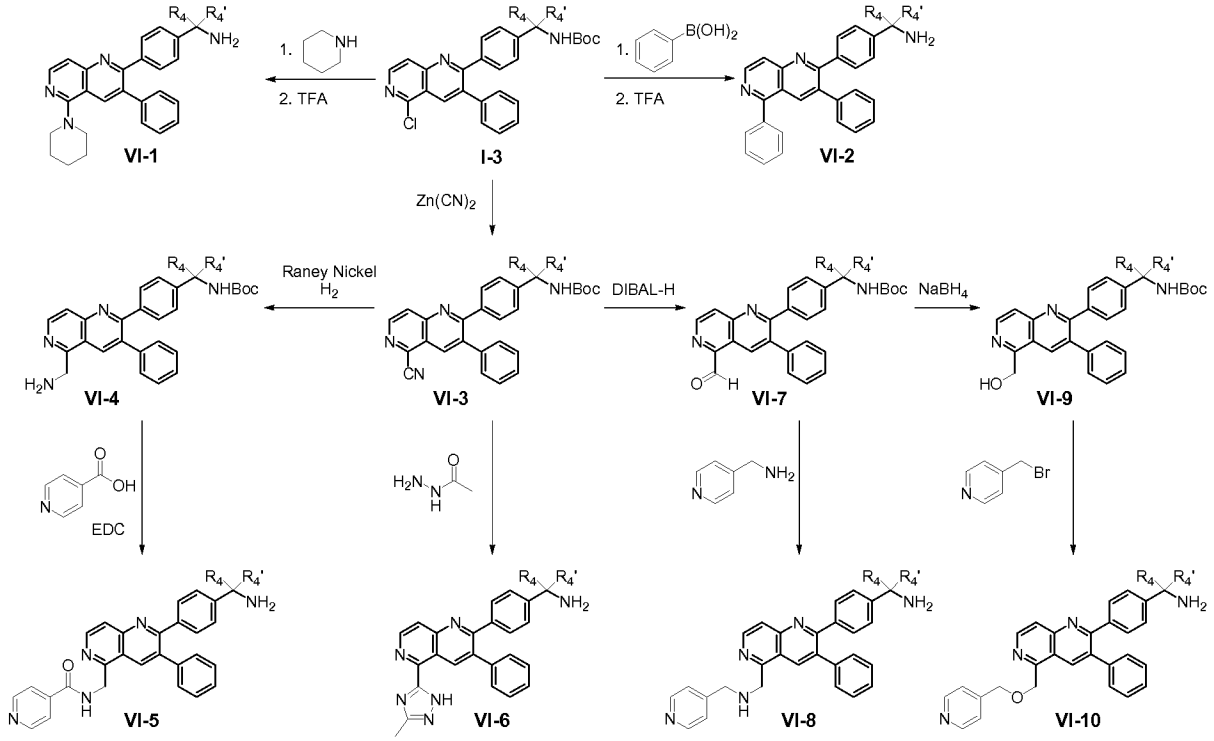

As illustrated in Reaction Scheme V, condensation between diamine **V-1** and keto-ester **V-2** under basic conditions gives bicyclic chloro-quinoxalinone **V-3**. Alkylation gives dione **V-4** and halogenation gives chloride **V-5**. Palladium-catalyzed reaction with boronate ester **II-4** and deprotection of the amine, in this case with hydrazine, generates **V-6**.

Reaction Scheme V




Compounds of the instant invention (see Formula A) in which $R^1$ is an alkyl, aryl, heteroaryl, acetylene, ether, amino, sulfide or nitrile group are prepared from the halogen precursor, such as chloride **I-3**, according to the procedures outlined in reaction Scheme VI. The bicycle ring systems can then be further functionalized using standard chemistries including Suzuki, sonogashira, cyanation, amine and alkoxide displacements, alkylations.Displacement of chloride **I-3** with an amine, alcohol, thiol or arylacetate under basic conditions gives **VI-2**. Chloride **I-3** also reacts with a Grignard reagent, boronate ester, boronic acid, stannane, acetylene or zinc cyanide in the presence of a metal such as palladium or iron to give **VI-1**. Deprotection under acidic conditions then gives **I-2**. The bicycle ring systems can then be further functionalized using standard chemistries including halogenation and couplings, as well as oxidation to N-oxides and cyanation, prior to amine deprotection. Compounds of the instant invention with appropriate $R^1$ groups can be further functionalized prior to amine deprotection using methods familiar to one of ordinary skill in the art. For example, nitrile **VI-3** is reduced to amine **VI-4**, which can be acylated to give **VI-5**. Nitrile **VI-3** is reacted with acyl-hydrazides to give **VI-6**, and nitrile **VI-3** is reduced with DIBAL-H to give aldehyde **VI-7**. Aldehyde **VI-7** is reacted with amines in the presence of a reducing agent to give amine **VI-8**. Alternatively, aldehyde **VI-7** is reduced with sodium borohydride to give alcohol **VI-9**, which is alkylated to give **VI-10**. Aldehyde **VI-7** and alcohol **VI-9** can be halogenated with Deoxo-Fluor to give fluorinated derivatives.

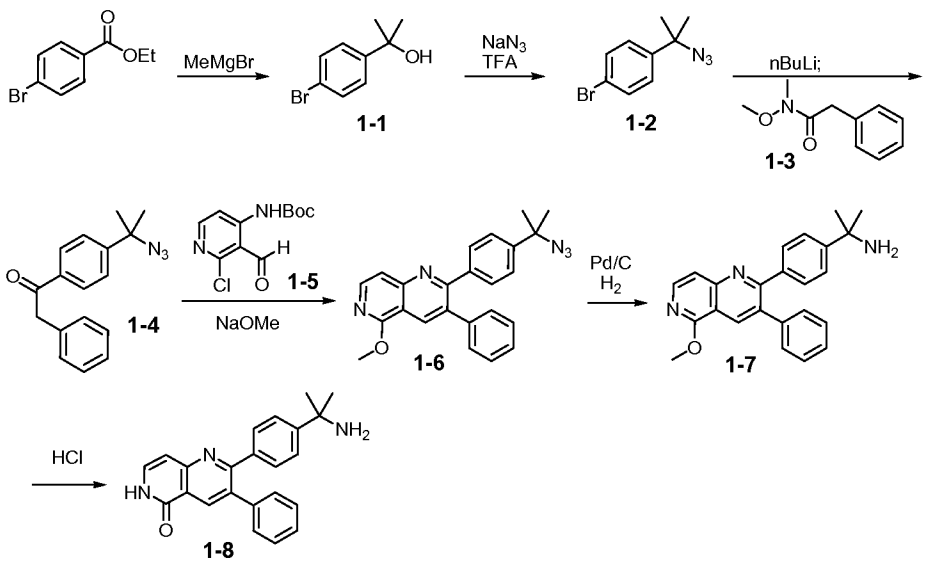
Reaction Scheme VI




## EXAMPLES

Examples and schemes provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

## SCHEME 1




2-[4-(1-amino-1-methylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**1-8**)

2-(4-bromophenyl)propan-2-ol (**1-1**)

Methylmagnesium bromide solution (1.4M in 75:25 toluene:THF, 20 mL, 27.5mmol) was added slowly to ethyl 4-bromobenzoate (2.5 g, 11 mmol) in THF (10mL) at -30°C. After 2hr, quenched with ammonium chloride and extracted with ether. The organic layer was washed with 1:1 brine:water, dried over magnesium sulfate, filtered, and concentrated to give **1-1** as a pale yellow oil. MS: 119.1 (M-17).

1-(1-azido-1-methylethyl)-4-bromobenzene (**1-2**)

A solution of TFA (4.4 mL, 45 mmol) in chloroform (10mL) was added slowly to a mixture of **1-1** (2.3 g, 11 mmol) and sodium azide (1.4 g, 22 mmol) in chloroform (10 mL) cooled to -5°C, maintaining the temperature below 0°C. The cooling bath was removed and the mixture was stirred overnight at rt. Concentrated ammonium hydroxide was added until basic. The organic layer was washed with 1:1 brine:water, dried over magnesium sulfate, filtered, concentrated to give **1-2** as a pale yellow oil. MS: 197.1 (M-44).

N-methoxy-N-methyl-2-phenylacetamide (**1-3**)

N,N'-Carbonyldiimidazole (6.0 g, 37 mmol) was added to phenylacetic acid (5.0 g, 37 mmol) in DMF (25 mL), resulting in considerable gas evolution. The mixture was heated to 40°C for 30min, followed by addition of N,O-dimethylhydroxylamine hydrochloride (3.9 g, 40 mmol). After 30 min at rt, quenched with ammonium chloride and extracted with 1:1 EtOAc:hexane, dried over magnesium sulfate, and concentrated to give **1-3** as a pale yellow oil. MS: 180.2 (M+1).

1-[4-(1-azido-1-methylethyl)phenyl]-2-phenylethanone (**1-4**)

A solution of nBuLi (1.6M in hexane, 2.9 mL, 4.6 mmol) was added dropwise to bromide **1-2** (1.0 g, 4.2 mmol) at -78°C, followed by addition of Weinreb amide **1-3** (0.76 g, 4.2 mmol, dissolved in 1 mL THF). After 45min at -78°C, quenched with ammonium chloride and extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated to give an oil. The crude product was purified via silica gel chromatography (0-20% EtOAc in hexane with 5% DCM) to give **1-4** as a cream-colored solid. MS: 280.3 (M+1).

2-[4-(1-azido-1-methylethyl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (**1-6**)

Sodium methoxide (25weight% in methanol, 0.3 mL) was added to **1-4** (100 mg, 0.36 mmol) and *tert*-butyl (2-chloro-3-formylpyridin-4-yl)carbamate (**1-5**) (110 mg, 0.43 mmol) in methanol (2.5 mL), then heated to 65°C for 2h. The mixture was cooled to rt, diluted with EtOAc, and acidified with 1N HCl. The aqueous was extracted with ethyl acetate and the combined organics were washed with 1:1 brine:water, dried over magnesium sulfate, filtered,

and concentrated to give a dark semi-solid. Purified via silica gel chromatography (0-45% EtOAc in hexane with 5% DCM) to give **1-6** as a clear oil. MS: 396.3 (M+1).

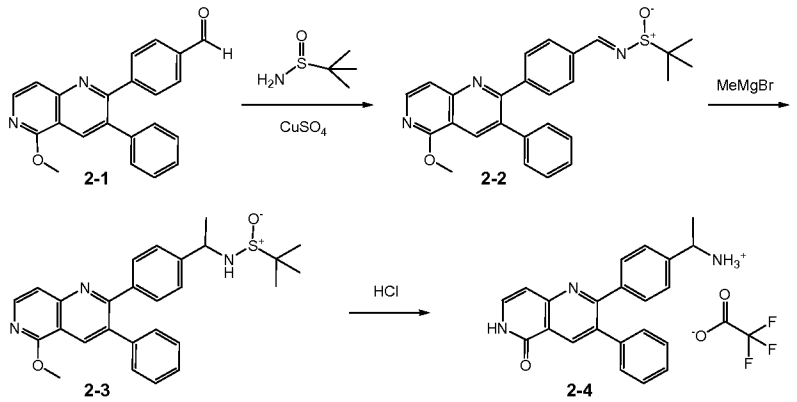
2-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-2-amine (**1-7**)

A solution of **1-6** (90 mg) in EtOH (9mL) was stirred under 1 atm hydrogen gas with 10% Pd/C (8 mg) for 2h. Filtered through celite and concentrated to give **1-7** as a colorless oil. MS: 370.3 (M+1).

2-[4-(1-amino-1-methylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**1-8**)

To **1-7** (82 mg, 0.22 mmol) in THF (10 mL) was added 12N HCl (2 mL). After 5h at rt, basified with saturated bicarbonate, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated to give **1-8** as an off-white solid. MS: 356.4 (M+1).

SCHEME 2




1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate (**2-4**)

N-{(1E)-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methylidene}-2-methylpropane-2-sulfinamide (**2-2**)

Racemic 2-methyl-2-propane-sulfinamide (740 mg, 6.1 mmol), cupric sulfate (930 mg, 5.8 mmol), and aldehyde **2-1** (900 mg, 2.6 mmol, Reference: Bilodeau, Mark T.; et. al. Bioorganic & Medicinal Chemistry Letters (2008), 18(11), 3178-3182) were stirred overnight at room temperature in methylene chloride (10 mL). The reaction mixture was then heated for 31h at 40°C. After cooling to rt, the mixture was then filtered through celite, concentrated to a minimum volume and purified via silica gel chromatography (0-70% EtOAc in hexane with 5% DCM) to give **2-2** as a white foam. MS: 444.2 (M+1).

N-{1-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propyl}-2-methylpropane-2-sulfinamide (**2-3**)

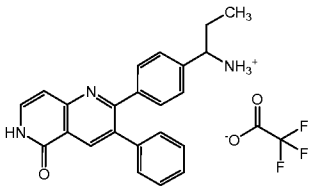
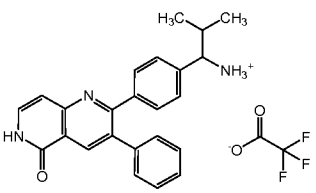
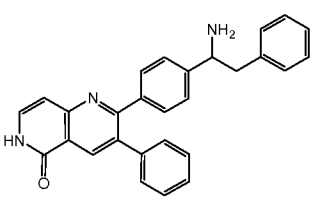
Methylmagnesium bromide (1M in THF, 0.6 mL, 0.6 mmol) was added slowly to a -78°C solution of **2-2** (100 mg, 0.23 mmol) in methylene chloride (10 mL). After 40min, the reaction was quenched with saturated sodium sulfate solution, added methylene chloride and magnesium sulfate, filtered and rinsed with EtOAc/DCM. The filtrate was concentrated to give **2-3** as an off-white solid. MS: 474.4 (M+1).

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate (**2-4**)

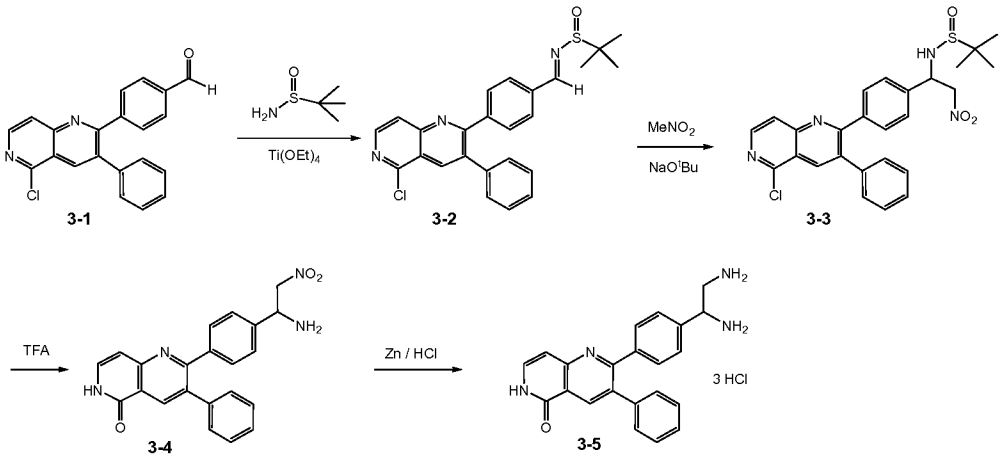
To a solution of **2-3** (130 mg, 0.27 mmol) in THF (5 mL) was added 12M HCl (1 mL) and stirred for 2h at rt. The reaction mixture was concentrated to a minimum volume and purified via reverse-phase chromatography. The pure fractions were combined, partially concentrated to a smaller volume and filtered to give **2-4** as a white solid. MS: 356.3 (M+1).

The following compounds in Table 1 were prepared according to the Reaction Schemes and Scheme 2.

Table 1

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **2-5** |  | 1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate | 356.4 | 356.3 |
| **2-6** |  | 2-methyl-1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium trifluoroacetate | 370.5 | 370.3 |
| **2-7** |  | 2-[4-(1-amino-2-phenylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6*H*)-one | 418.5 | 418.4 |

SCHEME 3




2-[4-(1,2-diammonioethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-1-ium trichloride (**3-5**)

N-{(1E)-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methylene}-2-methylpropane-2-sulfinamide (**3-2**)

To a solution of **3-1** (4.0 g, 12 mmol, Reference: WO2006135627A2, Dec. 21, 2006) in anhydrous THF (40 mL) was added 2-methyl-2-propane-sulfinamide (1.4 g, 12 mmol) and $Ti(OEt)_4$ (7.9 g, 35 mmol). The mixture was stirred at 60°C for 5h. The reaction was quenched with water (40 mL), filtered, and the resulting solution was extracted with EtOAc. The combined organic layer was washed with brine and dried over $Na_2SO_4$. Upon removal of the solvent, the residue was purified by silica gel chromatography to afford **3-2** as a solid. LC/MS: cal. 447.99; found 448.1

N-{1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-2-nitroethyl}-2-methylpropane-2-sulfinamide (**3-3**)

To a solution of nitromethane (1.8 g, 30 mmol) in 20 mL anhydrous DMSO was added sodium tert-butoxide (1.5 g, 15 mmol). The mixture was stirred at rt for 15 minutes, then **3-2** (1.7 g, 3.8 mmol) was added. The mixture was stirred for 2 hrs. The reaction was quenched with saturated $NH_4Cl$ and diluted with water. The mixture was extracted with EtOAc and washed with brine and concentrated to give crude **3-3**, which was used for next step without further purification. LC/MS: cal. 509.03; found 509.0

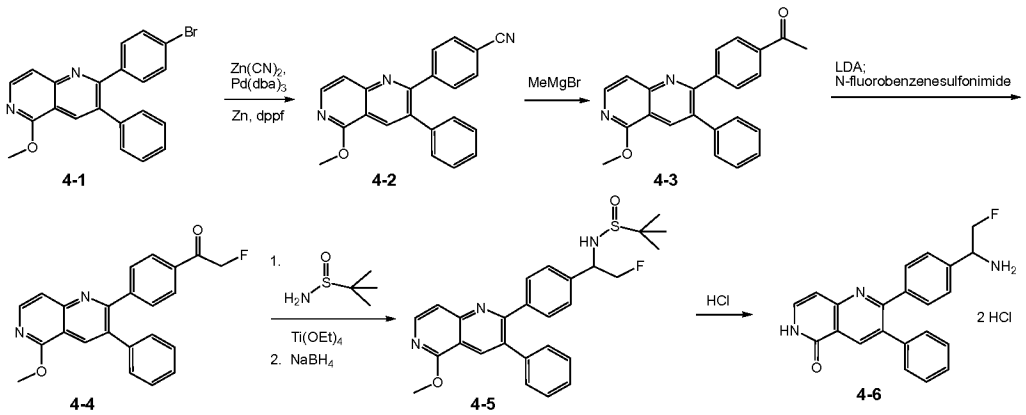
2-[4-(1-amino-2-nitroethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**3-4**)

To a solution of **3-3** (0.04 g, 0.08 mmol) in 0.5 mL DCM was added 0.25 mL TFA. The mixture was stirred for 3 hrs at rt. The mixture was concentrated, treated with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layer was concentrated and purified by reverse phase HPLC to provide **3-4**. LC/MS: cal. 386.41; found 387.

2-[4-(1,2-diaminoethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**3-5**)

To a solution of **3-4** (0.08 g, 0.2 mmol) in 0.3 mL AcOH was added Zn powder. The mixture was stirred for 60 minutes at rt. The mixture was filtered, washed with MeOH, concentrated and purified by reverse phase HPLC to provide **3-5**. MS $(M+1)^+$: observed = 357.1, calculated = 357.4.

SCHEME 4




2-[4-(1-ammonio-2-fluoroethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-1-ium dichloride (**4-6**)

4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzonitrile (**4-2**)

To a solution of **4-1** (2.0 g, 5.1 mmol, prepared from 1-(4-bromophenyl)-2-phenylethanone in a similar fashion as **2-1**) in DMF (30 mL) was added $Zn(CN)_2$ (1.2 g, 10 mmol), Zn powder (0.03 g, 0.5 mmol), $Pd_2(dba)_3$ (0.2 g, 0.2 mmol) and dppf (0.2 g, 0.4 mmol), followed by $N_2$ purging for 5 mins. The vessel was sealed and the mixture was heated in a microwave reactor for 30 mins at 130°C. The reaction was diluted with water and extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated and the residue was purified on silica gel chromatography to provide **4-2** as a solid. LC/MS: cal. 337.38; found 338.2

1-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanone (**4-3**)

To a solution of **4-2** (0.80 g, 2.2 mmol) in 20 mL anhydrous THF at -20°C was added methyl magnesium bromide (3 M, 1.2 mL, 3.6 mmol). The mixture was warmed to rt over 2 hrs. The reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated and the residue was purified via silica gel chromatography to afford **4-3** as a white solid. LC/MS: cal. 354.40; found 355.2

2-fluoro-1-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanone (**4-4**)

To a cooled (-78°C) solution of **4-3** (2.2 g, 6.2 mmol) in 30 mL THF was added LHMDS (1 M, 8.1 mL, 8.1 mmol). After 30 minutes, the mixture was warmed to 0°C for 10 minutes, and then cooled back to -78°C. N-fluorobenzenesulfonimide (3.9 g, 12 mmol) in 10 mL anhydrous THF was added dropwise. The mixture was stirred overnight while it slowly warmed to rt. The reaction was quenched with water and extracted with EtOAc. Upon removal of the solvent, the residue was purified via silica gel chromatography to afford **4-4**. LC/MS: cal. 372.39; found 373.1

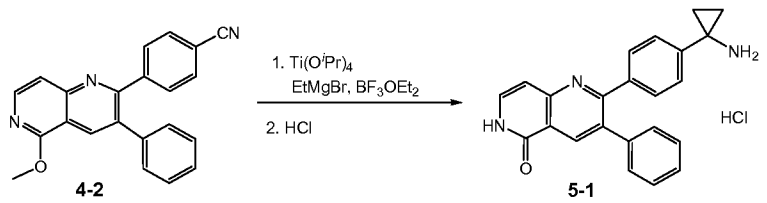
N-{2-fluoro-1-[4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}-2-methylpropane-2-sulfinamide (**4-5**)

To a solution of **4-4** (100 mg, 0.27 mmol) and (*S*)-2-methyl-2-propane-sulfinamide (52 mg, 0.43 mmol) in 0.5 mL anhydrous THF was added $Ti(OEt)_4$ (310 mg, 0.94 mmol, 70% purity). The mixture was stirred at 60°C for 8 hrs and cooled to rt. Sodium borohydride (20 mg, 0.54 mmol) was added in one portion. The mixture was stirred at rt for 2 hrs. The mixture was concentrated, 2 mL MeOH was added, followed by 2 mL water. The mixture was stirred for 2 hrs then extracted with EtOAc. The combined organic layers were dried, concentrated and the residue was purified via silica gel chromatography (10% EtOAc in hexane to 80% EtOAc in hexane) to afford the desired product (**4-5**) as a single stereoisomer, of which, the configuration was not determined; both isomers prepared independently from (R)- and (S)-2-methyl-2-propane-sulfinamide, respectively. LC/MS: cal. 477.59; found 478.3

2-[4-(1-amino-2-fluoroethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one (**4-6**)

**4-5** (70 mg, 0.15 mmol) was treated with 3 mL MeOH (sat with HCl) for 2 hrs and then heated in a microwave reactor at 100°C for 20 mins. Upon removal of the solvent, the desired product was obtained as a white solid; each enantiomer was independently prepared using this procedure. MS $(M+1)^+$: observed = 360.2, calculated = 360.4

SCHEME 5

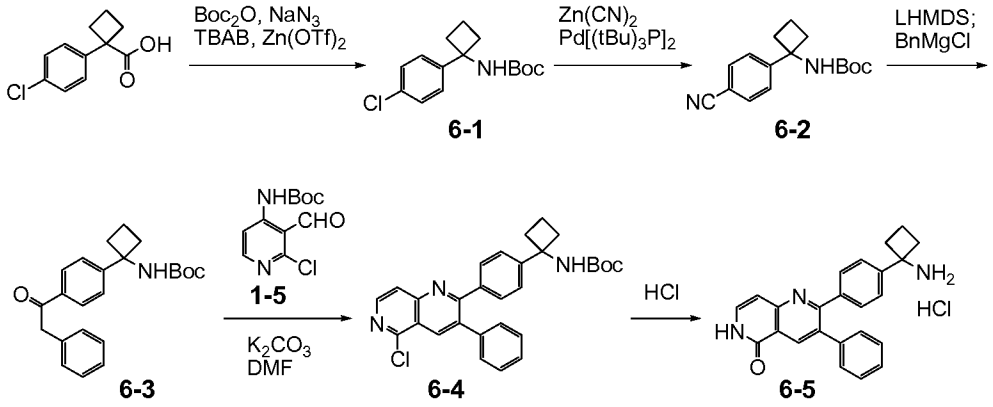



1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopropanaminium chloride (**5-1**)

To a cooled (-78°C) solution of **4-2** (0.2 g, 0.6 mmol) and $Ti(OiPr)_4$ (0.2 g, 0.6 mmol) in 10mL anhydrous ether was added ethylmagnesium bromide (3 M, 0.43 mL, 1.3 mmol).

The mixture was stirred for 10 mins at -78°C and warmed up to rt for 1 hr. $BF_3.OEt_2$ (0.5 g, 4 mmol) was added. The mixture was stirred at rt for 1 hr. 1 N HCl (3mL) was added and stirred overnight. The mixture was concentrated, treated with 5 mL MeOH and filtered. The filtrate was purified by reverse-phase HPLC to afford the desired product (**5-1**). MS $(M+1)^+$: observed = 354.2, calculated = 354.4

SCHEME 6




1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] cyclobutanaminium chloride (**6-5**)

tert-butyl [1-(4-chlorophenyl)cyclobutyl]carbamate (**6-1**)

To a round bottom flask was added 1-(4-chlorophenyl)cyclobutanecarboxylic acid (40.4 g, 192 mmol), di-tert-butyl dicarbonate (46.0 g, 211 mmol), sodium azide (43.6 g, 671 mmol), tetrabutylammonium bromide (9.27 g, 28.7 mmol), zinc trifluoromethanesulfonate (2.30 g, 6.32 mmol), and THF (1L). The reaction mixture was then heated to 60°C while stirring in a hot oil bath with a water cooled reflux condenser attached under an atmosphere of nitrogen for 18 hours. To the crude reaction mixture was added a saturated solution of sodium bicarbonate (100 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0-3% IPA/DCM) to give tert-butyl [1-(4-chlorophenyl)cyclobutyl]carbamate (**6-1**) as a white solid. HRMS (M+Na)+: observed = 304.1075, calculated = 304.1075.

tert-butyl [1-(4-cyanophenyl)cyclobutyl]carbamate (**6-2**)

To a solution of tert-butyl [1-(4-chlorophenyl)cyclobutyl]carbamate (**6-1**) (5.32 g, 18.9 mmol) in anhydrous 1,4 Dioxane (70 mL) was added zinc cyanide (2.44 g, 20.8 mmol), followed by bis(tri-t-butylphosphine)palladium(0) (0.965 g, 1.89 mmol). The reaction mixture was heated to 100°C while stirring in a hot oil bath with a water cooled reflux condenser attached under an atmosphere of nitrogen for 1.5 hours. The reaction mixture was then filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (0-

5% IPA/DCM) to give tert-butyl [1-(4-cyanophenyl)cyclobutyl] (**6-2**) as a waxy off-white/ yellow solid. HRMS (M+H)+: observed = 273.1598, calculated = 273.1597.

tert-butyl {1-[4-(phenylacetyl)phenyl]cyclobutyl}carbamate (**6-3**)

A solution of tert-butyl [1-(4-cyanophenyl)cyclobutyl]carbamate (**6-2**) (35.3 g, 129 mmol) in anhydrous THF (520 mL) was cooled to -78°C while stirring under an atmosphere of nitrogen. Then a 1.0 M solution of LHMDS in THF (200 mL, 200 mmol) was added dropwise over 20 minutes. The reaction mixture was stirred at -78°C under an atmosphere of nitrogen for 10 minutes, and then warmed to 0°C for 30 minutes. The reaction mixture was then cooled to -78°C while stirring under an atmosphere of nitrogen. Then a 2.0 M solution of benzylmagnesium chloride in THF (324 mL, 647 mmol) was added dropwise over 1 hour. The reaction mixture was then permitted to warm to 0°C. After 30 minutes at 0°C, reaction mixture was permitted to warm to room temperature and quenched by addition of a saturated solution of ammonium chloride (500 mL). The reaction was suspended in ethyl acetate, washed with a saturated solution of ammonium chloride, then a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (0-30% EtOAc/5% DCM/Hexane) to give tert-butyl {1-[4-(phenylacetyl)phenyl]cyclobutyl}carbamate (**6-3**) as a waxy off-white solid. HRMS (M+Na)+: observed = 388.1892, calculated = 388.1883.

tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl} carbamate (**6-4**)

To a round bottom flask was added tert-butyl{1[4(phenylacetyl)phenyl] cyclobutyl}carbamate (**6-3**) (2.7 g, 6.1 mmol), tert-butyl (2-chloro-3-formylpyridin-4-yl)carbamate (**1-5**) (1.6 g, 6.1 mmol), potassium carbonate (5.0 g, 6.0 mmol), and finally DMF (20 mL). The reaction mixture was heated to 80°C while stirring in a hot oil bath under an atmosphere of nitrogen for 15 hours. Then the reaction mixture was warmed to 120°C for 1 hour. The reaction mixture was then permitted to cool to room temperature, added water (20 mL), suspended in ethyl acetate, washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (5-50% EtOAc/5%DCM/ Hexane) to give tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**6-4**) as an off-white solid. HRMS (M+H)+: observed = 486.1954, calculated = 486.1943.

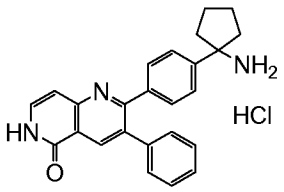
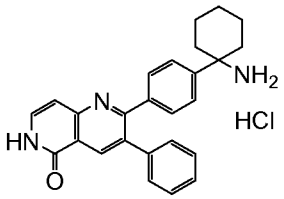
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] cyclobutanaminium chloride (**6-5**)

To a round bottom flask was added tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**) (0.49 g, 1.0 mmol), dioxane (1 mL) and 6N HCl in water (0.42 mL, 2.5 mmol). The reaction mixture was then heated to to 100°C while stirring in a hot oil bath. After 4 hours the reaction mixture was permitted to cool to room temperature, added water (20 mL), suspended in ethyl acetate, washed with a saturated solution

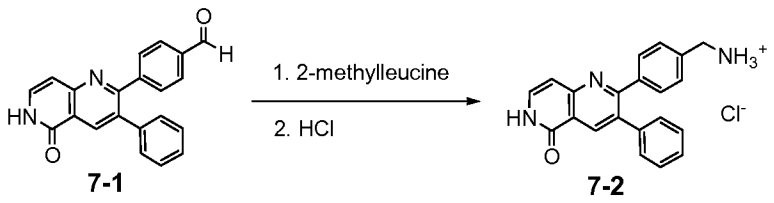
of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give 1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium chloride (**6-5**) as a yellow solid. HRMS (M+H)+: observed = 368.1731, calculated = 368.1758.

The following compounds in Table 2 were prepared according to the Reaction Schemes and Scheme 6.

Table 2

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **6-6** |  | 1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopentanaminium chloride | 382.1900 | 382.1914 |
| **6-7** |  | 1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclohexanaminium chloride | 396.2078 | 396.2071 |

SCHEME 7

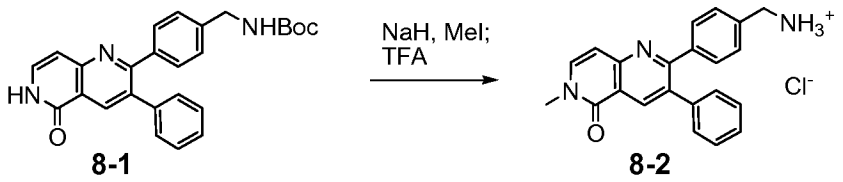



[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**7-2**)

4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)benzaldehyde (**7-1**; reference: Siu, T., et al. Bioorganic & Medicinal Chemistry Letters (**2008**), *18*(14), 4191-4194) (25 mg, 0.08 mmol) and 2-methylleucine (11 mg, 0.8 mmol) were dissolved in DMF (1 mL). The mixture was heated to 150°C for 30 minutes in a microwave reactor. The solvent was removed under reduced pressure and 3N HCl (1 mL) was added to the crude residue. The mixture was heated to 100°C for 1 hr in a microwave reactor, cooled to rt, and purified by

reverse phase HPLC for purification to give [4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**7-2**) as a yellow solid. MS (M+1): calculated = 327.4, observed = 328.1

SCHEME 8

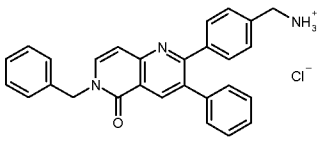
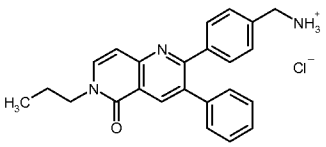
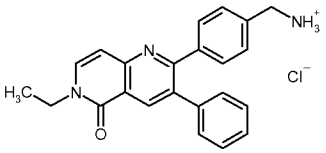



[4-(6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-2**).

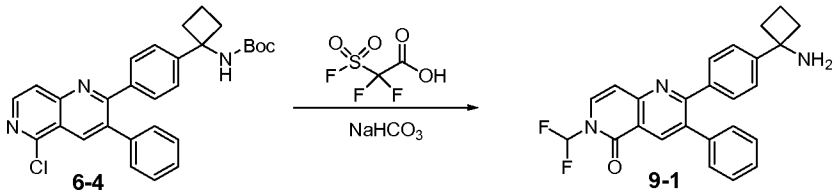
To a solution of *tert*-butyl [4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)benzyl]carbamate (**8-1**, 100 mg, 0.23 mmol, available from Boc-protection of **7-2** using the procedure reported for **62-5**) in THF (1 mL) was added NaH (6 mg, 0.23 mmol, 60% dispersion in mineral oil). The reaction was allowed to stir for 30 min. Methyl iodide (40 mg, 0.28 mmol) was then added. After stirring for 30 min., the solvent was removed under reduced pressure and the residue was taken up in 30% TFA in dichloromethane. After stirring for 30 min., the solvent was removed under reduced pressure. The crude residue was purified by reverse phase HPLC to yield [4-(6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**8-2**). MS (M+1): calculated =341.4, observed = 342.1

The compounds in Table 3 were prepared according to the Reaction Schemes and Scheme 8.

Table 3

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **8-3** |  | [4-(6-benzyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 417.5 | 418.1 |
| **8-4** |  | [4-(5-oxo-3-phenyl-6-propyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 369.5 | 370.2 |
| **8-5** |  | [4-(6-ethyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 355.4 | 356.2 |

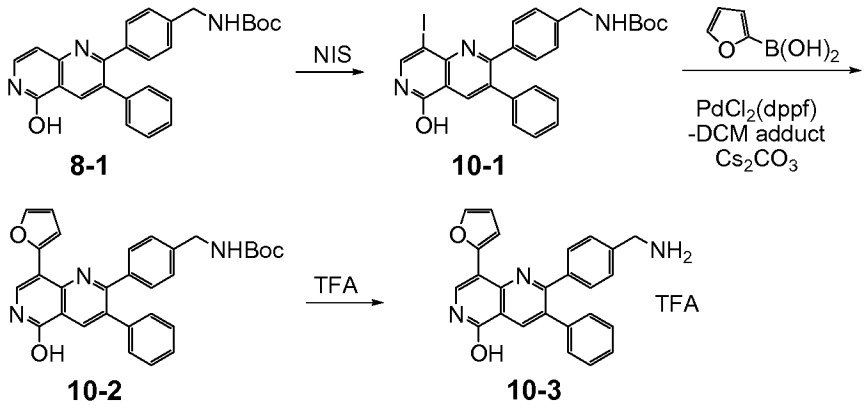
SCHEME 9




2-[4-(1-aminocyclobutyl)phenyl]-6-(difluoromethyl)-3-phenyl-1,6-naphthyridin-5(6H)-one (**9-1**)

A mixture of tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**, 50 mg) and difluoro(fluorosulfonyl)acetic acid (32 uL) in MeCN (1 mL) was stirred at 40°C for 24 h. The resulting mixture was diluted with EtOAc, washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 2-[4-(1-aminocyclobutyl)phenyl]-6-(difluoromethyl)-3-phenyl-1,6-naphthyridin-5(6H)-one (**9-1**) as colorless amorphous material. HRMS $(M+H)^+$: observed = 418.1728, calculated = 418.1731

SCHEME 10




{4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**10-3**)

tert-butyl [4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)benzyl] carbamate (**10-1**)

A mixture of tert-butyl [4-(5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate **8-1** (4.0 g, 9.4 mmol) in MeCN (25 mL) was treated with NIS (2.1 g, 9.4 mmol). The resulting mixture was heated at 120°C in the microwave for 5 minutes, resulting in a dark brown solution with a precipitate. The mixture was concentrated half way and then filtered to afford tert-butyl [4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**10-2**) as a brown solid. MS calculated M+H: 554.4; found 554.1

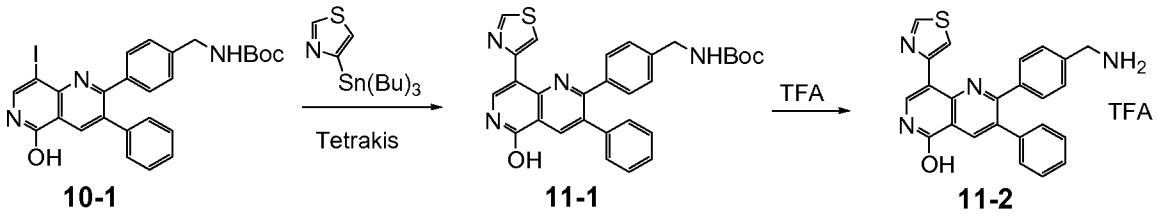
tert-butyl {4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**10-2**)

To a mixture of tert-butyl [4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**10-1**) (50 mg, 0.09 mmol), 2-furylboronic acid, and $PdCl_2(dppf)$-$CH_2Cl_2$ adduct (7 mg, 9 μmol) in THF (2 mL) was added cesium carbonate (0.8 mL, 0.8 mmol). The mixture was then heated at 140°C for 20 minutes in the microwave. Upon completion, the THF layer was decanted off and stirred with QuadraPure TU resin overnight. After filtration and solvent removal, the residue was purified by silica gel chromatography (0-75% EtOAc in Hexanes) to give tert-butyl {4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**10-2**).

{4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**10-3**)

**10-2** was dissolved in DCM (1 mL) and treated with TFA (0.2 mL) at room temperature for 30 minutes. The reaction mixture was concentrated to give desired product (**10-3**). MS calculated M+H-$NH_3$: 377.4; found 377.1

SCHEME 11




10-1 11-1 11-2

{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-2**)

tert-butyl {4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]benzyl}carbamate (**11-1**)

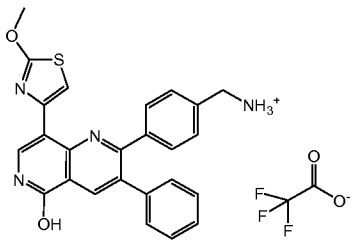
In a dried microwave tube were dissolved tert-butyl [4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**10-1**) (100 mg, 0.18 mmol) and 4-(tributylstannyl)-1,3-thiazole (160 mg, 0.43 mmol) in THF (2 mL). $N_2$ gas was then bubbled through the solution for 5 minutes before adding Tetrakis (21 mg, 0.018 mmol). $N_2$ gas was bubbled through the mixture for another 5 minutes and the mixture was then heated to dryness at 100°C on a heating block overnight. The resulting residue was taken up in DMF, treated with QuadraPure TU resin for 30 minutes and filtered. The mixture was purified by reverse phase HPLC to give tert-butyl {4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]benzyl}carbamate (**11-1**) as an orange residue. MS calculated M+H: 511.6; found 511.1

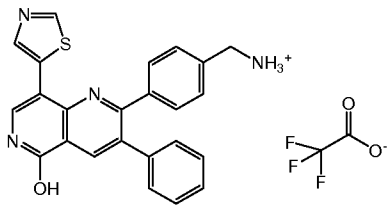
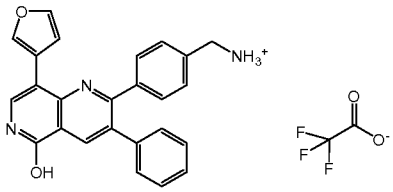
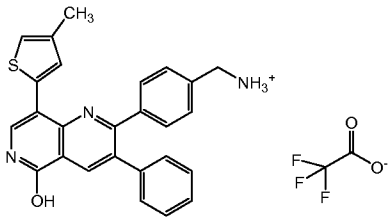
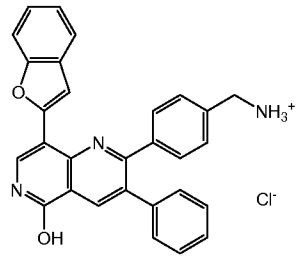
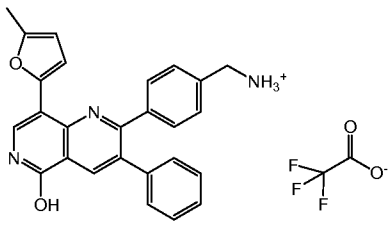
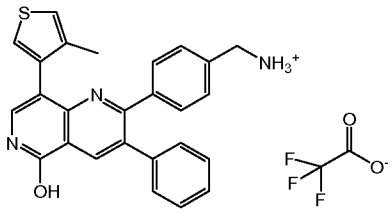
{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate (**11-2**)

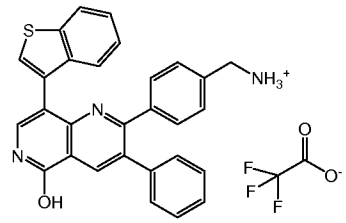
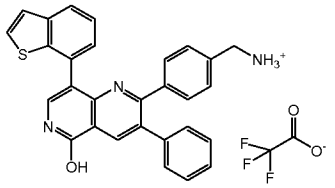
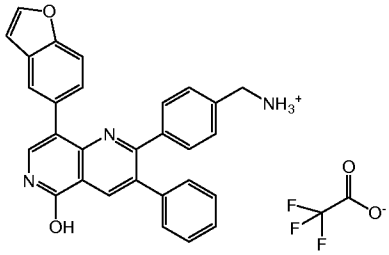
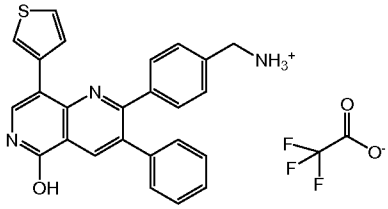
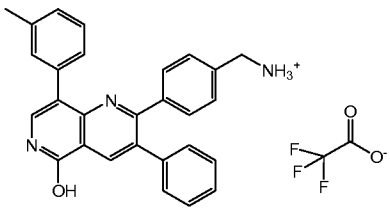
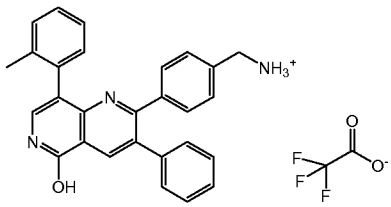
**11-1** was dissolved in DCM (1 mL) and treated with TFA (0.2 mL) at room temperature for 30 minutes. The reaction mixture was purified by reverse phase HPLC to afford desired product (**11-2**). MS calculated M+H: 411.5; found 411.1.

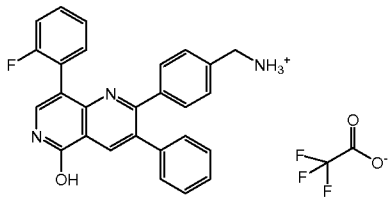
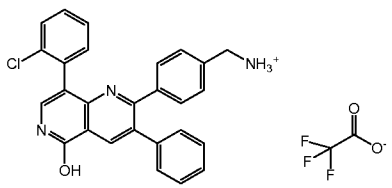
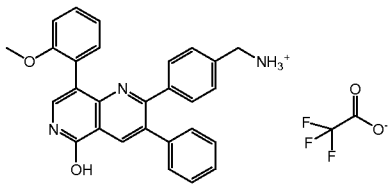
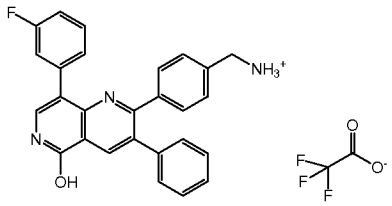
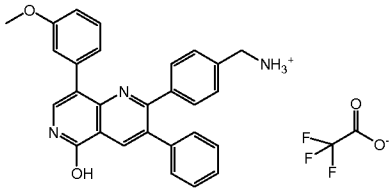
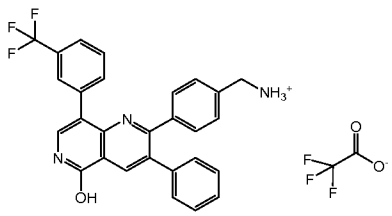
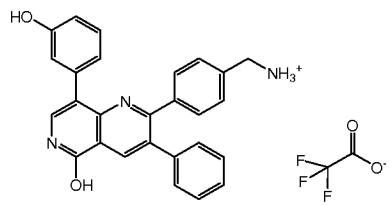
The following compounds in Table 4 were prepared according to the Reaction Schemes and Schemes 10 and 11.

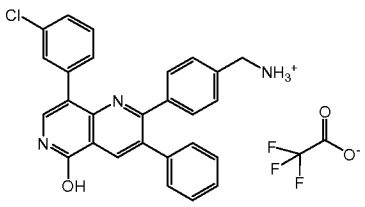
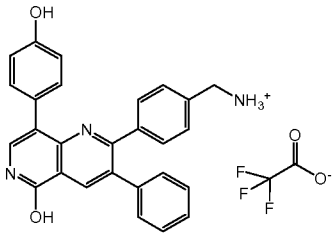
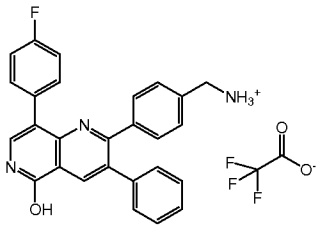
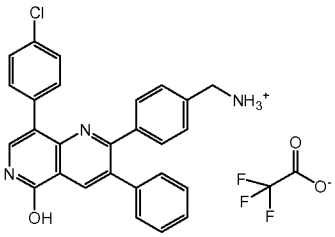
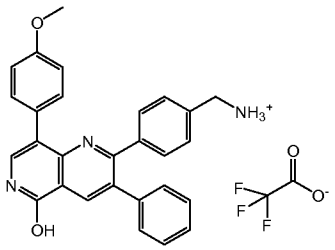
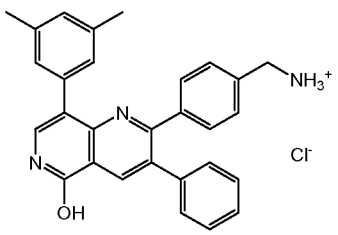
Table 4

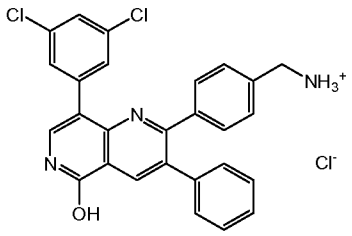
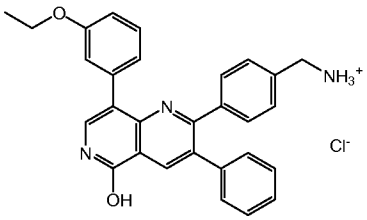
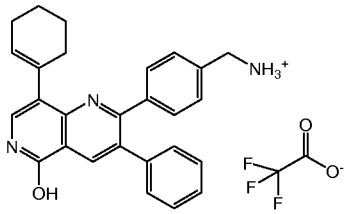
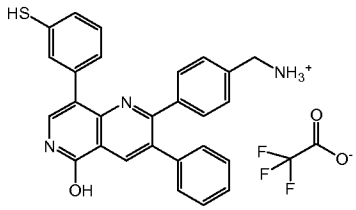
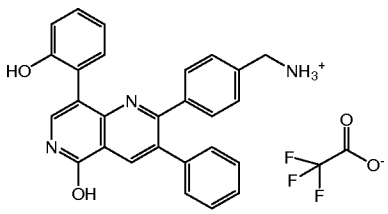
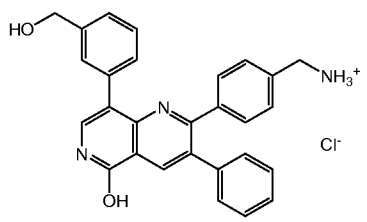
| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **11-3** |  | {4-[5-hydroxy-8-(2-methoxy-1,3-thiazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 441.5 | 441.0 |

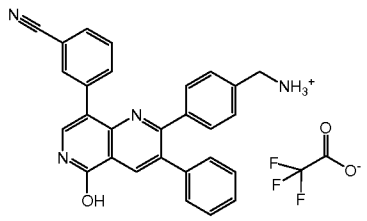
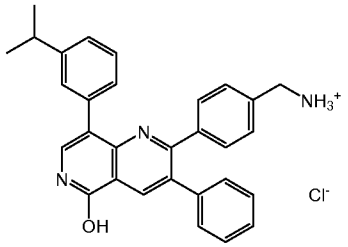
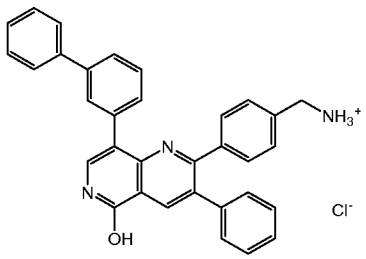
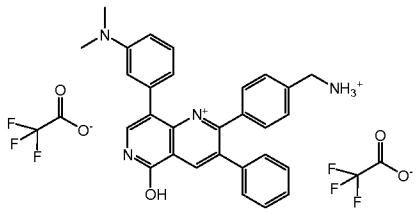
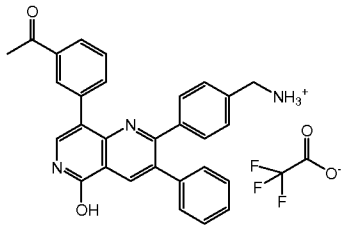
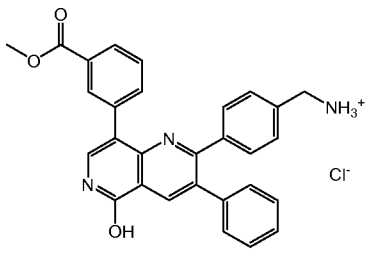
| | | | | |
|---|---|---|---|---|
| 11-4 |  | {4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 411.5 | 394.0 |
| 11-5 |  | {4-[8-(3-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 394.4 | 377.1 |
| 11-6 |  | {4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 424.5 | 407.1 |
| 11-7 |  | {4-[8-(1-benzofuran-2-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin -2-yl]phenyl}methanaminium chloride | 444.5 | 427.1 |
| 11-8 |  | {4-[5-hydroxy-8-(5-methyl-2-furyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 408.5 | 391.1 |
| 11-9 |  | {4-[5-hydroxy-8-(4-methylthien-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 424.5 | 407.1 |

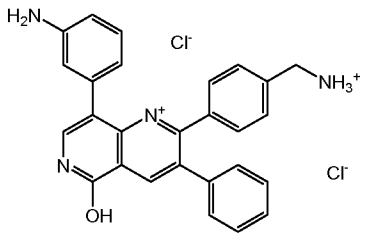
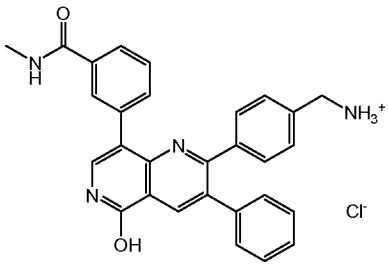
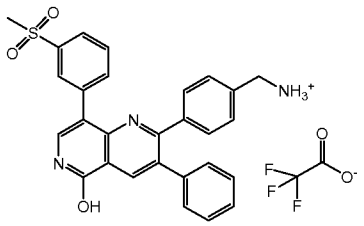
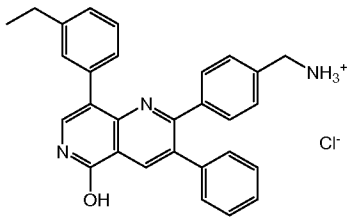
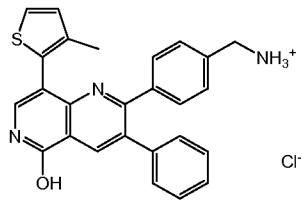
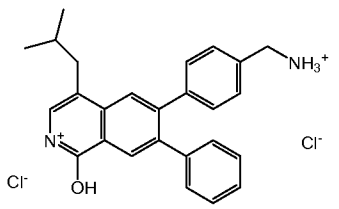
| | | | | |
|---|---|---|---|---|
| 11-10 |  | {4-[8-(1-benzothien-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 460.6 | 443.1 |
| 11-11 |  | {4-[8-(1-benzothien-7-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 460.6 | 443.1 |
| 11-12 |  | {4-[8-(1-benzofuran-5-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 444.5 | 427.1 |
| 11-13 |  | [4-(5-hydroxy-3-phenyl-8-thien-3-yl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate | 410.5 | 393.1 |
| 11-14 |  | {4-[5-hydroxy-8-(3-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanaminium trifluoroacetate | 418.5 | 401.1 |
| 11-15 |  | {4-[5-hydroxy-8-(2-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 418.5 | 401.1 |

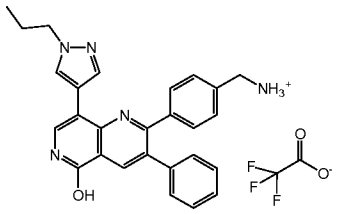
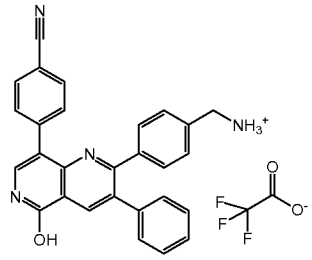
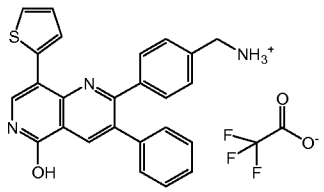
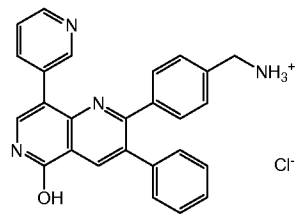
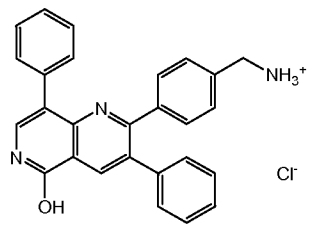
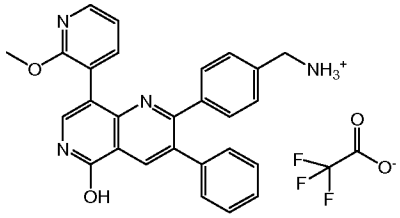
| | | | | |
|---|---|---|---|---|
| 11-16 |  | {4-[8-(2-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 422.5 | 405.1 |
| 11-17 |  | {4-[8-(2-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 438.9 | 421.1 |
| 11-18 |  | {4-[5-hydroxy-8-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 434.5 | 434.2 |
| 11-19 |  | {4-[8-(3-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 422.5 | 405.1 |
| 11-20 |  | {4-[5-hydroxy-8-(3-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 434.5 | 417.1 |
| 11-21 |  | (4-{5-hydroxy-3-phenyl-8-[3-(trifluoromethyl)phenyl]-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate | 472.5 | 455.1 |
| 11-22 |  | {4-[5-hydroxy-8-(3-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 420.5 | 403.1 |

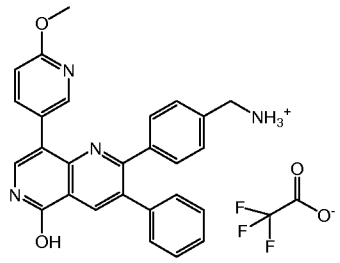
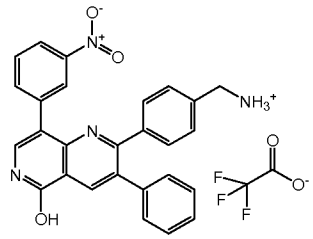
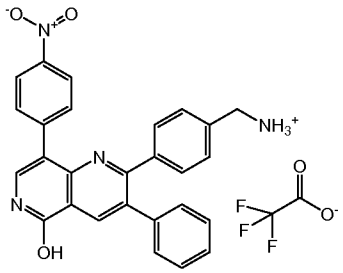
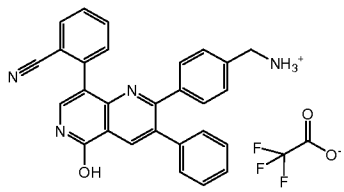
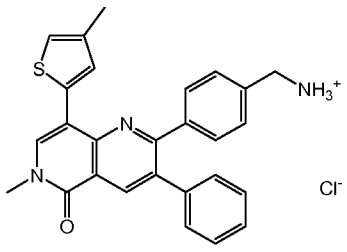
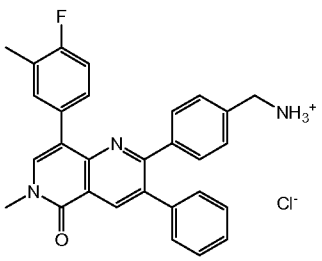
| | | | | |
|---|---|---|---|---|
| 11-23 |  | {4-[8-(3-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 438.9 | 421.1 |
| 11-24 |  | {4-[5-hydroxy-8-(4-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 420.5 | 403.1 |
| 11-25 |  | {4-[8-(4-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 422.5 | 405.1 |
| 11-26 |  | {4-[8-(4-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 438.9 | 421.1 |
| 11-27 |  | {4-[5-hydroxy-8-(4-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 434.5 | 417.1 |
| 11-28 |  | {4-[8-(3,5-dimethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 432.5 | 415.1 |

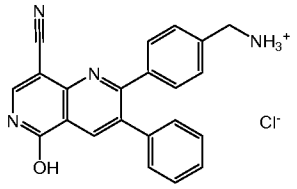
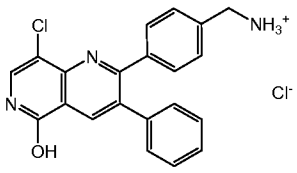
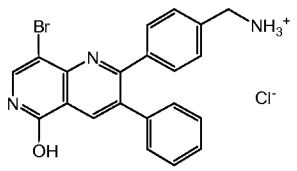
| | | | | |
|---|---|---|---|---|
| 11-29 |  | {4-[8-(3,5-dichlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 472.3 | 455.0 |
| 11-30 |  | {4-[8-(3-ethoxyphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 448.5 | 431.1 |
| 11-31 |  | [4-(8-cyclohex-1-en-1-yl-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate | 408.5 | 391.0 |
| 11-32 |  | {4-[5-hydroxy-8-(3-mercaptophenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 436.5 | 419.1 |
| 11-33 |  | {4-[5-hydroxy-8-(2-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 420.5 | 420.1 |
| 11-34 |  | (4-{5-hydroxy-8-[3-(hydroxymethyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride | 434.5 | 434.1 |

| | | | | |
|---|---|---|---|---|
| 11-35 |  | {4-[8-(3-cyanophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 429.5 | 429.1 |
| 11-36 |  | {4-[5-hydroxy-8-(3-isopropylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 446.6 | 429.1 |
| 11-37 |  | {4-[8-(1,1'-biphenyl-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 480.6 | 463.1 |
| 11-38 |  | 2-[4-(ammoniomethyl)phenyl]-8-[3-(dimethylamino)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridin-1-ium bis(trifluoroacetate) | 447.5 | 447.2 |
| 11-39 |  | {4-[8-(3-acetylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 446.5 | 446.1 |
| 11-40 |  | (4-{5-hydroxy-8-[3-(methoxycarbonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 462.5 | 462.1 |

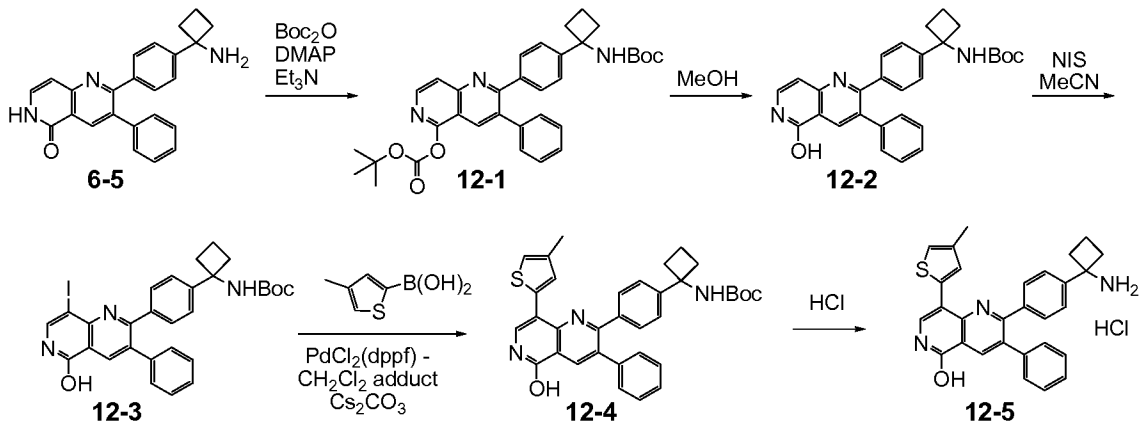
| | | | | |
|---|---|---|---|---|
| 11-41 |  | 8-(3-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridin-1-ium dichloride | 419.5 | 419.2 |
| 11-42 |  | [4-(5-hydroxy-8-{3-[(methylamino)carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 461.5 | 461.2 |
| 11-43 |  | (4-{5-hydroxy-8-[3-(methylsulfonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate | 482.6 | 466.2 |
| 11-44 |  | {4-[8-(3-ethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 432.5 | 415.2 |
| 11-45 |  | {4-[5-hydroxy-8-(3-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 424.5 | 407.1 |
| 11-46 |  | 6-[4-(ammoniomethyl)phenyl]-1-hydroxy-4-isobutyl-7-phenylisoquinolinium dichloride | 383.5 | 384.1 |

| | | | | |
|---|---|---|---|---|
| **11-47** |  | {4-[5-oxo-3-phenyl-8-(1-propyl-1*H*-pyrazol-4-yl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 436.5 | 436.1 |
| **11-48** |  | {4-[8-(4-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 429.5 | 429.1 |
| **11-49** |  | {4-[5-oxo-3-phenyl-8-(2-thienyl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 410.5 | 410.0 |
| **11-50** |  | [4-(5-oxo-3-phenyl-8-pyridin-3-yl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 405.5 | 405.0 |
| **11-51** |  | [4-(5-oxo-3,8-diphenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 404.5 | 404.1 |
| **11-52** |  | {4-[8-(2-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 435.5 | 435.1 |

| | | | | |
|---|---|---|---|---|
| 11-53 |  | {4-[8-(6-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 435.5 | 435.1 |
| 11-54 |  | {4-[8-(3-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 449.5 | 449.1 |
| 11-55 |  | {4-[8-(4-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 449.5 | 449.0 |
| 11-56 |  | {4-[8-(2-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 429.5 | 429.1 |
| 11-57 |  | {4-[6-methyl-8-(4-methyl-2-thienyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 438.6 | 438.2 |
| 11-58 |  | {4-[8-(4-fluoro-3-methylphenyl)-6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 450.5 | 450.2 |

| | | | |
|---|---|---|---|
| **11-59** |  | [4-(8-cyano-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 353.4 353.1 |
| **11-60** |  | [4-(8-chloro-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 362.8 362.2 |
| **11-61** |  | [4-(8-bromo-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 406.3 406.1 |

SCHEME 12




1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride (**12-5**)

2-(4-{1-[(tert-butoxycarbonyl)amino]cyclobutyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl tert-butyl carbonate (**12-1**)

To a solution of 2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-ol (**6-5**) (210 mg, 0.57 mmol) in DCM (6 mL) was added $Boc_2O$ (0.15 mL, 0.63 mmol) followed by DMAP (7.0 mg, 0.057 mmol). The reaction mixture was stirred at room temperature for 1 hour before adding $Et_3N$ (0.57 mmol). The mixture was allowed to stir at room temperature 2 days, and then another 2.3 eq of $Boc_2O$ was added and the mixture was heated at 30°C overnight. The solvent was removed in vacuo and the residue was suspended in a solution of saturated $NaHCO_3$ (10 mL), extracted into EtOAc, washed with water, dried over $Na_2SO_4$, filtered, and concentrated

in vacuo. The residue was purified via silica gel chromatography (0-100% EtOAc in Hexane) to give 2-(4-{1-[(tert-butoxycarbonyl)amino]cyclobutyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl tert-butyl carbonate (**12-1**). MS calculated M+H: 568.7; found 568.2

tert-butyl {1-[4-(5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**12-2**)

A solution of 2-(4-{1-[(tert-butoxycarbonyl)amino]cyclobutyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl tert-butyl carbonate (**12-1**) (88 mg, 0.16 mmol) in MeOH (4 mL) was heated at 100°C in the microwave for 15 minutes. The solvent was removed in vacuo to give tert-butyl {1-[4-(5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**12-2**) as a white solid. MS calculated M+H: 468.6; found 468.2

tert-butyl {1-[4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**12-3**)

To a solution of tert-butyl {1-[4-(5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**12-2**, 65 mg, 0.14 mmol) in MeCN (5 mL) was added NIS (34 mg, 0.15 mmol). The reaction mixture was stirred at 85°C for 30 minutes, another 0.1 eq of NIS was added and the reaction heated for 1 hour. The mixture was concentrated in vacuo and purified via silica gel chromatography (0-50% EtOAc in hexane) to give tert-butyl {1-[4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**12-3**) as a pale yellow solid. MS calculated M+H: 594.5; found 594.1

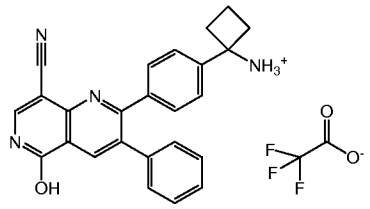
1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride (**12-5**)

To a mixture of tert-butyl {1-[4-(5-hydroxy-8-iodo-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**12-3**, 40 mg, 0.07 mmol), (4-methyl-2-thienyl)boronic acid (14 mg, 0.1 mmol), and $PdCl_2(dppf)$-$CH_2Cl_2$ adduct (6 mg, 7 μmol) in THF (2 mL) was added $Cs_2CO_3$ (0.8 mL, 0.8 mmol). The reaction mixture was heated at 140°C in the microwave for 20 minutes. The solvent was decanted off, stirred with QuadraPure TU resin for 3 hours and filtered. Following concentration, the residue was purified via silica gel chromatography (0-75% EtOAc in Hexanes) to give intermediate tert-butyl (1-{4-[5-hydroxy-8-(4-methyl-2-thienyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutyl)carbamate (**12-4**). **12-4** was dissolved in MeOH (1 mL) and treated with a saturated HCl in MeOH solution (2 mL). The solution was heated at 80°C in the microwave for 5 minutes and the solvent was removed in vacuo to afford 1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride (**12-5**) as a yellow solid. MS calculated M+H-$NH_2$: 447.6; found 447.1

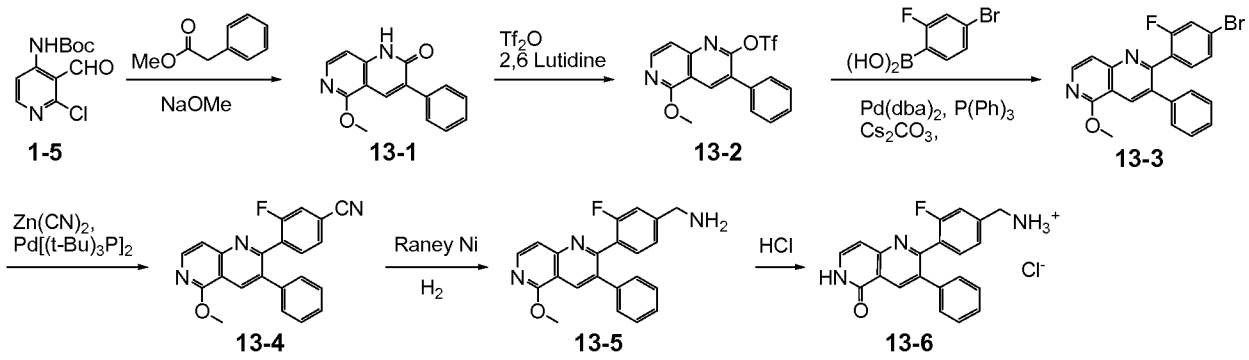
The compound in Table 5 was prepared according to the Reaction Schemes and Scheme 21.

Table 5

| Cmp | Structure | Name | MS m/z | MS m/z |
|---|---|---|---|---|

| | | (M+H): calc'd | (M+H): observed |
|---|---|---|---|
| **12-6**  | 1-[4-(8-cyano-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium trifluoroacetate | 392.5 | 394.1 |

SCHEME 13




[3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**13-6**)

5-methoxy-3-phenyl-1,6-naphthyridin-2(1*H*)-one (**13-1**)

To a round bottom flask was added *tert*-butyl (2-chloro-3-formylpyridin-4-yl)carbamate (**1-5**) (35.4 g, 138 mmol), methyl phenylacetate (22.8 g, 152 mmol), methanol (500 mL), and finally a 30% by weight solution of sodium methoxide in methanol (22.4 g, 414 mmol). The reaction mixture was then heated to 65°C while stirring in a hot oil bath with a water cooled reflux condenser attached under an atmosphere of nitrogen for 72 hours. The crude reaction mixture was then allowed to cool to room temperature, then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then triturated with diethyl ether/ methanol and filtered to give 5-methoxy-3-phenyl-1,6-naphthyridin-2(1*H*)-one (**13-1**) as a white solid. HRMS $(M+H)^+$: observed = 253.0969, calculated = 253.0972

5-methoxy-3-phenyl-1,6-naphthyridin-2-yl trifluoromethanesulfonate (**13-2**)

To a stirred solution of 5-methoxy-3-phenyl-1,6-naphthyridin-2(1*H*)-one (**13-1**) (2.76 g, 10.9 mmol) in DCM (30 mL) at 0°C under an atmosphere of nitrogen was added 2,6 lutidine (2.54 mL, 21.9 mmol), followed by the dropwise addition of triflic anhydride (TfOTf) (2.39 mL, 14.2 mmol). After 60 minutes the crude reaction mixture was poured into a saturated solution of sodium bicarbonate, then suspended in ethyl acetate, washed with a saturated solution

of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (1-30% EtOAc/5% DCM/Hexane) to give 5-methoxy-3-phenyl-1,6-naphthyridin-2-yl trifluoromethanesulfonate (**13-2**) as an off-white solid. MS $(M+H)^+$: observed = 385.1, calculated = 385.3

2-(4-bromo-2-fluorophenyl)-5-methoxy-3-phenyl-1,6-naphthyridine (**13-3**)

To a microwave vial was added 5-methoxy-3-phenyl-1,6-naphthyridin-2-yl trifluoromethanesulfonate (**13-2**) (0.3 g, 0.8 mmol), (4-bromo-2-fluorophenyl)boronic acid (0.7 g, 3 mmol), cesium carbonate (1 g, 4 mmol), triphenylphosphine (0.04 g, 0.2 mmol), followed by $Pd_2(dba)_3$ (0.05 g, 0.1 mmol), dioxane (2 mL) and DMF (0.3 mL). The reaction mixture was then heated under microwave irradiation at 150°C for 12 minutes. The crude reaction mixture was then allowed to cool to room temperature, diluted with methanol, filtered and concentrated. Purification of crude reaction mixture by reverse phase chromatography (Waters Sunfire MSC18, 10% acetonitrile / 0.1% trifluoroacetic acid / water → 100% acetonitrile / 0.1% trifluoroacetic acid / water) afforded 2-(4-bromo-2-fluorophenyl)-5-methoxy-3-phenyl-1,6-naphthyridine (**13-3**) as an off-white solid. HRMS $(M)^+$: observed = 409.0328, calculated = 409.0347

3-fluoro-4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzonitrile (**13-4**)

Procedure similar to that reported for **6-2** gave 3-fluoro-4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzonitrile (**13-4**) as a white solid. HRMS $(M+H)^+$: observed = 356.1182, calculated = 356.1194.

1-[3-fluoro-4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**13-5**)

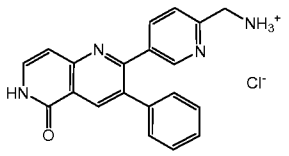
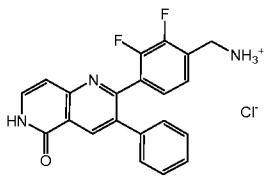
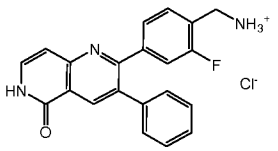
To a solution of 3-fluoro-4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzonitrile (**13-4**) (33 mg, 0.1 mmol) in methanol (2 mL) and DCM (2 mL) was added a 10% solution of ammonia in ethanol (2 mL) and Raney Nickel as a slurry in water (5 mg, 0.1 mmol). A balloon containing hydrogen was immediately attached and the vessel was purged with vacuum/hydrogen gas several times. The reaction mixture was then permitted to stir at room temperature under an atmosphere of hydrogen. After 3 hours, the crude reaction mixture was diluted with methanol, filtered & concentrated to give 1-[3-fluoro-4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine (**13-5**) as a white solid. HRMS $(M+H)^+$: observed = 360.1510, calculated = 360.1507.

[3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**13-6**)

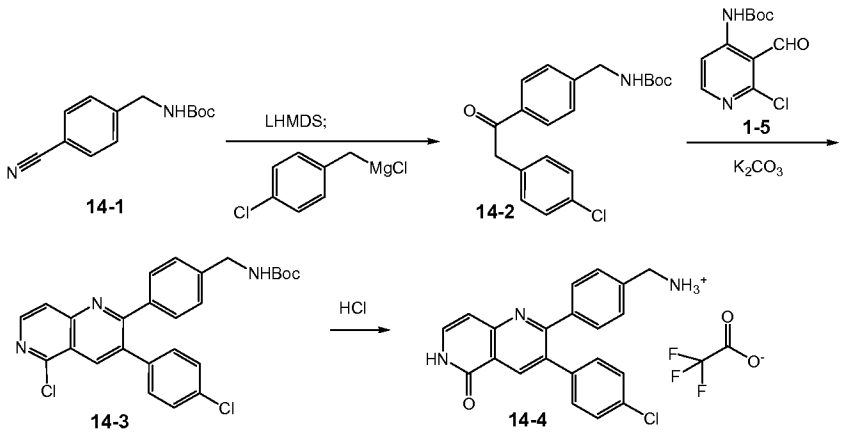
Procedure similar to that reported for **6-5** gave [3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**13-6**). HRMS $(M+H)^+$: observed = 346.1350, calculated = 346.1350.

The following compounds in Table 6 were prepared according to the Reaction Schemes and Scheme 13.

Table 6

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **13-7** |  | [5-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)pyridin-2-yl] methanaminium chloride | 329.1398 | 329.1397 |
| **13-8** |  | [2,3-difluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 364.1248 | 364.1256 |
| **13-9** |  | [2-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 346.1343 | 346.1350 |

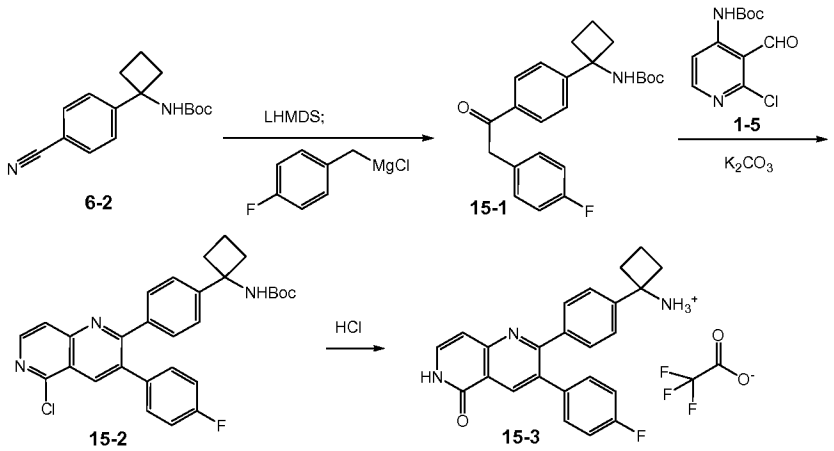
SCHEME 14




{4-[3-(4-chlorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**14-4**)

Procedures similar to that reported for Example 6 gave {4-[3-(4-chlorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate (**14-4**) after purification by reverse phase chromatography. MS m/z (M+H): observed 361.94, calc'd 361.1

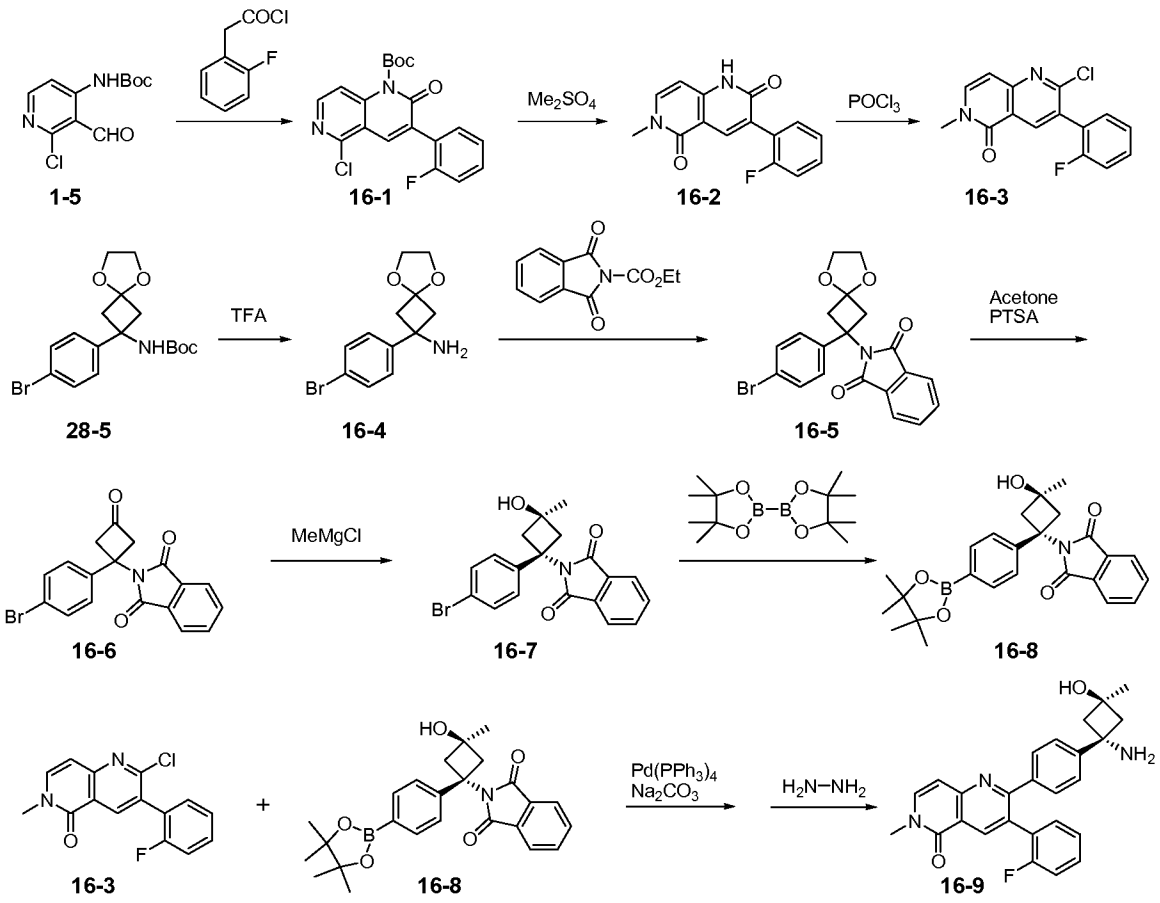
SCHEME 15




1-{4-[3-(4-fluorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} cyclobutanaminium trifluoroacetate (**15-3**)

Procedures similar to that reported for Example 6 gave 1-{4-[3-(4-fluorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} cyclobutanaminium trifluoroacetate (**15-3**) after purification by reverse phase chromatography. MS: 386.2 (M+1)

SCHEME 16




2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-9**)

tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**16-1**)

Procedure similar to that reported for **62-1** using (2-fluorophenyl)acetyl chloride and **1-5** gave tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**16-1**) as a colorless solid.

3-(2-fluorophenyl)-6-methyl-1,6-naphthyridine-2,5(1H,6H)-dione (**16-2**)

Procedure similar to that reported for **62-6** using tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**16-1**) gave 3-(2-fluorophenyl)-6-methyl-1,6-naphthyridine-2,5(1H,6H)-dione (**16-2**) as a colorless solid.

2-chloro-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-3**)

Procedure similar to that reported for **62-3** using 3-(2-fluorophenyl)-6-methyl-1,6-naphthyridine-2,5(1H,6H)-dione (**16-2**) gave 2-chloro-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-3**) as a colorless solid.

2-(4-bromophenyl)-5,8-dioxaspiro[3.4]octan-2-amine (**16-4**)

Procedure similar to that reported for **11-2** from tert-butyl [2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-5**) gave 2-(4-bromophenyl)-5,8-dioxaspiro[3.4]octan-2-amine (**16-4**).

2-[2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]-1H-isoindole-1,3(2H)-dione (**16-5**)

To a solution of 2-(4-bromophenyl)-5,8-dioxaspiro[3.4]octan-2-amine (**16-4**) (11 g, 39 mmol) in DCM (100 mL) and $Et_3N$ (7.8 g, 77 mmol) was added N-carbethoxyphthalimide (8.5 g, 39 mmol) and the mixture was heated at 80°C for 5 hours. The reaction was cooled to rt, added methanol and and stirred overnight. Filtered to give 2-[2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]-1H-isoindole-1,3(2H)-dione (**16-5**) as a white solid. MS (M+H)+: 415

2-[1-(4-bromophenyl)-3-oxocyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-6**)

To a solution of 2-[2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]-1H-isoindole-1,3(2H)-dione (**16-5**) (21.4 g, 51.6 mmol) in acetone (250 mL) was added p-toluenesulfonic acid (4.44 g, 25.8 mmol) and the mixture was heated to reflux over night. Cooled to rt, quenched with sat. $NaHCO_3$, poured into EtOAc, washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (1-75% EtOAc/Hexane) to give 2-[1-(4-bromophenyl)-3-oxocyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-6**) as a white solid. MS (M+H)+: 371

2-[trans-1-(4-bromophenyl)-3-hydroxy-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-7**)

To a solution of 2-[1-(4-bromophenyl)-3-oxocyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-6**) (2.0 g, 5.4 mmol) in THF (100 mL) cooled to -78°C was added methylmagnesium chloride (5.4 mL, 1M in THF). The reaction was slowly warmed to rt overnight. The reaction mixture was poured into sat. sodium bicarbonate, extracted with EtOAc, dried over sodium

sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (1-60% EtOAc/Hexane) to give 2-[trans-1-(4-bromophenyl)-3-hydroxy-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-7**) as a white solid. MS (M+H)+: 387

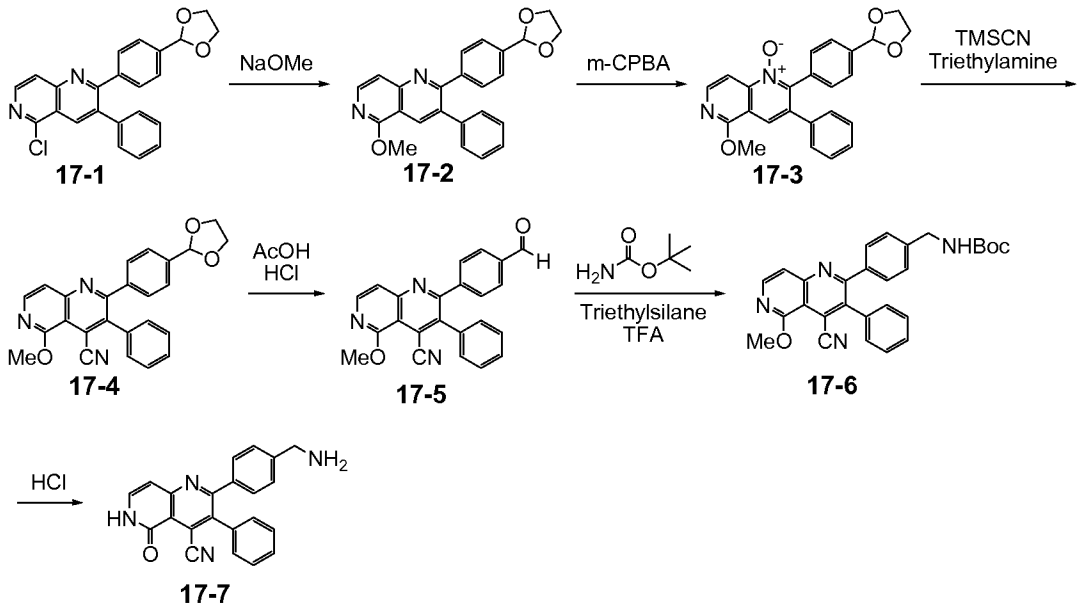
2-{trans-3-hydroxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**16-8**)

To a solution of 2-[trans-1-(4-bromophenyl)-3-hydroxy-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-7**) (1.4 g, 3.7 mmol) in DMF (25 mL) was added bis(pinacolato)diboron (1.0 g, 4.1 mmol), potassium acetate (1.6 g, 17 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.44 g, 0.56 mmol) and the mixture was heated to 90°C for 3 hours. The reaction mixture was poured into sat. sodium bicarbonate, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (1-60% EtOAc/Hexane) to give 2-{trans-3-hydroxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**16-8**) MS (M+H)+: 434

2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-9**)

To a solution of 2-chloro-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-3**) (0.20 mmol), 2-{trans-3-hydroxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**16-8**) (0.095 mmol), sodium carbonate (0.19 mmol), bis(tri-tert-butylphosphine)palladium(0) (0.095 mmol) in dioxane (4 mL) was heated in a microwave to 100°C for 10 min. The reaction mixture was poured into sat. sodium bicarbonate, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. Following purification by silica gel chromatography, a solution of the intermediate in ethanol and hydrazine was heated to 100°C for 1 hour. The reaction was concentrated and purified via reverse phase chromatography to give 2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one (**16-9**) as a colorless solid. HRMS (M+H)+: observed = 430.1935, calculated = 430.1931

SCHEME 17




2-[4-(aminomethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine-4-carbonitrile (**17-7**)

2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (**17-2**)

To a solution of anhydrous MeOH (50 mL) and sodium methoxide (70 mL, 310 mmol) was added 5-chloro-2-[4-(1,3-dioxolan-2-yl)phenyl]-3-phenyl-1,6-naphthyridine (17-**1**, Reference: WO2006135627A2, December 21, 2006) (7.0 g, 18 mmol). The mixture was stirred at 110°C for 5 hours. The volume of solvent was reduced to approximately half in vacuo and then water (200 mL) was added. The precipitate was filtered and dried azeotropically with toluene to give 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (**17-2**) as a brownish-yellow solid. MS M+H calculated: 384.43; found 385.2

2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine 1-oxide (**17-3**)

To a mixture of 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (**17-2**, 5.7 g, 15 mmol) in $CHCl_3$ (80 mL) was added mCPBA (3.7 g, 16 mmol) in portions. Upon addition of mCPBA, the mixture became an orange solution and then became cloudy again after approximately 1 hour. The reaction mixture was allowed to stir at room temperature for 21 hours. Another 1.5 eq of mCPBA was added in portions and stirred for 7.5 hours. The reaction was quenched with a saturated $NaHCO_3$ solution and was then extracted into EtOAc. The combined organic layers were concentrated in vacuo and the residue was purified by silica gel chromatography (0-90% EtOAc in hexanes) to afford 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine 1-oxide (**17-3**) as pale yellow solid. MS M+H calculated: 400.43; found 401.2

2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-4**)

To a mixture of 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine 1-oxide (**17-3**, 2.6 g, 6.5 mmol) in MeCN (50 mL) was added triethylamine (2.7 mL, 20 mmol) followed by trimethylsilyl cyanide (1.7 mL, 13 mmol). The reaction mixture was heated at 100 °C for 2 hours. Another 2eq of TMSCN were added and the heat was lowered to 60°C. After stirring overnight, another 6 eq of TMSCN were added and the reaction was heated at 100 °C for 4 hours. The reaction mixture was then cooled to rt, treated with a saturated solution of $NaHCO_3$ and extracted into DCM. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-4**) as a light brown solid. MS M+H calculated: 409.44; found 410.2

2-(4-formylphenyl)-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-5**)

A mixture of 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-4**) (1.7 g, 4.1 mmol) in AcOH (10 mL, 170 mmol) and HCl (10 mL, 120 mmol) was heated at 120°C under $N_2$ for 22 hours. The reaction mixture was allowed to cool and the solvent was removed in vacuo. The residue was dried azeotropically with toluene to give a brown solid. The solid was then treated with 50ml of water and filtered. The precipitate was collected and dried azeotropically with toluene to give 2-(4-formylphenyl)-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-5**) as a light brown solid. MS M+H calculated: 351.36; found 352.1

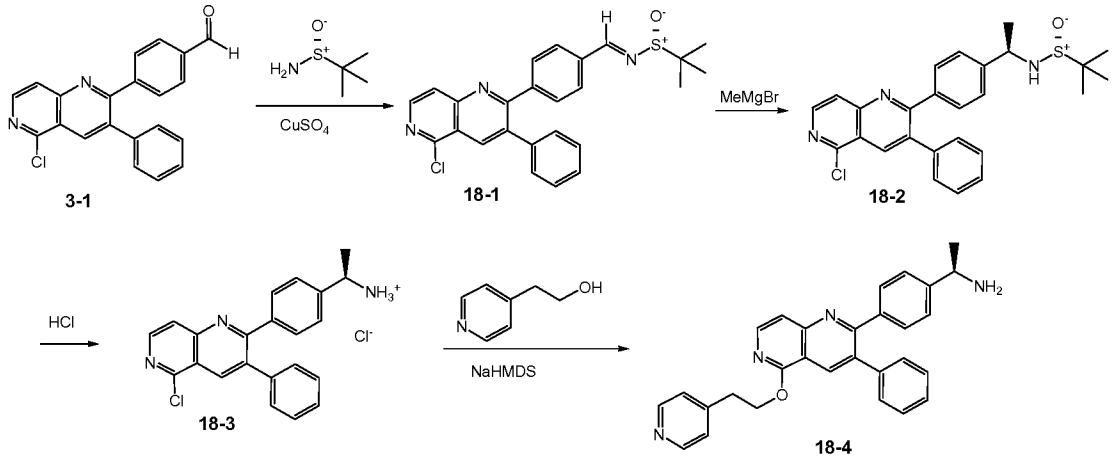
tert-butyl [4-(4-cyano-5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzyl] carbamate (**17-6**)

To a solution of 2-(4-formylphenyl)-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-5**, 1.3 g, 3.4 mmol) and tert-butyl carbamate (0.44 g, 3.8 mmol) in dry MeCN (15 mL) was added triethylsilane (4.9 mL, 31 mmol) followed by addition of TFA (1.1 mL, 14 mmol) at room temperature overnight. The solvent was removed in vacuo, the residue was treated with MeOH and water, cooled, and the precipitate was collected by filtration to give tert-butyl [4-(4-cyano-5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**17-6**) as a light brown solid. MS M+H calculated: 452.50; found 453.2

2-[4-(aminomethyl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-7**)

Procedure similar to that reported for **6-5** gave 2-[4-(aminomethyl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine-4-carbonitrile (**17-7**). MS: M+H-$NH_3$ calculated: 336.4; found 336.0

SCHEME 18




(1*R*)-1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**18-4**)

N-{(1E)-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methylidene}-2-methylpropane-2-sulfinamide (**18-1**)

(*S*-(-)-2-methyl-2-propane-sulfinamide (13 g, 110 mmol), cupric sulfate (17 g, 95 mmol) and **3-1** (17 g, 50 mmol) were stirred under nitrogen in methylene chloride (100 mL) at 40°C for 2d. The reaction mixture was cooled, filtered through celite, rinsed with methylene chloride, concentrated, and purified by silica gel chromatography (0-45% EtOAc in hexane with 5% DCM) to give **18-1** as a pale yellow foam. MS: 448.4 (M+1)

N-{1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}-2-methylpropane-2-sulfinamide (**18-2**)

To a cooled (-10 °C) solution of **18-1** (1.0 g, 2.2 mmol) in methylene chloride (10 mL) was added methylmagnesium bromide (6.5 mL, 9.1 mmol, 1.4M in 75:25 toluene:THF) dropwise. The reaction mixture was maintained at -10°C for 2h before quenching with saturated ammonium chloride solution and stirring overnight at rt. The resulting mixture was extracted with methylene chloride, washed with brine, dried over magnesium sulfate, filtered, concentrated, and purified by silica gel chromatography (0-5% MeOH in DCM) to give an off-white foam as 10:1 mixture of diastereomers. The diastereomers were separated by reverse phase HPLC to give **18-2** as a white solid as the major isomer. MS: 464.4 (M+1)

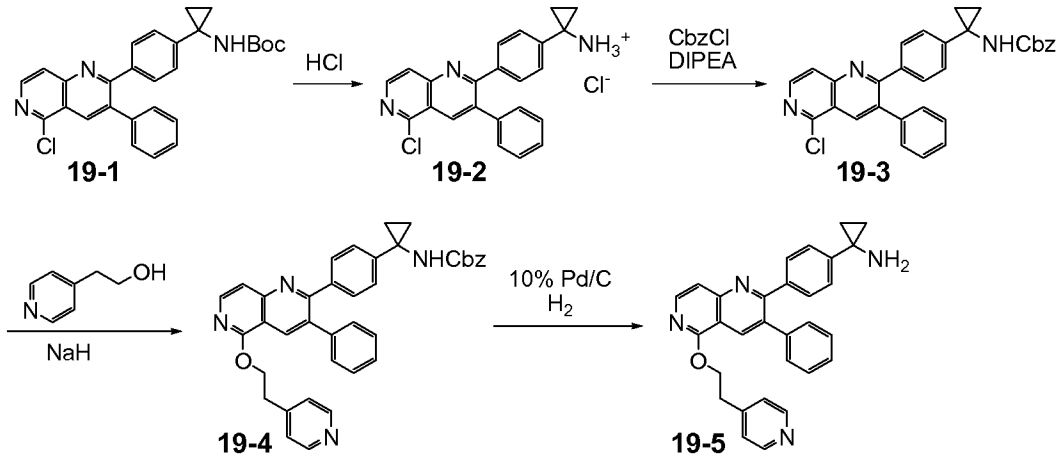
(1R)-1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanaminium chloride (**18-3**)

To a solution of **18-2** (230 mg, 0.49 mmol) in 1:1 EtOAc:DMC (10 mL) at 0°C was added 2N HCl in ether (3 mL). After 30 minutes, the reaction was concentrated to dryness to give **18-3**. MS: 360.1 (M+1)

(1*R*)-1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**18-4**)

Procedure similar to that reported for **19-4** gave (1*R*)-1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**18-4**). HRMS (M+1)+: observed = 447.2169, calculated = 447.2180.

SCHEME 19




1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl} cyclopropanamine (**19-5**)

tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclopropyl}carbamate (**19-1**)

Procedures similar to that reported for **6-4** (Reference: WO2006135627A2, December 21, 2006) gave tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl}carbamate (**19-1**) as a white solid. HRMS (M+H)+: observed = 472.1778, calculated = 472.1787.

1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropanaminium chloride (**19-2**)

To a solution of tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl}carbamate (**19-1**) (122 mg, 0.258 mmol) in anhydrous DCM (5 mL) was added a 4M solution of HCl in EtOAc (5 mL, 20 mmol). The reaction mixture was then permitted to stir at room temperature under an atmosphere of nitrogen for 30 minutes. The reaction mixture was then concentrated in vacuo to give 1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropanaminium chloride (**19-2**) as a yellow solid. MS (M+H)+: observed = 372.0, calculated = 372.9.

Benzyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl} carbamate (**19-3**)

To a solution of 1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclopropanaminium chloride (**19-2**) (110 mg, 0.27 mmol) in anhydrous DCM (5 mL) was added DIPEA (0.23 mL, 1.3 mmol) followed by benzylchloroformate (0.057 mL, 0.40 mmol). The reaction was permitted to stir at room temperature under an atmosphere of nitrogen for 30

minutes. The crude reaction mixture was then quenched by addition of water (20 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 15% acetonitrile / 0.1% trifluoroacetic acid / water → 100% acetonitrile / 0.1% trifluoroacetic acid / water) to give benzyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl}carbamate (**19-3**) as a yellow solid. HRMS $(M+H)^+$: observed = 502.2144, calculated = 502.2125.

Benzyl (1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropyl)carbamate (**19-4**)

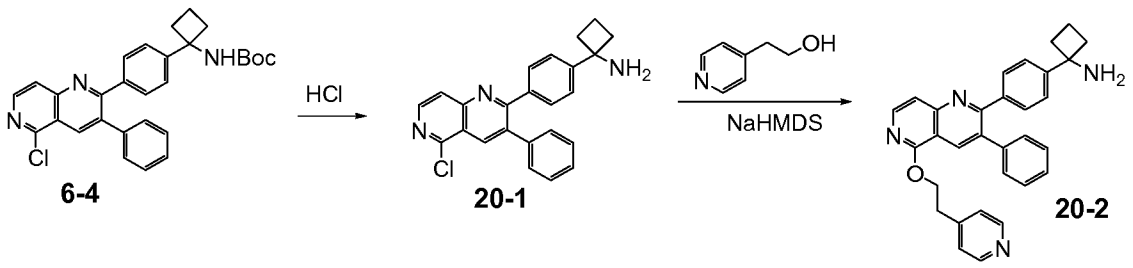
To a solution of benzyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl}carbamate (**19-3**) (44 mg, 0.087 mmol) and a 60% by weight suspension of sodium hydride in mineral oil (17 mg, 0.44 mmol) in anhydrous THF (2.5 mL) under an atmosphere of nitrogen, at room temperature was added 2-pyridin-4-ylethanol (0.029 mL, 0.26 mmol). The reaction was permitted to stir at room temperature under an atmosphere of nitrogen for 30 minutes. The crude reaction mixture was then quenched by addition of a saturated solution of sodium bicarbonate in water (20 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 15% acetonitrile / 0.1% trifluoroacetic acid / water → 100% acetonitrile / 0.1% trifluoroacetic acid / water). The appropriate fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give benzyl (1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropyl)carbamate (**19-4**) as a white solid. HRMS $(M+H)^+$: observed = 593.2556, calculated = 593.2547.

1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropanamine (**19-5**)

To a solution of benzyl (1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropyl)carbamate (**19-4**) (29 mg, 0.049 mmol) in methanol (2 mL) and DCM (2 mL) was added palladium on carbon (0.5 mg, 0.005 mmol). A balloon containing hydrogen was immediately attached and the reaction vessel was evacuated with vacuum and purged with hydrogen several times. The reaction mixture was then permitted to stir at room temperature under an atmosphere of hydrodgen. After 2 hours, the crude reaction mixture was diluted with methanol, then filtered and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water). The appropriate fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give 1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-

yl]phenyl}cyclopropanamine (**19-5**) as a pale yellow solid. HRMS (M+H)+: observed = 459.2158, calculated = 459.2180.

SCHEME 20




1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**20-2**)

1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**20-1**)

To a solution of tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**) (4.1 g, 8.3 mmol) in anhydrous DCM (30 mL) was added a 4M solution of HCl in EtOAc (42 mL, 170 mmol). The reaction mixture was then permitted to stir at room temperature under an atmosphere of nitrogen for 2 hours. The reaction mixture was then diluted with DCM (20 mL), quenched by addition of solid sodium bicarbonate, followed by a saturated solution of sodium bicarbonate and water. Then the mixture was suspended in ethyl acetate, washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give 1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**20-1**) as an off-white solid. MS (M+H)+: observed = 386.1424, calculated = 386.1419.

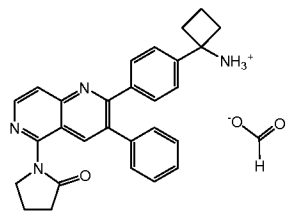
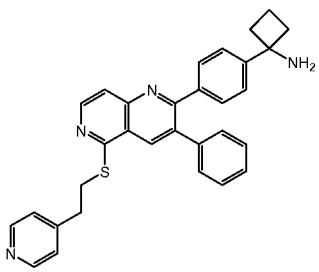
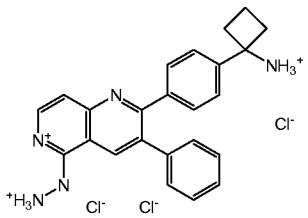
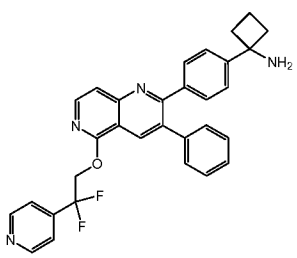
1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**20-2**)

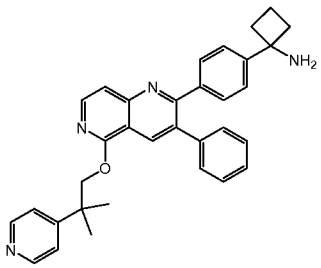
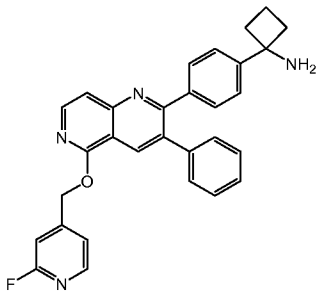
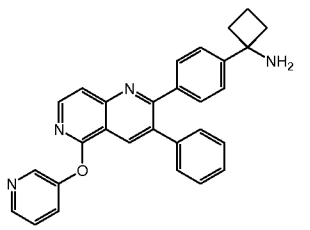
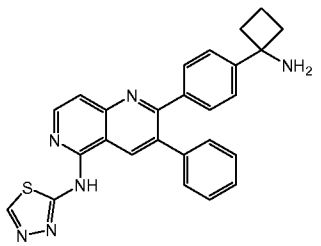
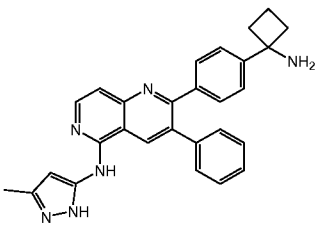
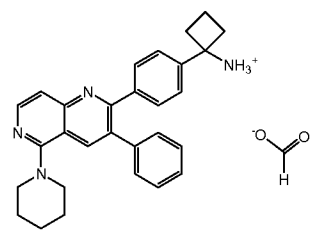
To a solution of 2-pyridin-4-ylethanol in anhydrous THF (5.70 mL, 5.70 mmol) under an atmosphere of nitrogen at room temperature was added a 1M solution of NaHMDS in THF (5.42 mL, 5.42 mmol) for 10 minutes. This mixture was then transferred via syringe to a solution of 1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**20-1**) (2.20 g, 5.70 mmol) in THF (30 mL) stirring under an atmosphere of nitrogen at room temperature. After 10 minutes, an additional batch of alkoxide was prepared as above (1M solution of 2-pyridin-4-ylethanol in anhydrous THF (5.70 mL, 5.70 mmol) was treated with a 1M solution of NaHMDS in THF (5.42 mL, 5.42 mmol) at room temperature for 10 minutes) and added to the reaction. After 90 minutes the crude reaction mixture was poured into a saturated solution of sodium bicarbonate, then suspended in ethyl acetate, washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by reverse phase column chromatography (Sunfire C18) eluting with 1 to 60% acetonitrile / (0.1% TFA / water) gradient. The appropriate fractions were

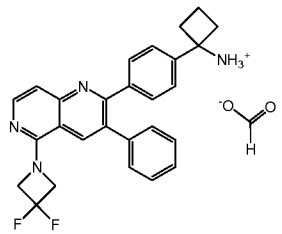
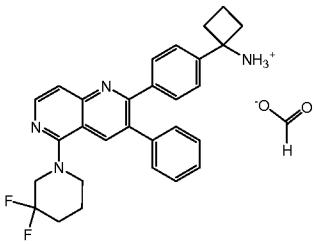
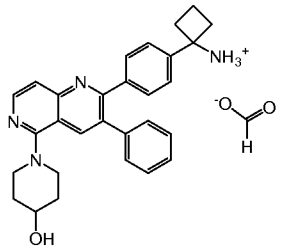
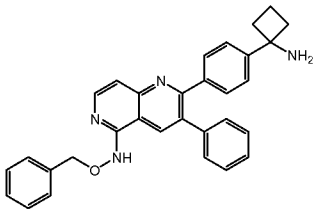
then free based by suspending in ethyl acetate, washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was then repurified by silica gel chromatography (ChiralPak AD chiral column) 40% Hexane, 60% IPA (isocratic). The appropriate fractions were then combined and the solvent was removed in vacuo, followed by lyopholization to give 1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine (**20-2**) as white solid. HRMS $(M+H)^+$: observed = 473.2332, calculated = 473.2336.

The following compounds in Table 7 were prepared according to the Reaction Schemes and Scheme 20.

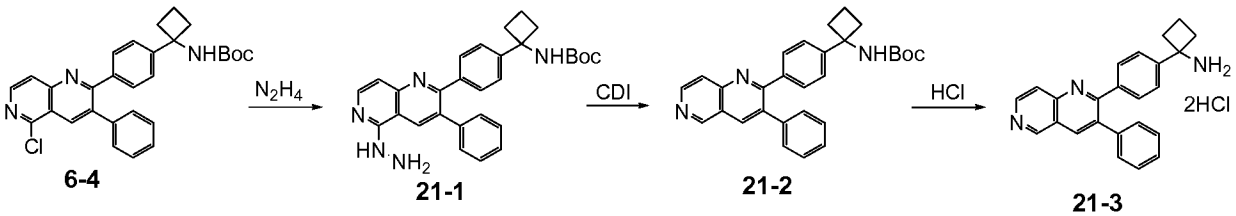
Table 7

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **20-7** |  | 1-{4-[5-(2-oxopyrrolidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate | 435.2185 | 435.2182 |
| **20-8** |  | 1-(4-{3-phenyl-5-[(2-pyridin-4-ylethyl)thio]-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine | 489.2108 | 489.2143 |
| **20-9** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-5-diazan-2-iumyl-3-phenyl-1,6-naphthyridin-6-ium trichloride | 382.2026 | 382.2040 |
| **20-10** |  | 1-(4-{5-[2,2-difluoro-2-(pyridin-4-yl)ethoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine | 509.2153 | 509.2151 |

| | | | | |
|---|---|---|---|---|
| **20-11** |  | 1-(4-{5-[2-methyl-2-(pyridin-4-yl)propoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine | 501.2654 | 501.2662 |
| **20-12** |  | 1-(4-{5-[(2-fluoropyridin-4-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine | 477.2 | 447.2 |
| **20-13** |  | 1-{4-[3-phenyl-5-(pyridin-3-yloxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine | 415.2028 | 445.2030 |
| **20-14** |  | 2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(1,3,4-thiadiazol-2-yl)-1,6-naphthyridin-5-amine | 451.1705 | 451.1720 |
| **20-15** |  | 2-[4-(1-aminocyclobutyl)phenyl]-N-(3-methyl-1H-pyrazol-5-yl)-3-phenyl-1,6-naphthyridin-5-amine | 447.2 | 447.2 |
| **20-16** |  | 1-{4-[3-phenyl-5-(piperidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate | 435.2549 | 435.2547 |

| | | | | |
|---|---|---|---|---|
| **20-17** |  | 1-{4-[5-(3,3-difluoroazetidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate | 443.2047 | 443.2043 |
| **20-18** |  | 1-{4-[5-(3,3-difluoropiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate | 471.236 | 471.2362 |
| **20-19** |  | 1-{4-[5-(4-hydroxypiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanaminium formate | 451.2498 | 451.2506 |
| **20-20** |  | 2-[4-(1-aminocyclobutyl)phenyl]-N-(benzyloxy)-3-phenyl-1,6-naphthyridin-5-amine | 473.2341 | 473.2339 |

SCHEME 21




2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**21-3**)

tert-butyl {1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**21-1**)

To a microwave vial was added tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**, 2.46 g, 5.06 mmol), anhydrous 1,4 Dioxane (15 mL), and finally anhydrous hydrazine (3.18 mL, 101 mmol). The reaction mixture was heated under microwave irradiation for 5 minutes at 100°C. The reaction mixture was then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give tert-butyl {1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**21-1**) as an orange solid. MS (M+H)+: observed = 482.3, calculated = 482.6.

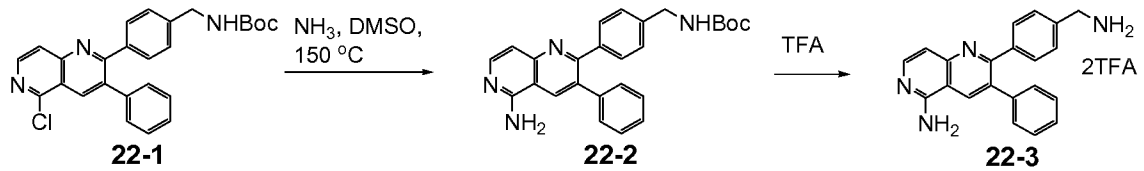
tert-butyl {1-[4-(3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**21-2**)

To a microwave vial was added tert-butyl {1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**21-1**, 100 mg, 0.21 mmol), CDI (41 mg, 0.25 mmol), and anhydrous Dioxane (1 mL). The reaction mixture was heated under microwave irradiation for 15 minutes at 100°C. The reaction mixture was then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl {1-[4-(3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**21-2**). MS (M+H)+: observed = 452.2, calculated = 452.6.

2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**21-3**)

Procedure similar to that reported for **19-2** gave 2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride (**21-3**) as a tan solid. HRMS (M+H)+: observed = 352.1835, calculated = 352.1808.

SCHEME 22




**22-1** **22-2** **22-3**

5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**22-3**)

*tert*-butyl [4-(5-amino-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**22-2**)

A solution of *tert*-butyl [4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**22-1** (Ref: WO2006135627, Dec. 21, 2006), 0.050 g, 0.11 mmol) in DMSO (1 mL) was treated with saturated $NH_3$/DMSO solution (5 mL) and the reaction mixture

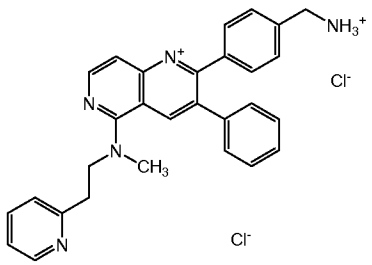
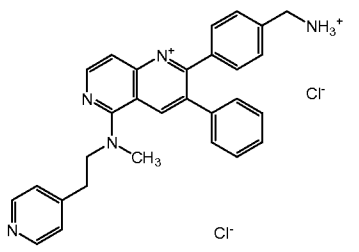
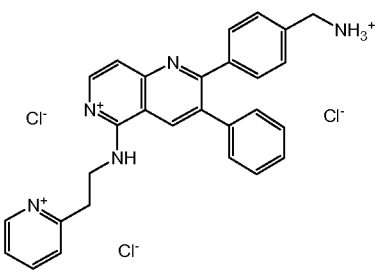
was heated at 100°C overnight. Another 10mL of saturated $NH_3$/DMSO was added and heated at 100°C for an additional 63 hours. The residue was purified by reverse phase HPLC to give *tert*-butyl [4-(5-amino-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**22-2**). MS calculated M+H: 427.5; found 427.1

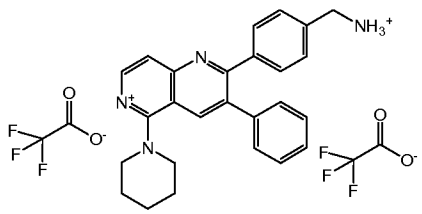
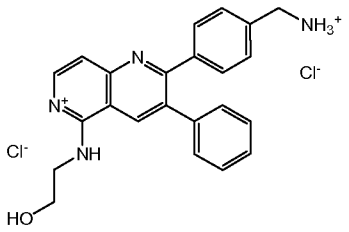
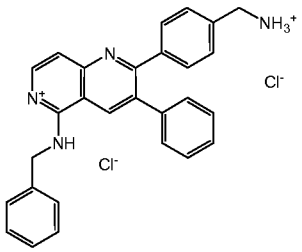
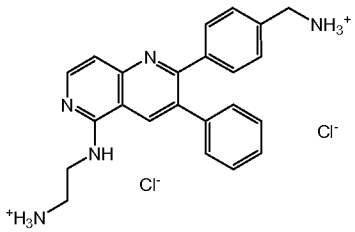
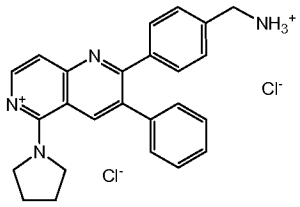
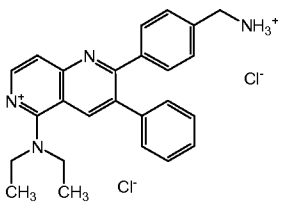
5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**22-3**)

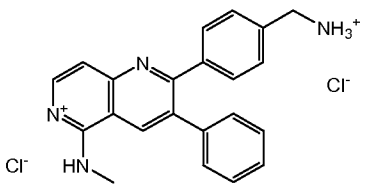
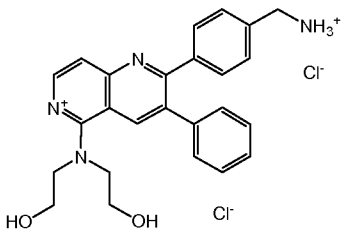
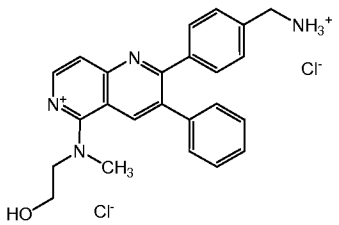
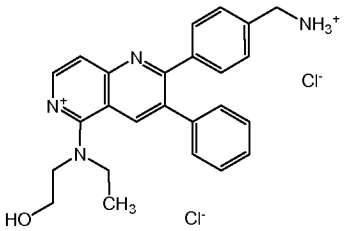
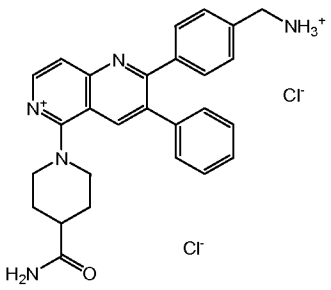
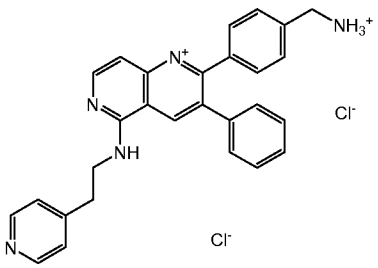
To a solution of *tert*-butyl [4-(5-amino-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**22-2**) (20 mg, 0.047 mmol) in DCM (1 mL) was added TFA (200 μL, 2.6 mmol). The reaction was allowed to stir at room temperature for 45 minutes and was concentrated in vacuo to yield 5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) (**22-3**) as a yellow residue. MS calculated M+H: 327.4; found 327.1.

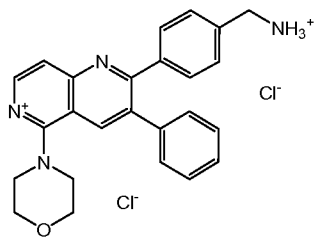
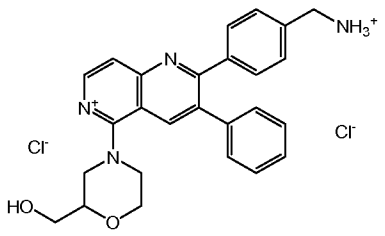
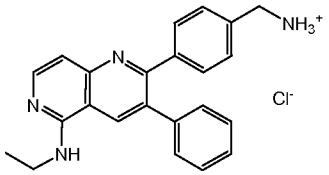
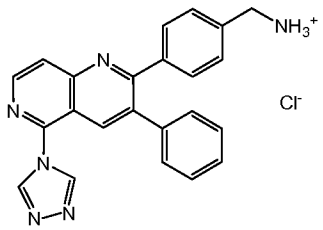
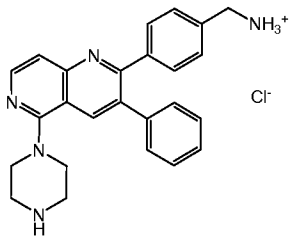
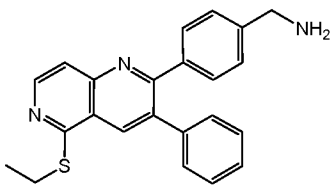
The following compounds in Table 8 were prepared according to the Reaction Schemes and Scheme 22.

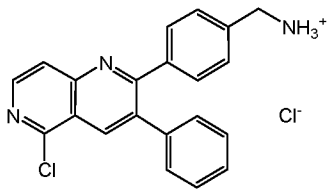
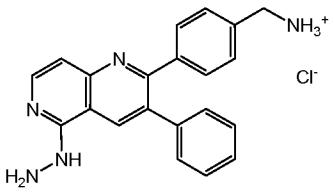
Table 8

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **22-4** |  | 2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-2-ylethyl)amino]-3-phenyl-1,6-naphthyridin-1-ium dichloride | 446.6 | 446.2 |
| **22-5** |  | 2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-4-ylethyl)amino]-3-phenyl-1,6-naphthyridin-1-ium dichloride | 446.6 | 446.2 |
| **22-6** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(2-pyridinium-2-ylethyl) amino]-1,6-naphthyridin-6-ium trichloride | 432.2183 | 432.2169 |

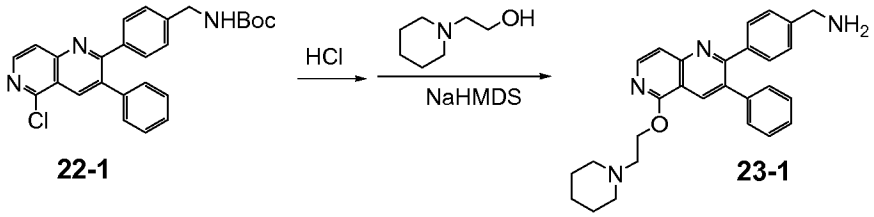
| | | | | |
|---|---|---|---|---|
| **22-7** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-piperidin-1-yl-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 395.5 | 395.0 |
| **22-8** |  | 2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 371.5 | 371.0 |
| **22-9** |  | 2-[4-(ammoniomethyl) phenyl]-5-(benzylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride | 417.5 | 417.1 |
| **22-10** |  | 2-({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}amino) ethanaminium dichloride | 370.5 | 370.0 |
| **22-11** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrrolidin-1-yl-1,6-naphthyridin-6-ium dichloride | 381.5 | 381.0 |
| **22-12** |  | 2-[4-(ammoniomethyl) phenyl]-5-(diethylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride | 383.5 | 383.1 |

| | | | | |
|---|---|---|---|---|
| **22-13** |  | 2-[4-(ammoniomethyl) phenyl]-5-(methylamino) -3-phenyl-1,6-naphthyridin-6-ium dichloride | 341.4 | 341.0 |
| **22-14** |  | 2-[4-(ammoniomethyl) phenyl]-5-[bis(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 415.5 | 415.0 |
| **22-15** |  | 2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)(methyl) amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 385.5 | 385.0 |
| **22-16** |  | 2-[4-(ammoniomethyl) phenyl]-5-[ethyl(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 399.5 | 399.1 |
| **22-17** |  | 5-[4-(aminocarbonyl)piperidin -1-yl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 438.5 | 438.1 |
| **22-18** |  | 2-[4-(ammoniomethyl)phenyl] -3-phenyl-5-[(2-pyridin-4-ylethyl)amino]-1,6-naphthyridin -1-ium dichloride | 432.5 | 432.2 |

| | | | | |
|---|---|---|---|---|
| **22-19** |  | 2-[4-(ammoniomethyl) phenyl]-5-morpholin-4-yl-3-phenyl-1,6-naphthyridin-6-ium dichloride | 397.2023 | 397.2038 |
| **22-20** |  | 2-[4-(ammoniomethyl )phenyl]-5-[2-(hydroxymethyl) morpholin-4-yl]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 427.2129 | 427.2147 |
| **22-21** |  | 2-[4-(aminomethyl)phenyl]-N-ethyl-3-phenyl-1,6-naphthyridin-5-amine | 355.5 | 355.2 |
| **22-22** |  | {4-[3-phenyl-5-(4H-1,2,4-triazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 379.4 | 379.2 |
| **22-23** |  | [4-(3-phenyl-5-piperazin-1-yl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 396.5 | 396.2 |
| **22-24** |  | 4-[5-(ethylthio)-3-phenyl-1,6-naphthyridin-2-yl]benzylamine | 372.5 | 372.2 |

| | | | | |
|---|---|---|---|---|
| **22-25** |  | [4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 345.8 | 345.8 |
| **22-26** |  | [4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 342.4 | 342.2 |

SCHEME 23

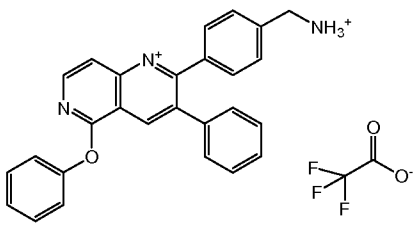


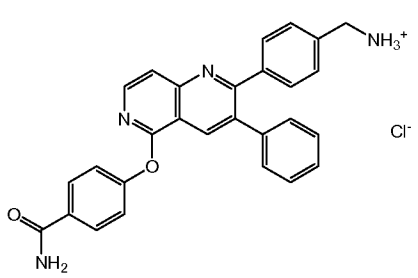
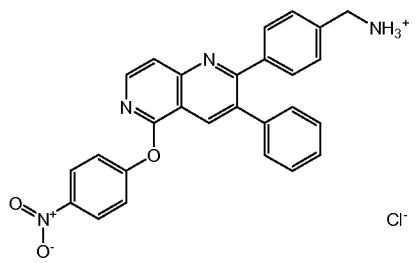
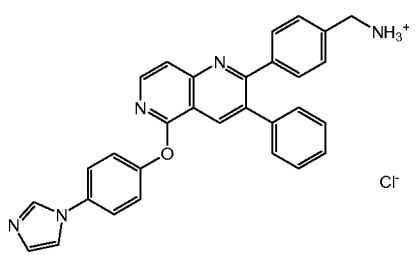
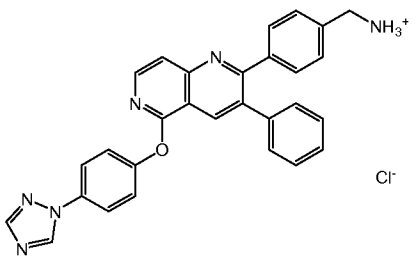
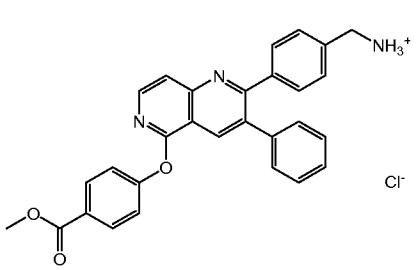

1-{4-[3-phenyl-5-(2-piperidin-1-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine (**23-1**)

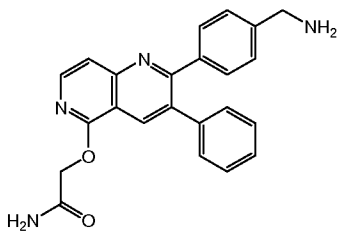
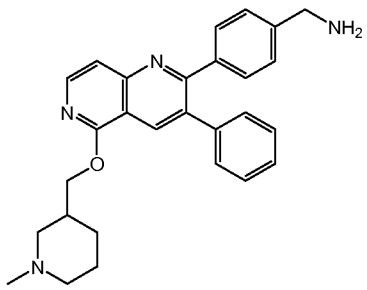
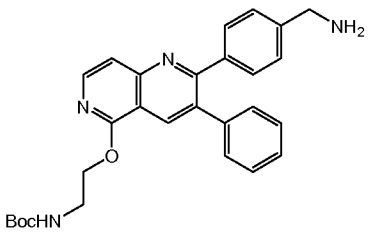
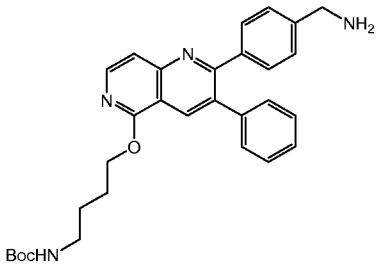
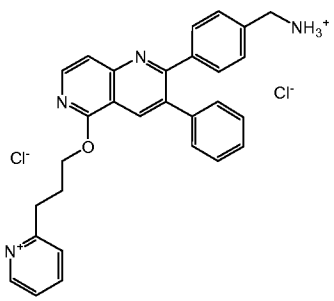
Procedure similar to that reported for Scheme **20** using **22-1** gave 1-{4-[3-phenyl-5-(2-piperidin-1-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine (**23-1**) as a solid. HRMS (M+H)+: observed = 439.2479, calculated = 439.2493.

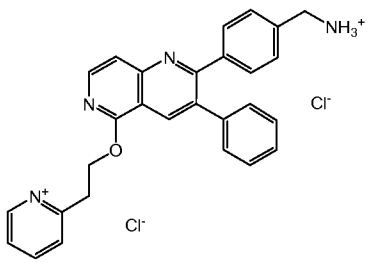
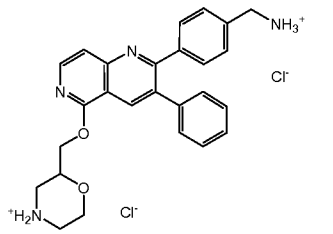
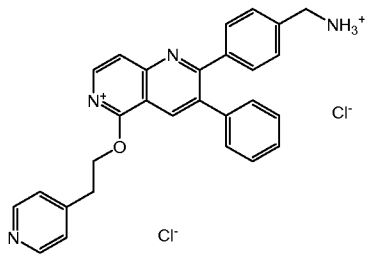
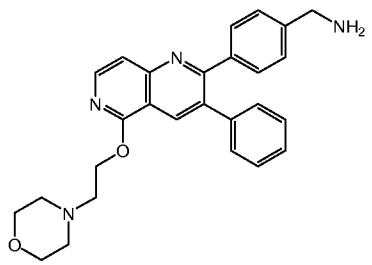
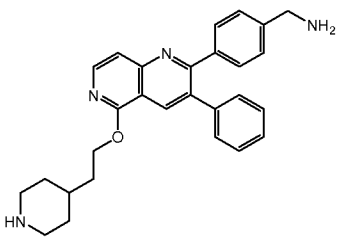
The following compounds in Table 9 were prepared according to the Reaction Schemes and Scheme 20.

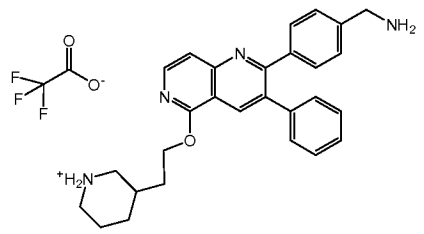
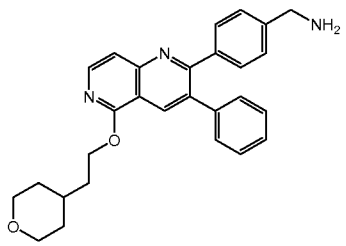
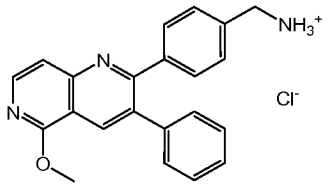
Table 9

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **23-2** |  | 2-[4-(ammoniomethyl) phenyl]-5-phenoxy-3-phenyl-1,6-naphthyridin-1-ium bis(trifluoroacetate) | 404.5 | 387.2 |

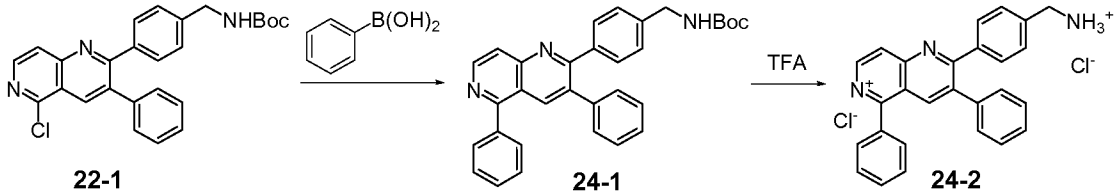
| | | | | |
|---|---|---|---|---|
| **23-3** |  | (4-{5-[4-(aminocarbonyl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 447.5 | 430.1 |
| **23-4** |  | {4-[5-(4-nitrophenoxy)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 449.5 | 432.1 |
| **23-5** |  | (4-{5-[4-(1H-imidazol-1-yl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 470.5 | 470.2 |
| **23-6** |  | (4-{3-phenyl-5-[4-(1H-1,2,4-triazol-1-yl)phenoxy]-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 471.5 | 454.1 |
| **23-7** |  | (4-{5-[4-(methoxycarbonyl) phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride | 462.5 | 445.1 |

| | | | | |
|---|---|---|---|---|
| **23-8** |  | 2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)acetamide | 385.4 | 385.1 |
| **23-9** |  | 1-(4-{5-[(1-methylpiperidin-3-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine | 439.6 | 439.2 |
| **23-10** |  | tert-butyl 2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethylcarbamate | 471.6 | 471.2 |
| **23-11** |  | tert-butyl 4-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)butylcarbamate | 499.6 | 499.3 |
| **23-12** |  | 2-[3-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)propyl]pyridinium dichloride | 477.2180 | 477.2176 |

| | | | | |
|---|---|---|---|---|
| **23-13** |  | 2-[2-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethyl]pyridinium dichloride | 433.2023 | 433.2018 |
| **23-14** |  | 2-[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)methyl]morpholin-4-ium dichloride | 427.2129 | 427.2147 |
| **23-15** |  | 2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-6-ium dichloride | 433.2023 | 433.2058 |
| **23-16** |  | 1-{4-[5-(2-morpholin-4-ylethoxy)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine | 441.2285 | 441.2268 |
| **23-17** |  | 1-{4-[3-phenyl-5-(2-piperidin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}methanamine | 439.2493 | 439.2504 |

| | | | | |
|---|---|---|---|---|
| **23-18** |  | 3-[2-({2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) ethyl]piperidinium | 439.6 | 439.2 |
| **23-19** |  | 1-(4-{3-phenyl-5-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]-1,6-naphthyridin-2-yl}phenyl)methanamine | 440.2333 | 440.2346 |
| **23-20** |  | 4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl) benzylamine | 342.4 | 342.3 |

SCHEME 24




**22-1** **24-1** **24-2**

2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridin-6-ium dichloride (**24-2**)

*tert*-butyl [4-(3,5-diphenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**24-1**)

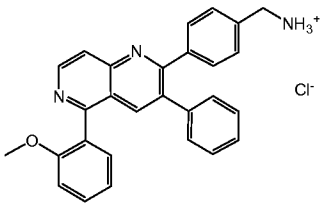
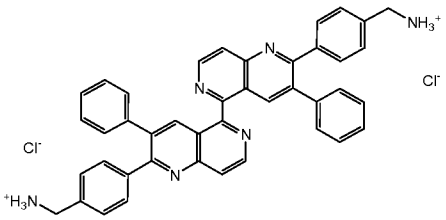
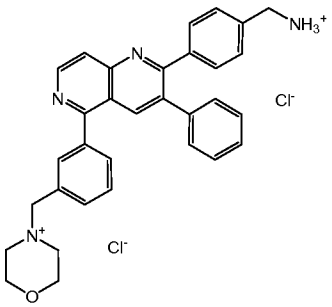
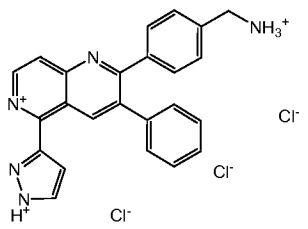
To a solution of *tert*-butyl [4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**22-1**, 0.050 g , 0.11 mmol), phenylboronic acid (0.035 g, 0.12 mmol), cesium carbonate (0.11 g, 0.34 mmol) and $Pd(Ph_3P)_2Cl_2$ (0.016 g, 0.022 mmol) in a 7/3/1 mixture of dioxane/ethanol/water (3 ml) was heated to 100°C in a microwave for 10 minutes. The reaction was concentrated and purified by reverse phase chromatography to give *tert*-butyl [4-(3,5-diphenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**24-1**) as a white solid. MS ($M+H^+$): 488

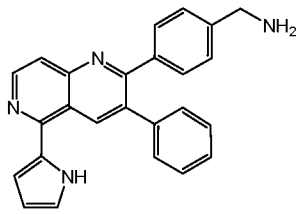
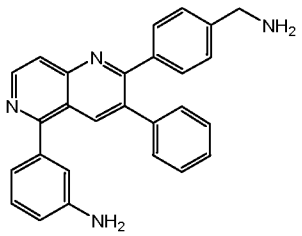
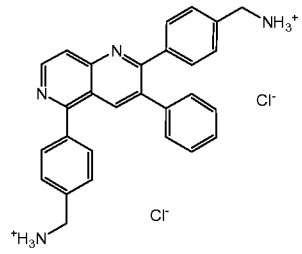
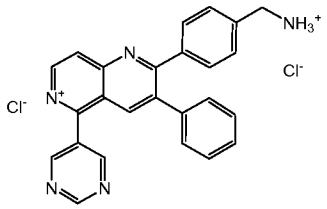
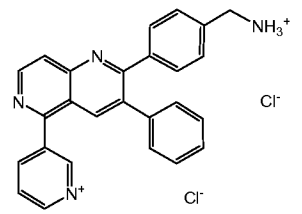
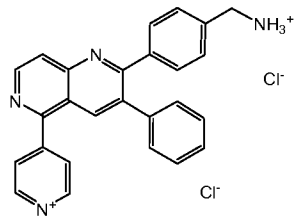
2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridin-6-ium dichloride (**24-2**)

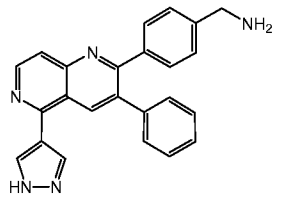
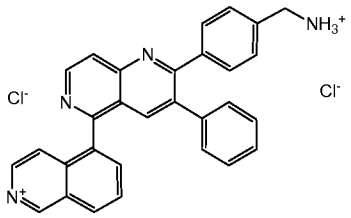
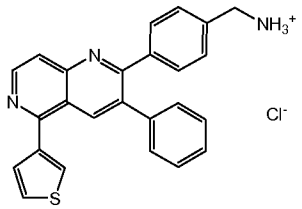
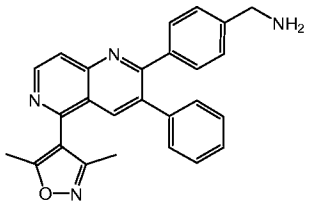
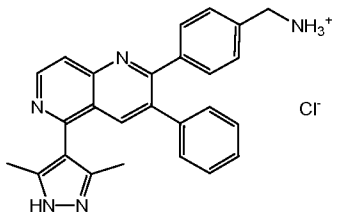
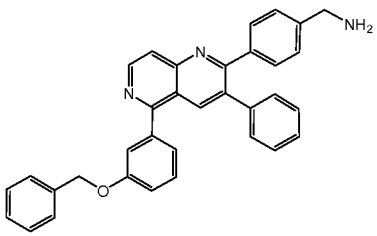
To a solution of *tert*-butyl [4-(3,5-diphenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**24-1**) was added TFA (2 mL) and DCM (2 mL) and the reaction was stirred at rt for 1 hour. The mixture was concentrated and purified via reversephase chromatography to give 2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridin-6-ium dichloride (**24-2**). MS $(M+H)^+$: observed = 388.5, calculated = 388.6

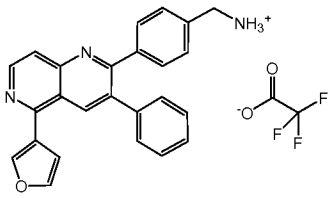
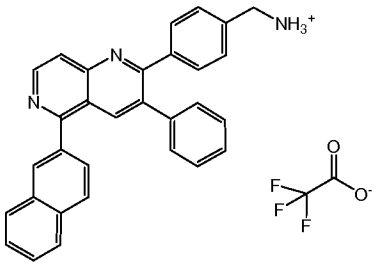
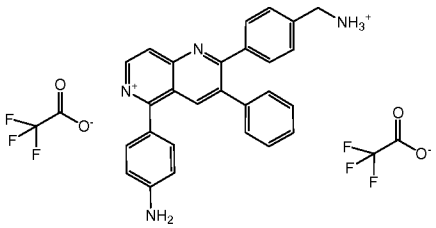
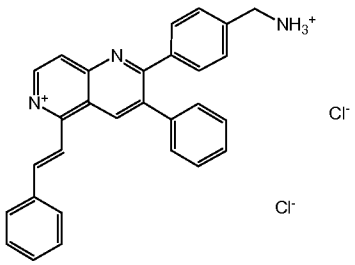
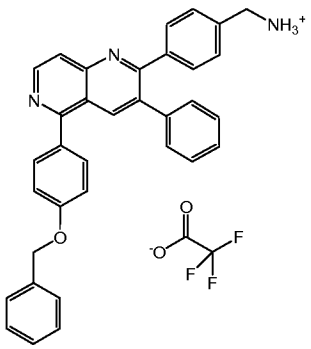
The compounds in Table 10 were prepared according to the Reaction Schemes and Scheme 24.

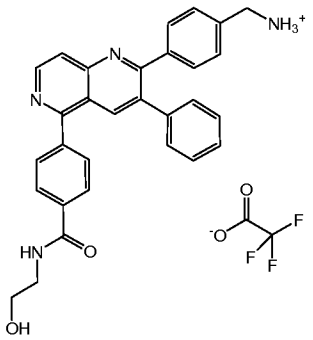
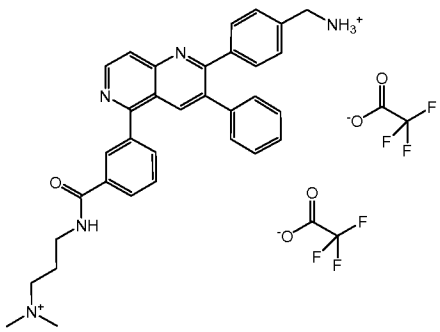
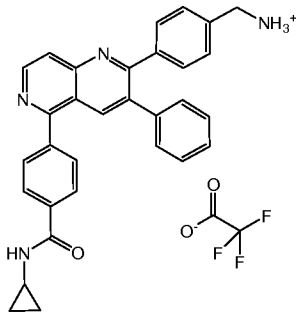
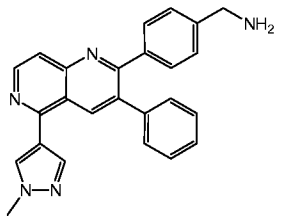
Table 10

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **24-3** |  | {4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 418.5 | 418.2 |
| **24-4** |  | [(3,3'-diphenyl-5,5'-bi-1,6-naphthyridine-2,2'-diyl)di-4,1-phenylene] dimethanaminium dichloride | 621.2761 | 621.2717 |
| **24-5** |  | 4-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}benzyl)morpholin-4-ium dichloride | 487.2493 | 487.2516 |
| **24-6** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(1H-pyrazol-1-ium-3-yl)-1,6-naphthyridin-6-ium trichloride | 378.6 | 378.5 |

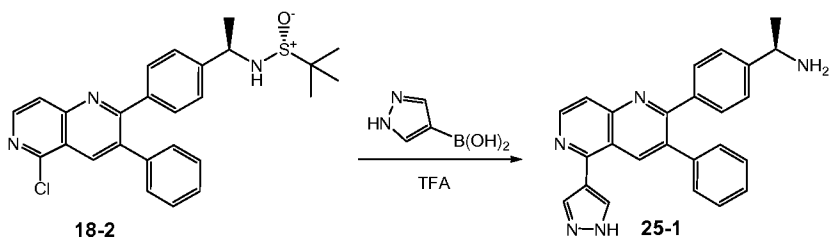
| | | | | |
|---|---|---|---|---|
| **24-7** |  | 1-{4-[3-phenyl-5-(1H-pyrrol-2-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine | 377.5 | 377.4 |
| **24-8** |  | 3-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}aniline | 403.5 | 403.5 |
| **24-9** |  | [(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene]dimethanaminium dichloride | 417.8 | 417.8 |
| **24-10** |  | 2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-pyrimidin-5-yl-1,6-naphthyridin-6-ium dichloride | 390.6 | 390.5 |
| **24-11** |  | 3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridinium dichloride | 389.6 | 389.6 |
| **24-12** |  | 4-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridinium dichloride | 389.6 | 389.6 |

| | | | | |
|---|---|---|---|---|
| **24-13** |  | 1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine | 378.4 | 378.4 |
| **24-14** |  | 5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}isoquinolinium dichloride | 439.6 | 439.7 |
| **24-15** |  | {4-[3-phenyl-5-(3-thienyl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 394.6 | 394.6 |
| **24-16** |  | 1-{4-[5-(3,5-dimethylisoxazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine | 407.6 | 407.5 |
| **24-17** |  | {4-[5-(3,5-dimethyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 406.6 | 406.6 |
| **24-18** |  | 1-(4-{5-[3-(benzyloxy)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine | 494.6 | 494.6 |

| | | | | |
|---|---|---|---|---|
| **24-19** |  | 1-(4-{5-[3-(benzyloxy)phenyl] -3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine | 378.5 | 378.5 |
| **24-20** |  | {4-[5-(2-naphthyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 438.5 | 438.5 |
| **24-21** |  | 5-(4-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 403.5 | 403.5 |
| **24-22** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(E)-2-phenylvinyl]-1,6-naphthyridin-6-ium dichloride | 414.5 | 414.5 |
| **24-23** |  | (4-{5-[4-(benzyloxy)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate | 494.6 | 494.6 |

| | | | | |
|---|---|---|---|---|
| 24-24 |  | {4-[5-(4-{[(2-hydroxyethyl) amino] carbonyl}phenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 475.6 | 475.6 |
| 24-25 |  | 3-[(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} benzoyl)amino]-N,N-dimethylpropan-1-aminium bis(trifluoroacetate) | 516.7 | 516.7 |
| 24-26 |  | [4-(5-{4-[(cyclopropylamino) carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium trifluoroacetate | 471.6 | 471.6 |
| 24-27 |  | 1-{4-[5-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine | 392.5 | 392.5 |

SCHEME 25



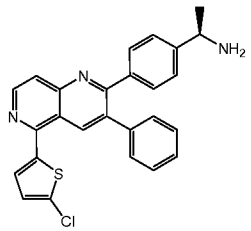
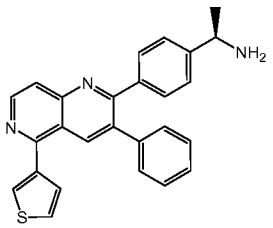
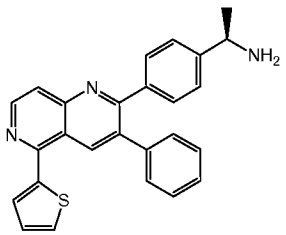
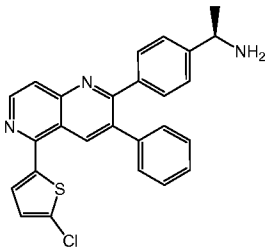

18-2 25-1

(1*R*)-1-{4-[3-phenyl-5-(1*H*-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-1**)

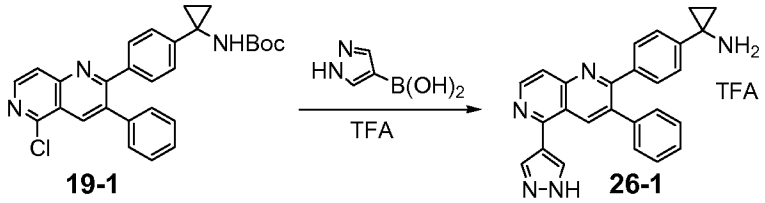
Procedure similar to that reported for Scheme **24** using **18-2** gave (1*R*)-1-{4-[3-phenyl-5-(1*H*-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine (**25-1**) as a solid. MS $(M+H)^+$: observed = 392.1, calculated = 392.5

The following compounds in Table 11 were prepared according to the Reaction Schemes and Scheme 25.

Table 11

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **25-2** |  | {4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium chloride | 418.5 | 418.2 |
| **25-3** |  | (1R)-1-{4-[3-phenyl-5-(thiophen-3-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine | 408.1534 | 408.1529 |
| **25-4** |  | (1R)-1-{4-[3-phenyl-5-(thiophen-2-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine | 408.1534 | 408.1533 |
| **25-5** |  | (1R)-1-{4-[5-(5-chlorothiophen-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}ethanamine | 442.1145 | 442.1143 |

SCHEME 26

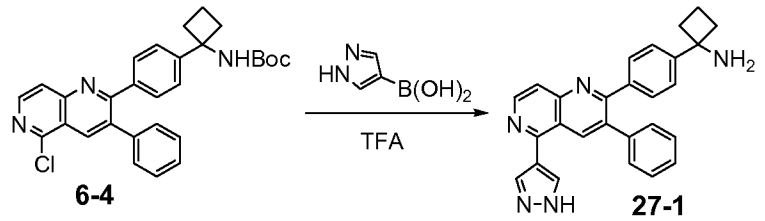



19-1 26-1

1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclopropanaminium trifluoroacetate (**26-1**)

Procedure similar to that reported for Scheme **24** using **19-1** gave 1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclopropanaminium trifluoroacetate (**26-1**) as a solid. MS $(M+H)^+$: observed = 404.1887, calculated = 404.1870

SCHEME 27



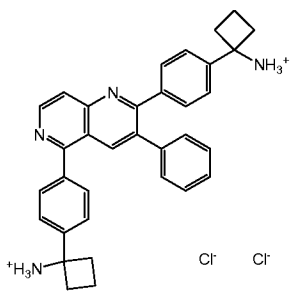

6-4 27-1

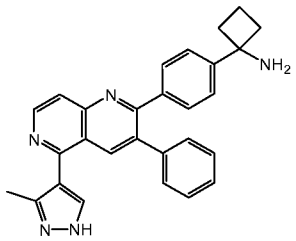
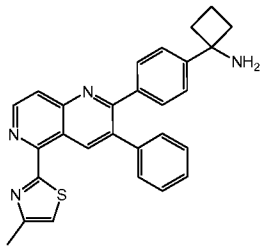
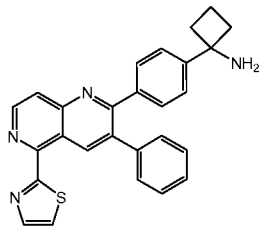
1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**27-1**)

Procedure similar to that reported for Scheme **24** using **6-4** gave 1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**27-1**) as a solid. HRMS (M+H)+: observed = 418.1805, calculated = 418.1810

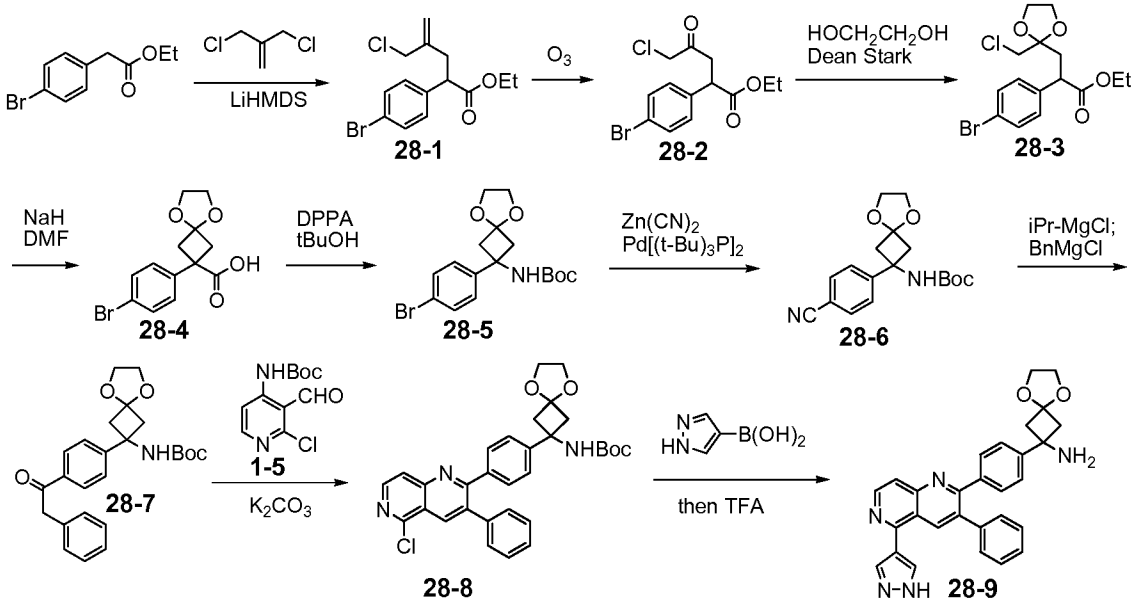
The compounds in Table 12 were prepared according to the Reaction Schemes and Scheme 27.

Table 12

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **27-2** |  | 1,1'-[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene]dicyclobutanaminium dichloride | 482.552 | 483.2041 |

| | | | |
|---|---|---|---|
| **27-3** |  | 1-{4-[5-(3-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine | 432.2188 432.2186 |
| **27-4** |  | 1-{4-[5-(4-methyl-1,3-thiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine | 449.1800 449.1803 |
| **27-5** |  | 1-{4-[3-phenyl-5-(1,3-thiazol-2-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine | 435.1643 435.1645 |

SCHEME 28




2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro[3.4]octan-2-amine (**28-9**)

Ethyl 2-(4-bromophenyl)-4-(chloromethyl)pent-4-enoate (**28-1**)

To a solution of ethyl (4-bromophenyl)acetate (143 g, 588 mmol) in THF (800 mL) was added LHMDS (1.13 eq in THF) at -78°C. After 30 minutes, the reaction mixture was added to a solution of 3-chloro-2-chloromethyl-1-propene (147 g, 1200 mmol) in THF (500 mL) at -78°C via cannula. The reaction was allowed to slowly warm from -78°C to rt over 15 hours. The reaction mixture was poured into sodium bicarbonate, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography eluting with 1-20% Etoac/Hexane. The appropriate fractions were combined and the solvent removed in vacuo to give benzyl 4-(1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (**28-1**) as a clear oil. MS ($M+H^+$): 332.5

Ethyl 2-(4-bromophenyl)-5-chloro-4-oxopentanoate (**28-2**)

Through a solution of ethyl 2-(4-bromophenyl)-4-(chloromethyl)pent-4-enoate (**28-1**, 7.3 g, 25 mmol) in methanol (40 mL) and DCM (40 mL) at -78°C was bubbled $O_3$ until the reaction turned slightly blue (6 hours). The reaction was allowed to stir for an additional 1 hour, at which time $N_2$ gas was bubbled through the reaction mixture until the solution was colorless. Excess methyl sulfide (3.8 g, 60 mmol) was added to the reaction and the mixture was allowed to warm from -78°C to rt. The reaction mixture was poured into saturated sodium bicarbonate, extracted with DCM, dried over sodium sulfate filtered and concentrated. The crude residue was purified by column chromatography eluting with 1-20% EtOAc/Hexane. The appropriate fractions were combined and the solvent removed in vacuo to give ethyl 2-(4-bromophenyl)-5-chloro-4-oxopentanoate (**28-2**) as a solid. MS ($M+H^+$): 153.2

Ethyl 2-(4-bromophenyl)-3-[2-(chloromethyl)-1,3-dioxolan-2-yl]propanoate (**28-3**)

To a solution of ethyl 2-(4-bromophenyl)-5-chloro-4-oxopentanoate (**28-2**) (35 g, 105 mmol) and ethylene glycol (20 g, 320 mmol) in toluene (300 mL) was added para-toluenesulfonic acid (100 mg) and the reaction was heated to reflux with a dean stark trap for 6 hours. The reaction mixture was concentrated was purified by column chromatography eluting with 0-50% EtOAc/Hexane. The appropriate fractions were combined, concentrated, and the resulting solid was recrystallized from EtOAc and hexane to give ethyl 2-(4-bromophenyl)-3-[2-(chloromethyl)-1,3-dioxolan-2-yl]propanoate (**28-3**) as a white solid MS ($M+H^+$): 378.

2-(4-Bromophenyl)-5,8-dioxaspiro[3.4]octane-2-carboxylic acid (**28-4**)

To a solution of ethyl 2-(4-bromophenyl)-3-[2-(chloromethyl)-1,3-dioxolan-2-yl]propanoate (**28-3**) (27 g, 72 mmol) cooled to -78°C in DMF (200 mL) was added NaH (8.6 g, 210 mmol) and the reaction was allowed to slowly warm from -78°C to rt. Once at rt, 1N NaOH (100 mL) was added and the reaction mixture was stirred over night. The crude reaction mixture was poured into saturated sodium bicarbonate and washed with chloroform. The aqueous layer was acidified with HCl, extracted with chloroform, dried over sodium sulfate filtered and concentrated. The crude residue was purified by column chromatography eluting with 1-50% EtOAc/Hexane. The appropriate fractions were concentrated and recrystallized from

EtOAc/hexane to give 2-(4-bromophenyl)-5,8-dioxaspiro[3.4]octane-2-carboxylic acid (**28-4**) as a white solid. MS ($M+H^+$): 314

tert-Butyl [2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-5**)

To a solution of 2-(4-bromophenyl)-5,8-dioxaspiro[3.4]octane-2-carboxylic acid (**28-4**) (40.7 g, 130 mmol) in tert-butanol (230 mL, 3.25 mol)was added DPPA (35.8 g, 130 mmol) and the reaction was heated to 100°C overnight under $N_2$. The reaction mixture was poured into saturated sodium bicarbonate, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography eluting with 7-50% EtOAc/Hexane. The appropriate fractions were combined and the solvent removed in vacuo to give tert-butyl [2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-5**). MS ($M+H^+$): 385

tert-butyl [2-(4-cyanophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-6**)

To a solution of tert-butyl [2-(4-bromophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-5**) (21.3 g, 55.5 mmol) in dioxane (100 mL) and DMF (100 mL) was added zinc cyanide (6.52 g, 55.5 mmol) and bis(tri-t-butylphosphine)palladium(0) (2.84 g, 5.55 mmol) and the reaction was heated to 120°C under $N_2$ for 1 hour. The reaction mixture was cooled to rt, filtered, and concentrated. The crude residue was purified by column chromatography eluting with 1-60% EtOAc/Hexane. The appropriate fractions were combined and the solvent removed in vacuo to give tert-butyl [2-(4-cyanophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-6**). MS ($M+H^+$): 331

tert-butyl {2-[4-(phenylacetyl)phenyl]-5,8-dioxaspiro[3.4]oct-2-yl}carbamate (**28-7**)

To a solution of tert-butyl [2-(4-cyanophenyl)-5,8-dioxaspiro[3.4]oct-2-yl]carbamate (**28-6**) (15.0 g, 45.4 mmol) in THF (150 mL) at -78°C was added isopropylmagnesium chloride (22.7 mL, 45.4 mmol, 2M in THF). After 1 hour, benzylmagnesium chloride (68 mL, 135 mmol, 2M in THF) was added and the reaction was allowed to slowly warm to rt over 5 hours. The reaction mixture was poured into saturated ammonium chloride, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography eluting with 1-60% EtOAc/Hexane. The appropriate fractions were combined and the solvent removed in vacuo to give tert-butyl {2-[4-(phenylacetyl)phenyl]-5,8-dioxaspiro[3.4]oct-2-yl}carbamate (**28-7**). MS (M+H+): 424

tert-butyl {2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro [3.4]oct-2-yl}carbamate (**28-8**)

To a solution of tert-butyl {2-[4-(phenylacetyl)phenyl]-5,8-dioxaspiro[3.4]oct-2-yl}carbamate (**28-7**) (8.8 g, 20.8 mmol) in DMF (100 mL) was added potassium carbonate (14.4 g, 104 mmol) and **1-5** (5.33 g, 20.8 mmol) and the reaction mixture was heated 80°C over night. The reaction mixture was poured into saturated sodium bicarbonate, extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography eluting with 1-80% EtOAc/Hexane. The appropriate fractions were combined

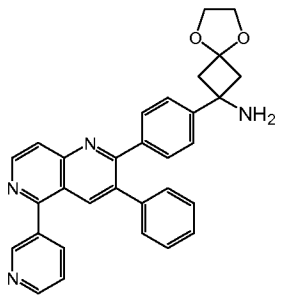
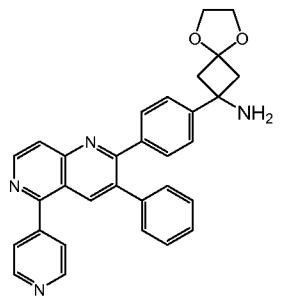
and the solvent removed in vacuo to give tert-butyl {2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro[3.4]oct-2-yl}carbamate (**28-8**). MS (M+H+): 545

2-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine (**28-9**)

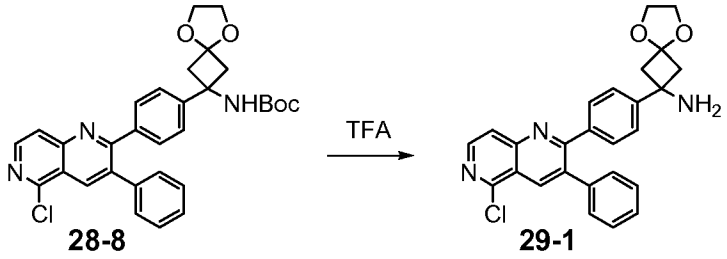
Procedure similar to that reported for Scheme 24 using **28-8** gave tert-butyl (2-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]oct-2-yl)carbamate. To a solution of tert-butyl (2-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]oct-2-yl)carbamate in DCM (50 mL) was added TFA (30 mL) and the reaction was stirred at rt for 1 hour. Poured into 1N NaOH (150 mL), added saturated sodium bicarbonate (150 mL), extracted with EtOAc, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by reverse phase LC and recrystalization from EtOAc and Hexane to give 2-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine (**28-9**) as a solid. HRMS $(M+H)^+$: observed = 444.1474, calculated = 444.1509

The compounds in Table 13 were prepared according to the Reaction Schemes and Scheme 28.

Table 13

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **28-10** |  | 2-{4-[3-phenyl-5-(pyridin-3-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine | 487.2134 | 487.2136 |
| **28-11** |  | 2-{4-[3-phenyl-5-(pyridin-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine | 487.2 | 487.2 |

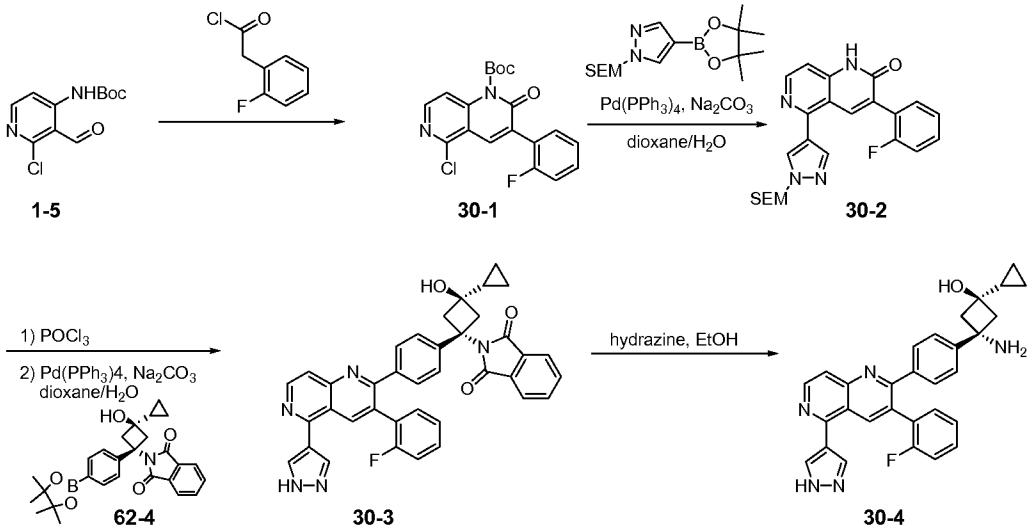
SCHEME 29




2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro [3.4]octan-2-amine (**29-1**)

Procedure similar to that reported for **28-9** gave 2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro[3.4]octan-2-amine (**29-1**) as a solid. MS (M+H+): 444

SCHEME 30




trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**30-4**)

tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**30-1**)

Procedure similar to that reported for (**62-1**) using (2-fluorophenyl)acetyl chloride gave tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**30-1**) as a colorless solid.

3-(2-fluorophenyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)-1,6-naphthyridin-2(1H)-one (**30-2**)

A mixture of tert-butyl 5-chloro-3-(2-fluorophenyl)-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**30-1**, 300 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazole (286 mg), $Pd(PPh_3)_4$ (92 mg) and 3M $Na_2CO_3$ (0.800 mL) in 1,4-dioxane (8 mL) was stirred at 100°C overnight. The reaction mixture was diluted with EtOAc, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 3-(2-fluorophenyl)-5-(1-{[2-

(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)-1,6-naphthyridin-2(1H)-one (**30-2**) as a colorless solid.

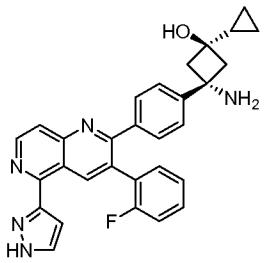
2-(trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}-3-hydroxycyclobutyl)-1H-isoindole-1,3(2H)-dione (**30-3**)

A mixture of 3-(2-fluorophenyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)-1,6-naphthyridin-2(1H)-one (**30-2**, 330 mg) in $POCl_3$ (5 mL) was stirred at 100°C for 3 h. Following evaporation, the residue was diluted with EtOAc, washed with aq. $NaHCO_3$ and water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-chloro-3-(2-fluorophenyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)-1,6-naphthyridine. A mixture of 2-chloro-3-(2-fluorophenyl)-5-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrazol-4-yl)-1,6-naphthyridine (42 mg), boronate **62-4** (57 mg), $Pd(PPh_3)_4$ (26 mg) and 3M $Na_2CO_3$ (0.11 mL) in 1,4-dioxane (1 mL) was heated under microwave irradiation at 140°C for 1 h. The reaction mixture was diluted with EtOAc, filtered through a celite pad, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-(trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)- 1,6-naphthyridin-2-yl]phenyl}-3-hydroxycyclobutyl)-1H-isoindole-1,3(2H)-dione (**30-3**) as a yellow amorphous material.

trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**30-4**)

A mixture of 2-(trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl] phenyl}-3-hydroxycyclobutyl)-1H-isoindole-1,3(2H)-dione (**30-3**, 24 mg, 0.039 mmol) and hydrazine monohydrate (0.2 ml, 0.039 mmol) in EtOH (3 ml) was stirred at 90°C for 3 h. The reaction mixture was diluted with $CHCl_3$, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**30-4**) as a colorless amorphous material. HRMS (M+H)+: observed = 492.2196, calculated = 492.2200

SCHEME 31

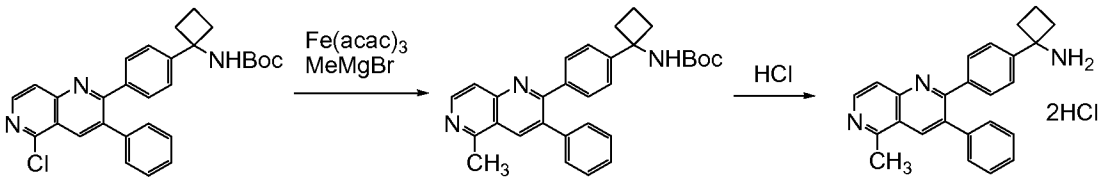



**31-1**

trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-3-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**31-1**)

Procedures similar to that reported for Scheme 30 gave trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-3-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**31-1**). HRMS (M+H)+: observed = 492.2197, calculated = 492.2200

SCHEME 32




**6-4** **32-1** **32-2**

2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridin-1-ium dichloride (**32-2**)

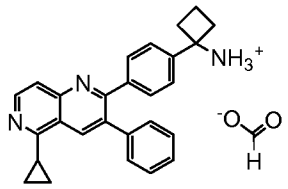
*tert*-butyl {1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl} carbamate (**32-1**)

To a round bottom flask was added *tert*-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**, 2.16 g, 4.44 mmol), ferric acetylacetonate (0.157 g, 0.444 mmol), and anhydrous THF (25 mL). The reaction mixture was cooled to -78°C under an atmosphere of nitrogen and a 1.4 M solution (THF:toluene 25:75) of methylmagnesium bromide (19 mL, 26.6 mmol) was added. After 40 minutes, the reaction mixture was quenched at -78°C by addition of a saturated solution of ammonium chloride (20 mL), then permitted to warm to room temperature, suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (0-8% IPA/DCM) to give *tert*-butyl {1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl} carbamate (**32-1**) as a yellow solid. HRMS $(M+H)^+$: observed = 466.2503, calculated = 466.2489

2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridin-1-ium dichloride (**32-2**)

To a stirred solution of *tert*-butyl {1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**32-1**) (100 mg, 0.215 mmol) in DCM (3 mL), and MeOH (3 mL) was added a 4M solution of HCl in EtOAc (5 mL, 20 mmol). The reaction mixture was then permitted to stir at room temperature for 4 hours. The crude reaction mixture was then concentrated in vacuo to give 2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridin-1-ium dichloride (**32-2**) as a yellow solid. HRMS $(M+H)^+$: observed = 366.1972, calculated = 366.1965

SCHEME 33

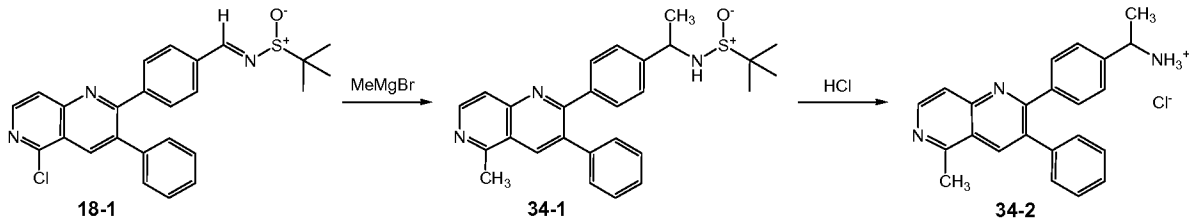


33-1

1-[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium formate (**33-1**)

Procedures similar to that reported for Scheme 32 gave 1-[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium formate (**33-1**). HRMS (M+H)+: observed = 392.2130, calculated = 392.2127

SCHEME 34




18-1 34-1 34-2

1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanaminium chloride (**34-2**)

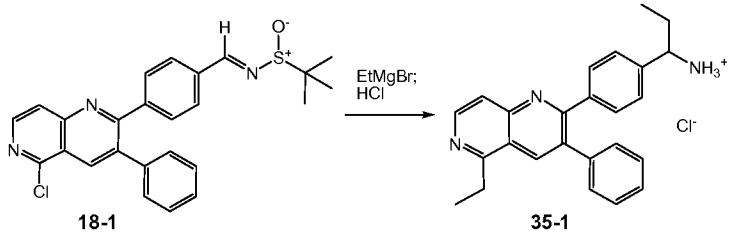
*tert*-butyl({1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] ethyl}amino)sulfoniumolate (**34-1**)

Procedure similar to that reported for **18-1** gave *tert*-butyl({1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}amino)sulfoniumolate (**34-1**) as minor product. MS (M+1): 444.3

1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanaminium chloride (**34-2**)

Procedure similar to that reported for **18-4** gave 1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanaminium chloride (**34-2**). MS (M+1): observed 340.2, calculated MS: 340.4

SCHEME 35

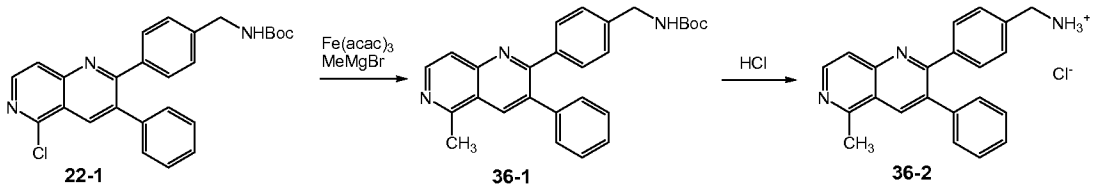



18-1 35-1

1-[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium chloride (**35-1**)

Procedure similar to that reported for **34-2** gave 1-[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-1-aminium chloride (**35-1**). MS (M+1): observed 368.3, calculated MS: 368.5

SCHEME 36



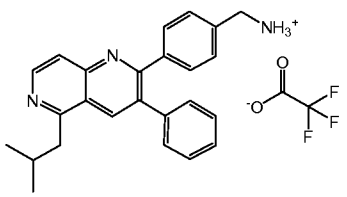
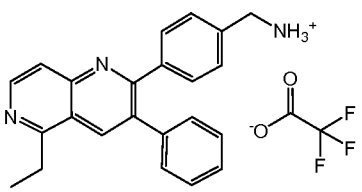
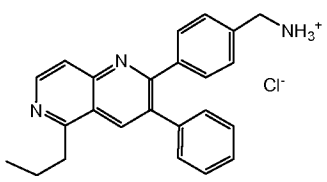

22-1 36-1 36-2

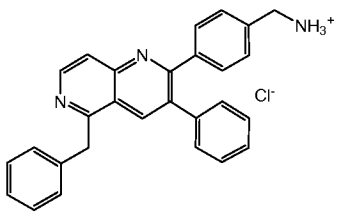
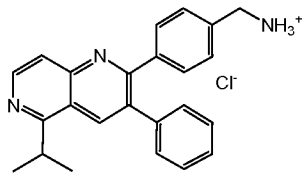
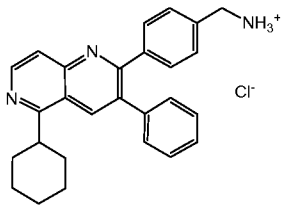
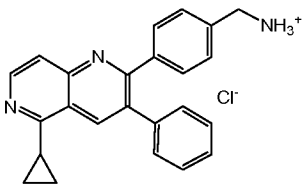
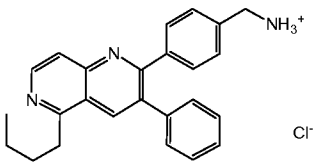
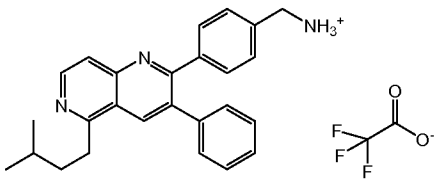
[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-2**)

Procedure similar to that reported for Scheme 32 gave [4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**36-2**). MS (M+1): observed 326.2, calculated 326.4

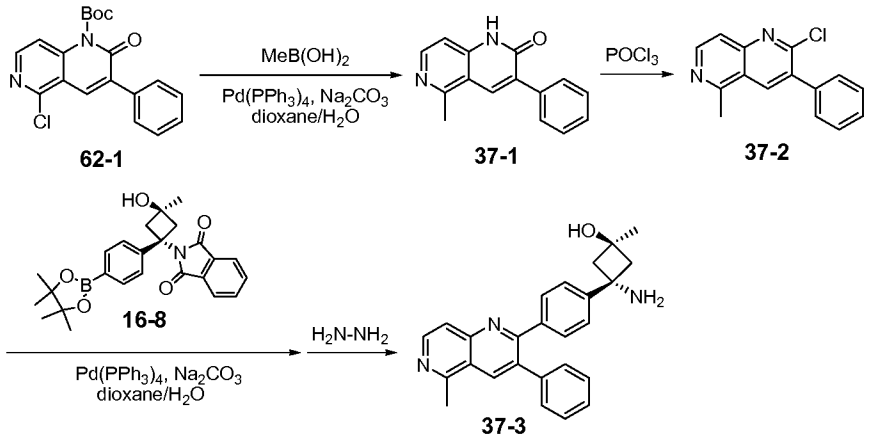
The compounds in Table 14 were prepared according to the Reaction Schemes and Scheme 36.

Table 14

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **36-3** |  | [4-(5-isobutyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium trifluoroacetate | 368.5 | 368.6 |
| **36-4** |  | [4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium trifluoroacetate | 340.4 | 340.5 |
| **36-5** |  | [4-(3-phenyl-5-propyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 354.5 | 354.2 |

| | | | | |
|---|---|---|---|---|
| **36-6** |  | [4-(5-benzyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 402.5 | 402.2 |
| **36-7** |  | [4-(5-isopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 354.5 | 354.2 |
| **36-8** |  | [4-(5-cyclohexyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 394.5 | 394.3 |
| **36-9** |  | [4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 352.5 | 352.2 |
| **36-10** |  | [4-(5-butyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanaminium chloride | 368.5 | 368.0 |
| **36-11** |  | {4-[5-(3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 382.2278 | 382.2280 |

SCHEME 37




trans-3-amino-1-cyclopropyl-3-{4-[3-phenyl-5-methyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**37-3**)

5-methyl-3-phenyl-1,6-naphthyridin-2(1H)-one (**37-1**)

A mixture of tert-butyl 5-chloro-2-oxo-3-phenyl-1,6-naphthyridine-1(2H)-carboxylate (**62-1**, 300 mg), methylboronic acid (131 mg), Pd(PPh3)4 (126 mg) and 3M Na2CO3 (1.092 mL) in 1,4-dioxane (10 mL) was heated under microwave irradiation at 140°C for 2h. Water (10 mL) was added to the reaction mixture and the precipitate was collected by filtration and dried in vacuo to give 5-methyl-3-phenyl-1,6-naphthyridin-2(1H)-one (**37-1**). This material was used for next reactions without further purification.

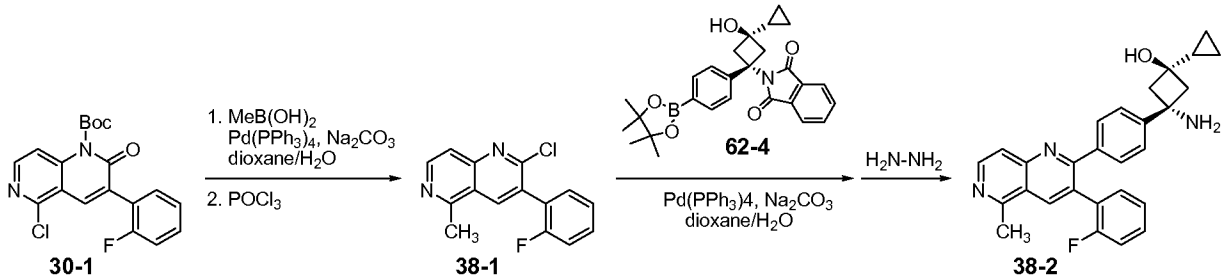
2-chloro-5-methyl-3-phenyl-1,6-naphthyridine (**37-2**)

Procedure similar to that reported for **62-3** using 5-methyl-3-phenyl-1,6-naphthyridin-2(1H)-one (**37-1**) gave 2-chloro-5-methyl-3-phenyl-1,6-naphthyridine (**37-2**) as a colorless solid.

trans-3-amino-1-methyl-3-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanol (**37-3**)

Procedure similar to that reported for **16-9** gave trans-3-amino-1-cyclopropyl-3-{4-[3-phenyl-5-methyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**37-3**) as a colorless solid. HRMS (M+H)+: observed = 396.2073, calculated = 396.2076

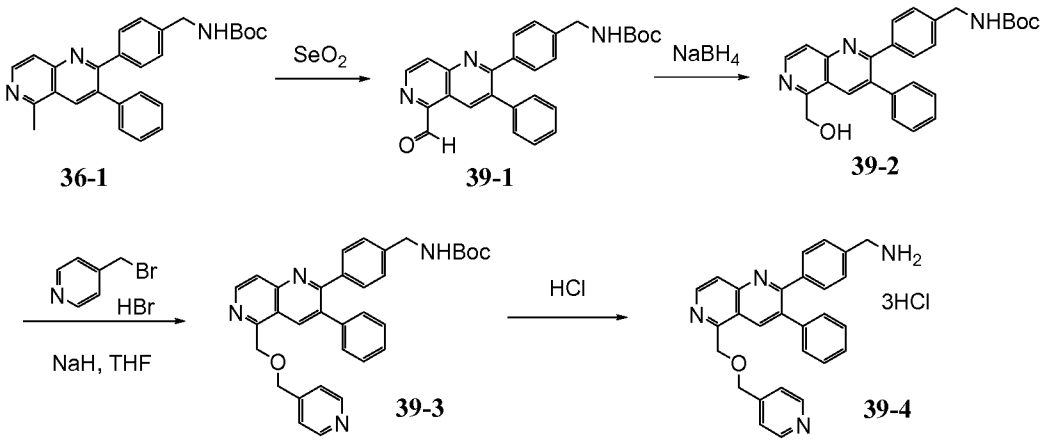
SCHEME 38




trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-methyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**38-2**)

Procedure similar to that reported for Scheme 30 using methylboronic acid gave trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-methyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**38-2**). HRMS (M+H)+: observed = 440.2134, calculated = 440.2138

SCHEME 39




2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(pyridinium-4-ylmethoxy)methyl]-1,6-naphthyridin-6-ium trichloride (**39-4**)

tert-butyl [4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**39-1**)

Procedure similar to that reported for **41-1** using **36-1** gave tert-butyl [4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**39-1**) as a solid.

tert-butyl {4-[5-(hydroxymethyl)-3-phenyl-1,6-naphthyridin-2-yl] benzyl}carbamate (**39-2**)

To a stirred solution of tert-butyl [4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**39-1**) (380 mg, 0.87 mmol) in methanol (6 mL) at 0°C was added sodium borohydride (66 mg, 1.7 mmol). The reaction mixture was then permitted to stir at 0°C under an atmosphere of nitrogen. After 10 minutes, the crude reaction mixture was then quenched by addition of a saturated solution of sodium bicarbonate in water (10 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl {4-[5-(hydroxymethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**39-2**) as a tan solid. HRMS (M+H)+: observed = 442.2117, calculated = 442.2125

tert-butyl (4-{3-phenyl-5-[(pyridin-4-ylmethoxy)methyl]-1,6-naphthyridin-2-yl}benzyl)carbamate (**39-3**)

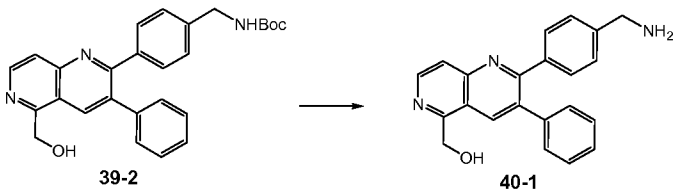
To a round bottom flask was added tert-butyl {4-[5-(hydroxymethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**39-2**) (48 mg, 0.109 mmol), 4-(bromomethyl)pyridinium bromide (30.2 mg, 0.120 mmol), anhydrous THF (1.5 mL), anhydrous

DMF (1.5 mL) (for solubility), and finally a 60% by weight suspension of sodium hydride in mineral oil (17.39 mg, 0.435 mmol). The reaction mixture was permitted to stir at room temperature under an atmosphere of nitrogen. After 1 hour the crude reaction mixture mixture was then quenched by addition of a saturated solution of sodium bicarbonate in water (10 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 50% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl (4-{3-phenyl-5-[(pyridin-4-ylmethoxy)methyl]-1,6-naphthyridin-2-yl}benzyl)carbamate (**39-3**) as an off-white solid. HRMS (M+H)+: observed = 533.2539, calculated = 533.2547

2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(pyridinium-4-ylmethoxy)methyl]-1,6-naphthyridin-6-ium trichloride (**39-4**)

Procedure similar to that reported for **19-2** using **39-3** gave 2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(pyridinium-4-ylmethoxy)methyl]-1,6-naphthyridin-6-ium trichloride (**39-4**) as a tan solid. HRMS (M+H)+: observed = 433.2018, calculated = 433.2023

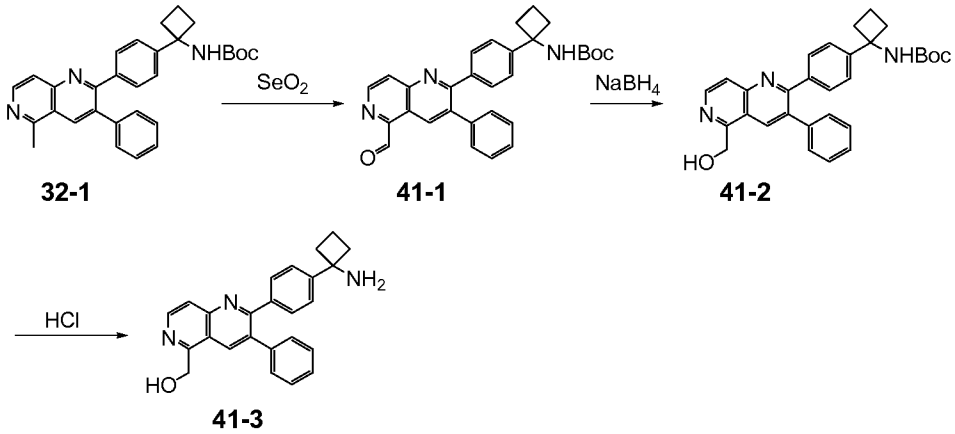
SCHEME 40




{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**40-1**)

Procedure similar to that reported for **19-2** gave {2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**40-1**). MS: 342.2 (M+1)

SCHEME 41




{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**41-3**)

tert-butyl {1-[4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**41-1**)

To a solution of tert-butyl {1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**32-1**) (1.4 g, 3.1 mmol) in anhydrous dioxane (20 mL) was added selenium dioxide (0.38 g, 3.4 mmol). The reaction mixture was then heated to reflux (110°C) with a water cooled reflux condenser attached under an atmosphere of nitrogen while stirring. After 60 minutes, the crude reaction mixture was permitted to cool to room temperature, filtered, then concentrated filtrate in vacuo. The resulting residue was purified by silica gel chromatography (0-60% EtOAc/5% DCM/Hexane) to give tert-butyl {1-[4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**41-1**) as a tan solid. MS (M+H)+: observed = 480.1, calculated = 480.6

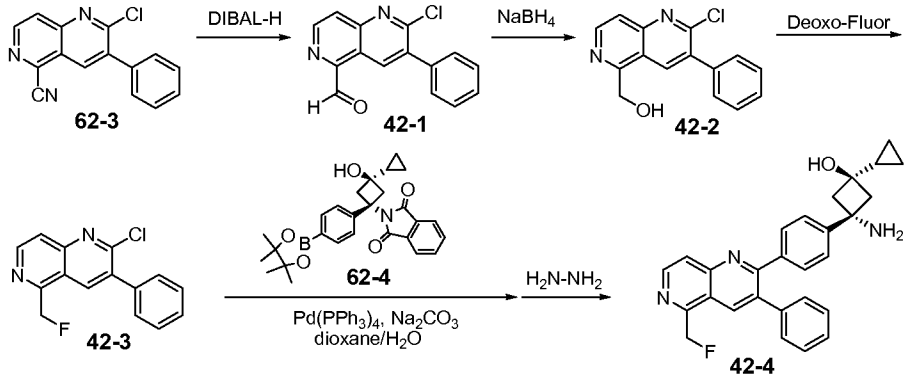
tert-butyl {1-[4-(5-hydroxymethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**41-2**)

Procedure similar to that for **39-2** using *tert*-butyl {1-[4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**41-1**) gave *tert*-butyl {1-[4-(5-hydroxymethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**41-2**) as a colorless amourphous material.

{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**41-3**)

Procedure similar to that for **19-2** gave {2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol (**41-3**) as a colorless solid. HRMS (M+H)+: observed = 382.1913, calculated = 382.1919

SCHEME 42




trans-3-amino-1-cyclopropyl-3-{4-[5-(fluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**42-4**)

(2-chloro-3-phenyl-1,6-naphthyridin-5-yl)methanol (**42-2**)

To a solution of 2-chloro-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-3**, 100 mg) in THF (10 mL) was added DIBAL-H (0.41 mL, 1.0M in toluene) dropwise at -78°C for 10 min. The mixture was stirred at -78°C for 3h and then warmed up to rt and stirred for 1h. The reaction mixture was poured into 1N $H_2SO_4$ and extracted with EtOAc. The combined organic layers were washed with water, dried ($Na_2SO_4$) and concentrated in vacuo to give crude **41-1**. The residue was dissolved in methanol (2 mL) and sodium borohydride (40 mg) was added at rt. The mixture was stirred at rt for 2 h. The reaction mixture diluted with AcOEt, washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give (2-chloro-3-phenyl-1,6-naphthyridin-5-yl)methanol (**42-2**) as a colorless solid.

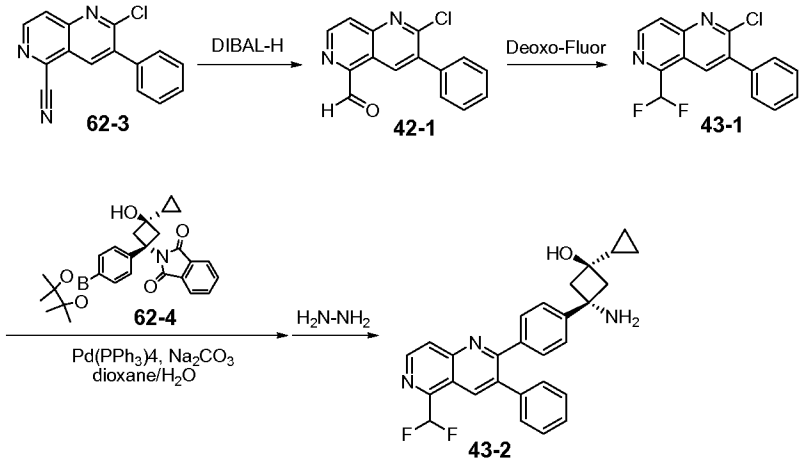
2-chloro-5-(fluoromethyl)-3-phenyl-1,6-naphthyridine (**42-3**)

To a solution of (2-chloro-3-phenyl-1,6-naphthyridin-5-yl)methanol (**42-2**, 100 mg) in $CHCl_3$ (10 mL) was added Dioxo-Fluor (0.18 mL) dropwise at 0°C for 10 min. The mixture was stirred at 0°C for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-chloro-5-(fluoromethyl)-3-phenyl-1,6-naphthyridine (**42-3**) as a colorless solid.

trans-3-amino-1-cyclopropyl-3-{4-[5-(fluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**42-4**)

Procedure similar to that reported for **16-9** gave trans-3-amino-1-cyclopropyl-3-{4-[5-(fluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol (**42-4**) as a colorless solid. HRMS (M+H)+: observed = 384.1873, calculated = 384.1876

SCHEME 43




trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**43-3**)

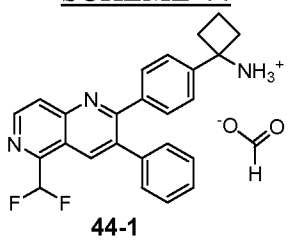
2-chloro-5-(difluoromethyl)-3-phenyl-1,6-naphthyridine (**43-1**)

To a solution of 2-chloro-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-3**, 100 mg) in THF (10 mL) was added DIBAL-H (0.414 mL, 1.0 M in toluene) dropwise at -78°C for 10 min. The mixture was stirred at -78°C for 3 h and then warmed up to rt and stirred for 1h. The reaction mixture was poured into 1N $H_2SO_4$ and extracted with EtOAc. The combined organic layers were washed with water, dried ($Na_2SO_4$) and concentrated in vacuo to give **42-1**. To the crude residue of **42-1** dissolved in $CHCl_3$ (5 mL) was added Deoxo-Fluor (0.173 mL) at rt. The mixture was stirred at 0°C for 2 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-chloro-5-(difluoromethyl)-3-phenyl-1,6-naphthyridine (**43-1**) as a colorless solid.

trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**43-2**)

Procedure similar to that for **16-9** gave trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**42-3**) as a colorless solid. HRMS (M+H)+: observed = 458.2045, calculated = 458.2044

SCHEME 44

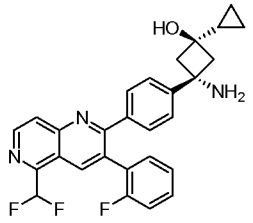


**44-1**

1-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**44-1**)

Procedure similar to that reported for **43-2** using tert-butyl {1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}carbamate (Reference: US2007/024722) gave 1-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine (**44-1**). HRMS (M+H)+: observed = 402.1777, calculated = 402.1782

SCHEME 45

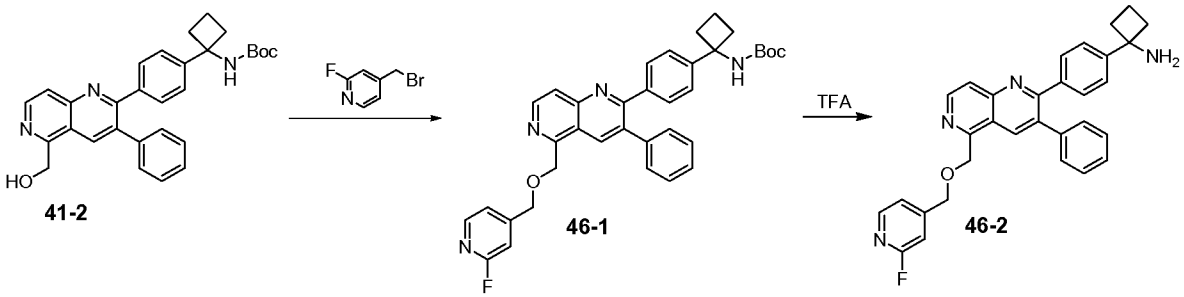



**45-1**

trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-(2-fluorophenyl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**45-1**)

Procedure similar to that reported for **43-2** using gave trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-(2-fluorophenyl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol (**45-1**). HRMS (M+H)+: observed = 476.1949, calculated = 476.1950

SCHEME 46




**41-2** **46-1** **46-2**

1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**46-2**)

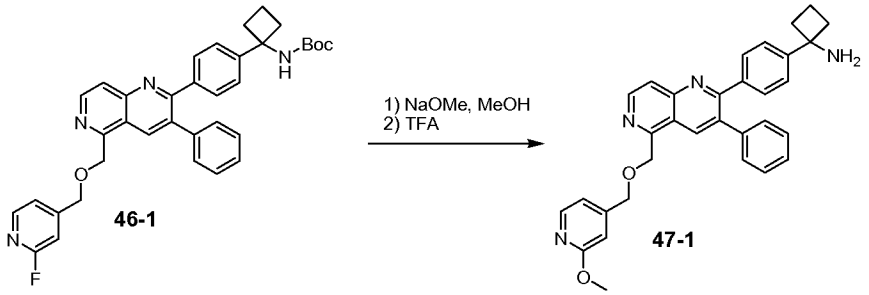
tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**46-1**)

Procedure similar to that for 3**9-3** using **41-2** gave tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl -1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**46-1**) as a tan solid.

1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**46-2**)

tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**46-1**) (20 mg) was dissolved with TFA (0.1 mL) and stirred for 1h. The mixture was concentrated in vacuo and the residue was purified by reverse phase HPLC to give 1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**46-2**) as a colorless amorphous. MS (M+H)+: observed = 491.2, calculated = 491.2

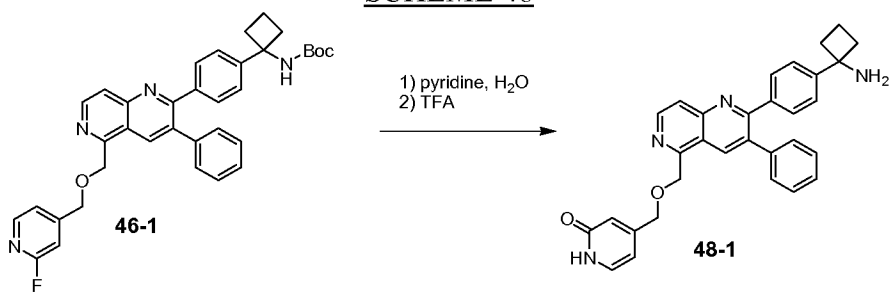
SCHEME 47




1-[4-(5-{[(2-methoxypyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**47-1**)

A mixture of tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl) phenyl]cyclobutyl}carbamate (**46-1**) (20 mg) and NaOMe (50 mg) in MeOH (1 mL) was stirred at 70°C for 4 h. The reaction mixture was diluted with EtOAc, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was dissolved with TFA (0.10 mL) and stirred at rt for 1h. The mixture was concentrated in vacuo and the residue was purified by reverse phase HPLC to give 1-[4-(5-{[(2-methoxypyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**47-1**) as a colorless amorphous material. MS (M+H)+: observed = 503.2, calculated = 503.2

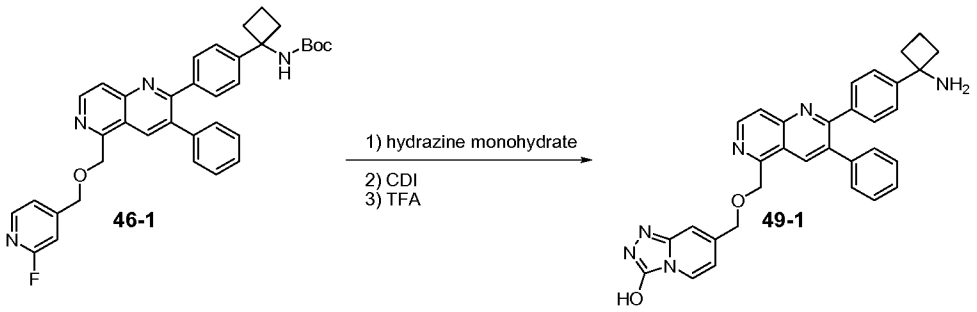
SCHEME 48




4-[({2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methoxy)methyl]pyridin-2(1H)-one (**48-1**)

A mixture of tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl) phenyl]cyclobutyl}carbamate (**46-1**) (20 mg) in pyridine (2 mL) and water (2 mL) was stirred at 70°C for overnight. The mixture was diluted with EtOAc, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by reverse phase HPLC to give 4-[({2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methoxy)methyl]pyridin-2(1H)-one (**48-1**) as colorless amorphous material. HRMS (M+H)+: observed = 489.2300, calculated = 489.2291

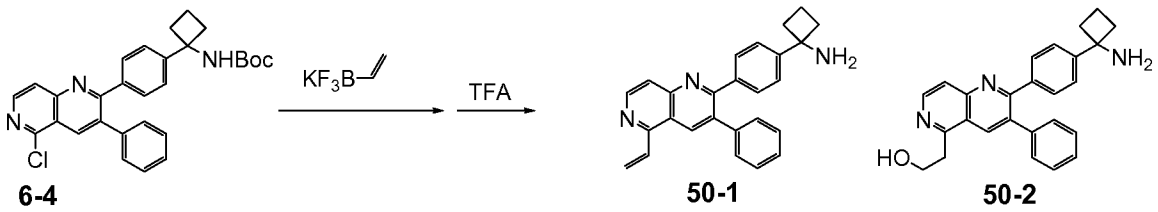
SCHEME 49




1-[4-(5-{[(3-hydroxy[1,2,4]triazolo[4,3-a]pyridin-7-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**49-1**)

A mixture of tert-butyl {1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl) phenyl]cyclobutyl}carbamate (**46-1**) (60 mg) and hydrazine monohydrate (50 uL) in 1,4-dioxane (1 ml) was stirred at 100°C for overnight. The reaction mixture was concentrated in vacuo. The residue was dissolved in THF (1 mL) and CDI (100 mg) was added. The mixture was stirred at 70°C for 4 h and then the reaction mixture was concentrated in vacuo. The residue was dissolved with TFA (0.10 mL) and stirred at rt for 1h. The reaction mixture was concentrated in vacuo and the residue was purified by reverse phase HPLC to give 1-[4-(5-{[(3-hydroxy[1,2,4]triazolo[4,3-a]pyridin-7-yl) methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanaminium trifluoroacetate (**49-1**) as a colorless amouphous material. MS (M+H)+: observed = 529.2, calculated = 529.2

SCHEME 50



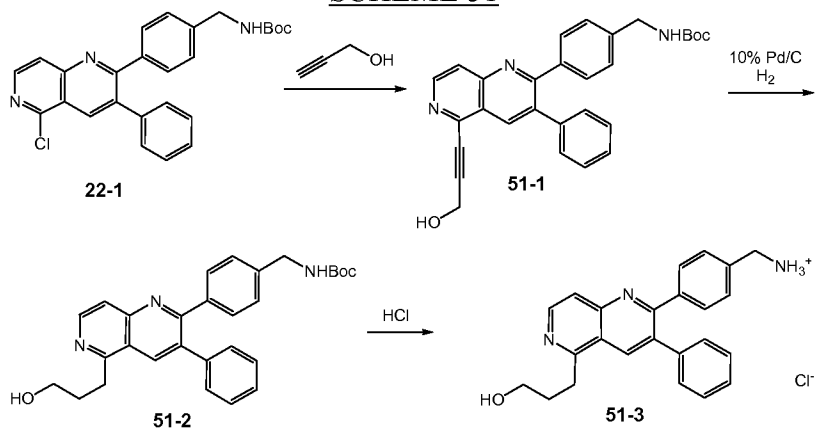

1-[4-(5-ethenyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**50-1**) and 2-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}ethanol (**50-2**)

A mixture of tert-butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**6-4**) (100 mg), $PdCl_2(dppf)$ (34 mg), triethylamine (34 uL) and potassium vinyltrifluorobrate (30 mg) in dioxane was stirred at 100°C for 6 h. The reaction mixture was diluted with EtOAc, filtered through a celite pad, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give a mixture of N-Boc protected (**50-1** and **50-2**). The mixture was dissolved with TFA (0.20 mL) and the mixture was stirred for 1h. The reaction mixture was dissolved with MeOH, neutralized with NaOH, extracted with EtOAc. The organic layer was washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 1-[4-(5-ethenyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**50-1**) and 2-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}ethanol (**50-2**) as colorless amorphous materials, respectively.

**50-1** HRMS (M+H)+: observed = 378.1953, calculated = 378.1970

**50-2** HRMS (M+H)+: observed = 396.2072, calculated = 396.2076

SCHEME 51




{4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-3**)

*tert*-butyl {4-[5-(3-hydroxyprop-1-yn-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**51-1**)

To a mixture of **22-1** (410 mg, 0.91 mmol), copper(I) iodide (24 mg, 0.13 mmol) and trans-bis(triphenylphosphine)palladium(II) chloride (10 mg, 0.014mmol) in DMF (10 mL) were added DIEA (0.57 mL, 4.1 mmol) and propargyl alcohol (0.085 mL, 1.4 mmol). The reaction mixture was stirred overnight at rt, then water was added and extracted with methylene chloride. Purified by silica gel chromatography (0-8% MeOH in DCM) to give the desired product as an orange solid. MS: 466.2 (M+1)

*tert*-butyl {4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**51-2**)

A suspension of **51-1** (372 mg, 0.8 mmol) and 10% palladium on carbon (50 mg, 0.05 mmol) was stirred in ethanol (30 mL), methanol (5 mL), and ethyl acetate (5 mL) under a balloon of hydrogen overnight. The reaction mixture was filtered through celite and concentrated to give the alcohol **51-2** as a foam. MS: 470.2 (M+1)

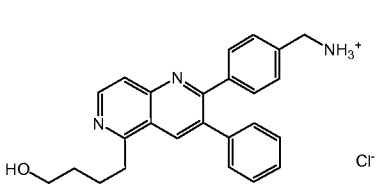
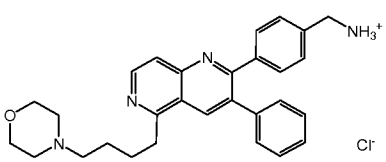
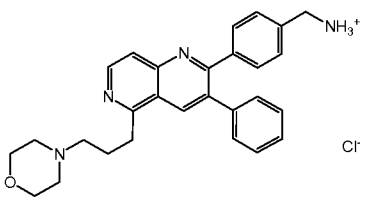
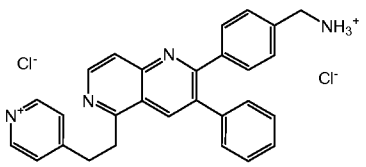
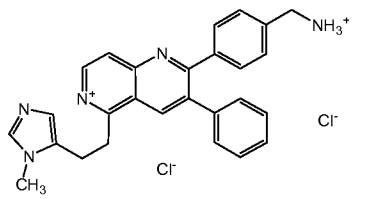
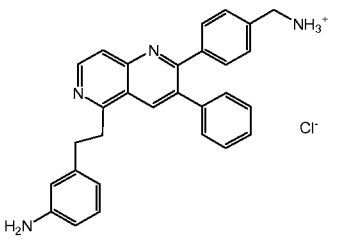
{4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-3**)

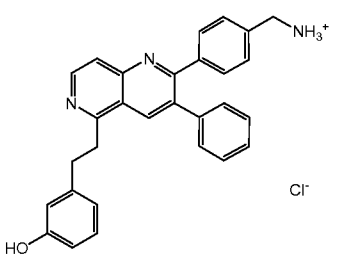
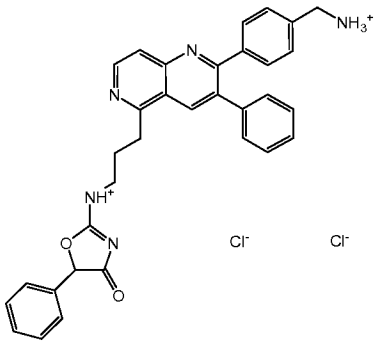
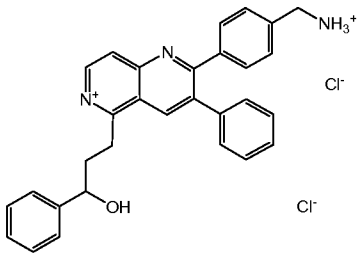
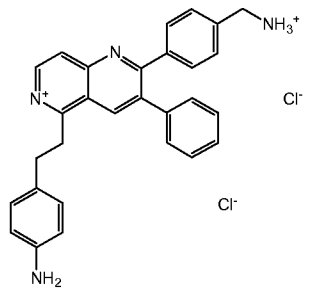
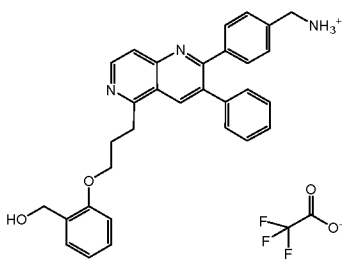
Procedure similar to that reported for 12-5 gave {4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**51-3**). MS: observed = 370.0, calculated = 370.5

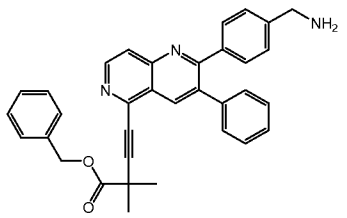
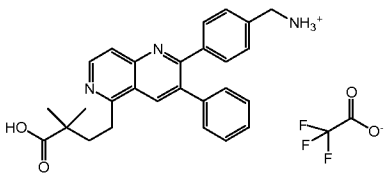
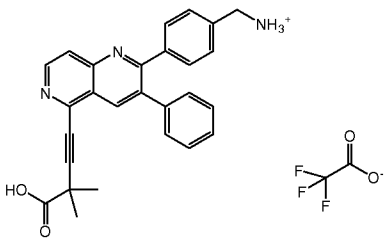
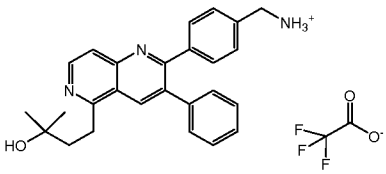
The compounds in Table 15 were prepared according to the Reaction Schemes and Scheme 51.

Table 15

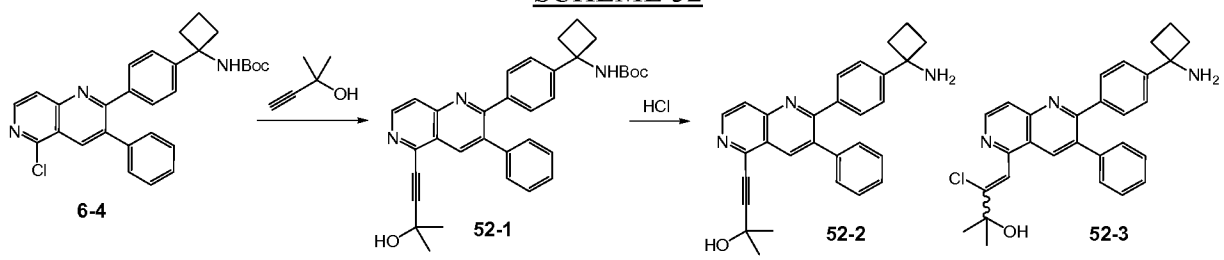
| Cmp | Structure | Name | MS m/z (M+H): | MS m/z (M+H): |
|---|---|---|---|---|

| | | | calc'd | observed |
|---|---|---|---|---|
| **51-4** |  | {4-[5-(4-hydroxybutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 384.5 | 384.1 |
| **51-5** |  | {4-[5-(4-morpholin-4-ylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 453.6 | 453.0 |
| **51-6** |  | {4-[5-(3-morpholin-4-ylpropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 439.6 | 439.0 |
| **51-7** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethyl)-1,6-naphthyridin-6-ium dichloride | 417.5 | 417.2 |
| **51-8** |  | 2-[4-(ammoniomethyl) phenyl]-5-[2-(1-methyl-1H-imidazol-5-yl)ethyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 420.5 | 420.2 |
| **51-9** |  | (4-{5-[2-(3-aminophenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl )methanaminium chloride | 431.6 | 431.2 |

| | | | | |
|---|---|---|---|---|
| **51-10** |  | (4-{5-[2-(3-hydroxyphenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride | 432.5 | 432.2 |
| **51-11** |  | N-(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}propyl)-4-oxo-5-phenyl-4,5-dihydro-1,3-oxazol-2-aminium dichloride | 528.6 | 528.2 |
| **51-12** |  | 2-[4-(ammoniomethyl) phenyl]-5-(3-hydroxy-3-phenylpropyl)-3-phenyl-1,6-naphthyridin-6-ium dichloride | 446.6 | 446.2 |
| **51-13** |  | 5-[2-(4-aminophenyl)ethyl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-6-ium dichloride | 431.6 | 431.2 |
| **51-14** |  | [4-(5-{3-[2-(hydroxymethyl) phenoxy]propyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium trifluoroacetate | 476.6 | 476.2 |

| | | | | |
|---|---|---|---|---|
| **51-15** |  | benzyl 4-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2,2-dimethylbut-3-ynoate | 512.2333 | 512.2337 |
| **51-16** |  | {4-[5-(3-carboxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 426.2176 | 426.2177 |
| **51-17** |  | {4-[5-(3-carboxy-3-methylbut-1-yn-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 422.1863 | 422.1865 |
| **51-18** |  | {4-[5-(3-hydroxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanaminium trifluoroacetate | 398.2227 | 398.2229 |

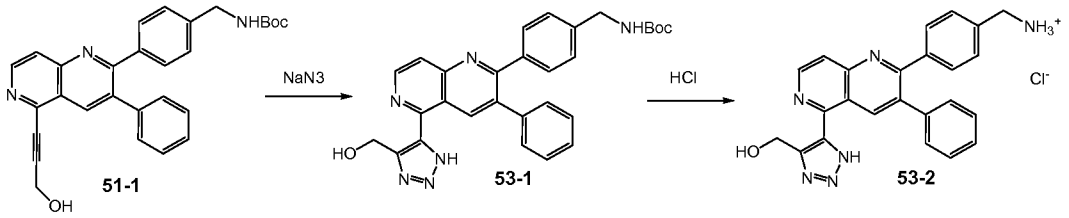
SCHEME 52




4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-methylbut-3-yn-2-ol (52-2) and 4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-3-chloro-2-methylbut-3-en-2-ol (**52-3**)

Procedure similar to that reported for Scheme **51** gave 4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-methylbut-3-yn-2-ol (**52-2**) and 4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-3-chloro-2-methylbut-3-en-2-ol (**52-3**) as colorless solids, respectively. **52-2**: HRMS (M+H)+: observed = 434.2220, calculated = 434.2232; **52-3**: HRMS (M+H)+: observed = 470.1996, calculated = 470.1999

SCHEME 53




(4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**53-2**)

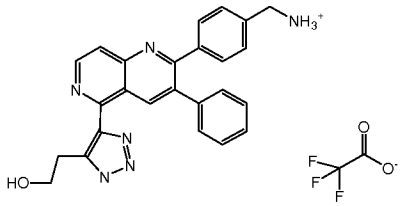
tert-butyl (4-{5-[4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}benzyl)carbamate (**53-1**)

A mixture of **51-1** (63 mg, 0.13 mmol) and sodium azide (52 mg, 0.84 mmol) in DMF (3 mL) were heated to 75°C for 15h. Water was added to the reaction mixture and extracted with ethyl acetate to give crude product, which was purified via silica chromatography (0-8%MeOH in MC over 17 min) to give the cyclized triazole as a brown oil. MS: 509.2 (M+1)

(4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**53-2**)

Procedure similar to that reported for **19-2** gave (4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**53-2**). MS (M+1): observed = 409.1, calculated = 409.5

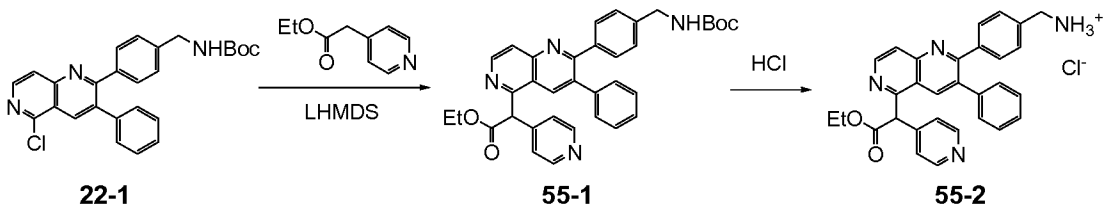
SCHEME 54




(4-{5-[5-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate (**54-1**)

Procedure similar to that reported for **53-2** gave (4-{5-[5-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate (**54-1**). MS (M+1): observed = 423.1, calculated = 422.5

SCHEME 55




{4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**55-2**)

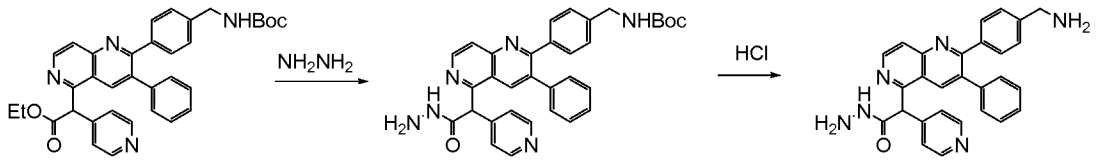
ethyl [2-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl](pyridin-4-yl)acetate (**55-1**)

A solution of ethyl pyridine-4-ylacetate (3.8 mL, 25 mmol) in THF (75 mL) was cooled to -78°C and was then treated with LiHMDS (25 mL, 25 mmol). This mixture was stirred at -78°C for 1 hour. The ice bath was removed and tert-butyl [4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate **22-1** (5.0 g, 11 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 20 hours. Another 1 equivalent of both ethyl pyridine-4-ylacetate and LiHMDS were added and stirred at room temperautre for 5 hours. The reaction was quenched with a saturated $NH_4Cl$ solution (30 mL). The solution was then concentrated in vacuo, treated with a saturated solution of $NaHCO_3$ and was then extracted with EtOAc. The combined organic layers were washed with water followed by brine then dried over $Na_2SO_4/MgSO_4$, filtered, and concentrated in vacuo. The oil was then taken up in DCM and was purified by silica gel chromatography (0-70% EtOAc in Hexane) to give desired product (**55-1**) as an orange solid. MS calculated M+H: 575.7; found 575.3

{4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**55-2**)

A solution of ethyl [2-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl](pyridin-4-yl)acetate (**55-1**) (20 mg, 0.035 mmol) in MeOH (1 mL) was treated with a saturated MeOH/HCl solution (1 mL) and was then heated at 80°C in the microwave for 5 minutes. Upon completion, the solvent was removed in vacuo. The residue was taken up in DMSO (1 mL) and was neutralized with 1N NaOH. The resulting solution was purified by reverse phase HPLC to give {4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**55-2**) as a dark pink residue. MS calculated M+H: 475.5; found 475.2

SCHEME 56




2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide (**56-2**)

tert-butyl {4-[5-(2-hydrazino-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**56-1**)

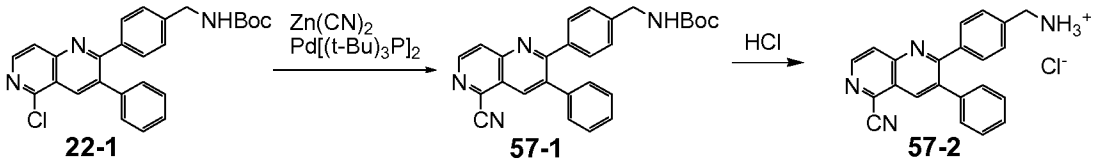
To a solution of [2-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-3-phenyl-1,6-naphthyridin-5-yl](pyridin-4-yl)acetate (**55-1**) (1.5 g, 2.6 mmol) in EtOH (8 mL) was added hydrazine (8.0 mL, 250 mmol). The solution was then stirred at room temperature for 25 minutes. The solvent was removed in vacuo and the residue was dried azeotropically with

toluene once. The solid was then dissolved in a small amount of $CHCl_3$ and was dried azeotropically with toluene. This was repeated a second time to give tert-butyl {4-[5-(2-hydrazino-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**56-1**) as yellow powder. MS calculated M+H: 561.6; found 561.1

2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide (**56-2**)

Procedure similar to that reported for **19-2** gave 2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide (**56-2**). MS calculated M+H: 461.5; found 461.3

SCHEME 57




[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**57-2**)

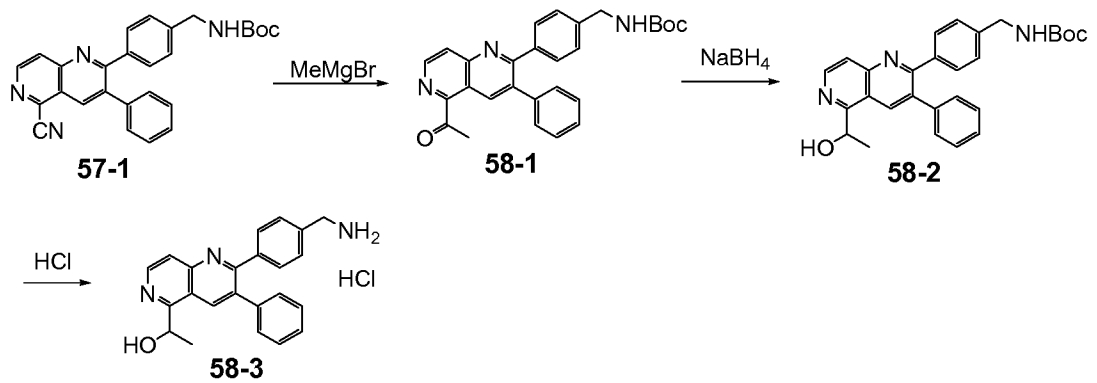
tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**57-1**)

Procedure similar to that reported for (**6-2**) using **22-1** gave tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**57-1**). MS (M+H)+: observed = 437.4, calculated = 437.5

[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**57-2**)

Procedure similar to that reported for **19-2** gave [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**57-2**) as a solid. HRMS (M+H)+: observed = 337.1545, calculated = 337.1448

SCHEME 58



{4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**58-3**)

tert-butyl [4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**58-1**)

To a stirred solution of tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**57-1**) (120 mg, 0.27 mmol) in anhydrous THF (2 mL), at -78°C (dry ice/ acetone bath) was added a 1.4 M solution (THF:toluene 25:75) of methylmagnesium bromide (0.50 mL, 0.70 mmol) while stirring under an atmosphere of nitrogen. After 20 minutes, the reaction mixture was permitted to warm to room temperature. After an additional 60 minutes, the reaction mixture was quenched by addition of a saturated solution of ammonium chloride (5 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 100% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl [4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**58-1**) as a tan solid. HRMS (M+H)+: observed = 454.2126, calculated = 454.2125

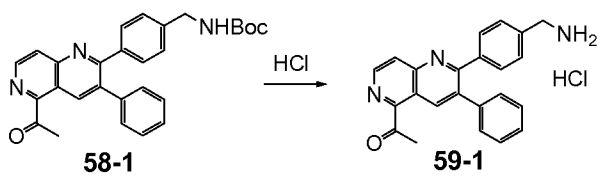
tert-butyl {4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl} carbamate (**58-2**)

Procedure similar to that for **39-2** gave tert-butyl {4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**58-2**) as a tan solid. HRMS (M+H)+: observed = 456.278, calculated = 456.2282

{4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**58-3**)

Procedure similar to that for **19-2** gave {4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**58-3**) as a green solid. HRMS (M+H)+: observed = 356.1758, calculated = 356.1758

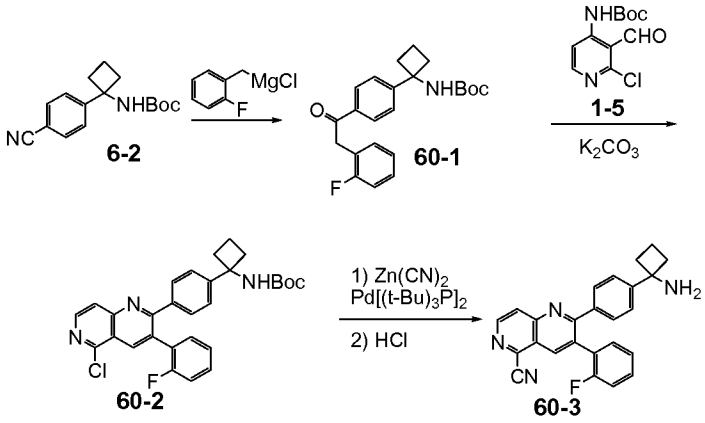
SCHEME 59




[4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**59-1**)

Procedure similar to that reported for **19-2** gave [4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride (**59-1**) as a yellow solid. HRMS (M+H)+: observed = 354.1607, calculated = 354.1601

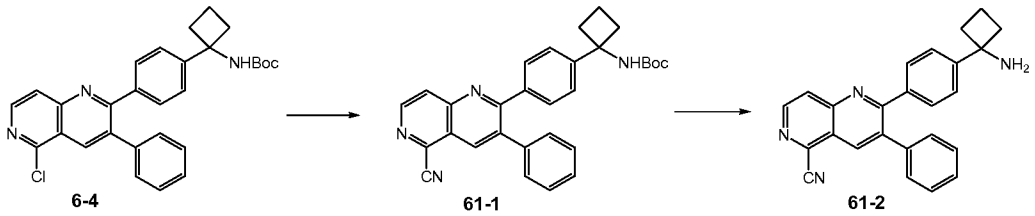
SCHEME 60




2-[4-(1-aminocyclobutyl)phenyl]-3-(2-fluorophenyl)-1,6-naphthyridine-5-carbonitrile (**60-3**)

Procedure similar to that reported for Scheme 6 and Scheme 57 gave 2-[4-(1-aminocyclobutyl)phenyl]-3-(2-fluorophenyl)-1,6-naphthyridine-5-carbonitrile (**60-3**). HRMS (M+H)+: observed = 395.1676, calculated = 395.1672

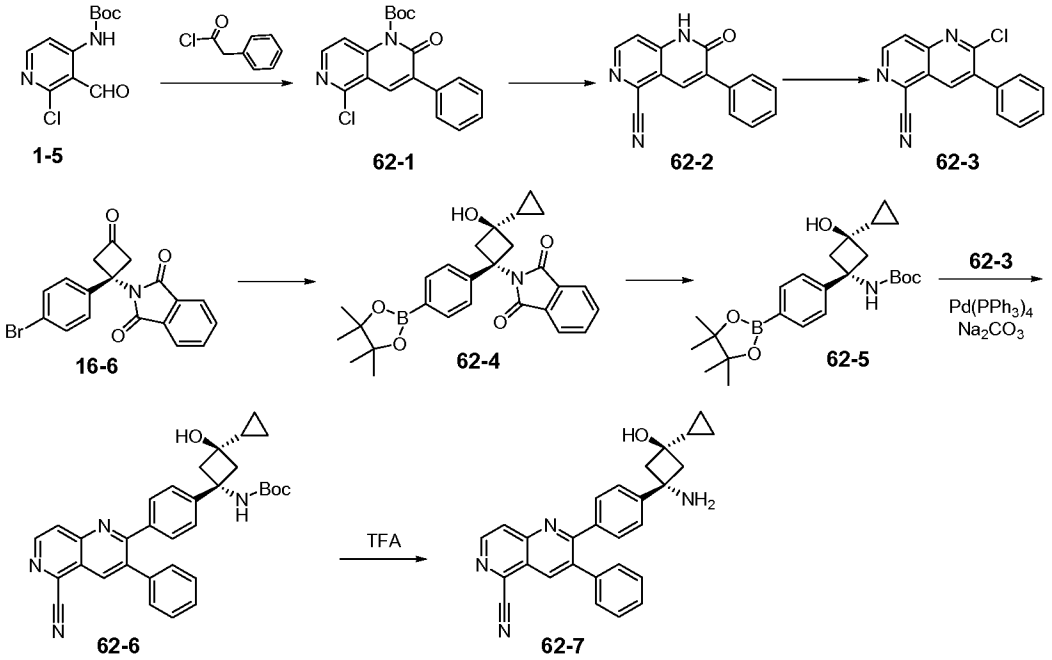
SCHEME 61




2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**61-2**)

Procedure similar to that reported for Scheme 6 and Scheme 57 using **6-4** gave 2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**61-2**). **61-1**: HRMS (M+H)+: observed = 502.1836, calculated = 502.1809; **61-2**: HRMS (M+H)+: observed = 377.1779, calculated = 377.1761

SCHEME 62




2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-7**)

tert-Butyl 5-chloro-2-oxo-3-phenyl-1,6-naphthyridine-1(2H)-carboxylate (**62-1**)

To a solution of tert-butyl (2-chloro-3-formyl-4-pyridinyl)carbamate (**1-5**) (10 g, 39 mmol) and DBU (12 mL, 78 mmol) in THF (130 mL) was added phenylacethyl chloride (5.7 mL, 43 mmol) at 0°C. The reaction was allowed to slowly warm to room temperature for overnight. The solvent was removed under reduced pressure, and the residue was diluted with EtOAc, washed with 1N HCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give tert-butyl 5-chloro-2-oxo-3-phenyl-1,6-naphthyridine-1(2H)-carbamate (**62-1**) as a colorless solid.

2-oxo-3-phenyl-1,2-dihydro-1,6-naphthyridine-5-carbonitrile (**62-2**)

A mixture of tert-butyl 5-chloro-3-phenyl-2-oxo-1,6-naphthyridine-1(2H)-carboxylate (**62-1**) (300 mg, 0.84 mmol), zinc cyanide (99 mg, 0.84 mmol), zinc (11 mg, 0.17 mmol) and palladium tetrakis(triphenylphosphine) (97 mg, 0.084 mmol) in 1,4-dioxane (5 mL) and DMF (2 ml) was stirred at 100°C for overnight. The resulting mixture was poured into water. The appeared precipitate was collected by filtration and dried in vacuo to give 2-oxo-3-phenyl-1,2-dihydro-1,6-naphthyridine-5-carbonitrile (**62-2**) as a pale brown solid.

2-chloro-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-3**)

2-oxo-3-phenyl-1,2-dihydro-1,6-naphthyridine-5-carbonitrile (**62-2**) (330 mg) in $POCl_3$ (5 mL) was stirred at 100°C for 3 h. Following evaporation, the residue was diluted with EtOAc, washed with aq. $NaHCO_3$ and water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-chloro-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-3**).

2-{trans-3-hydroxy-3-cyclopropyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**62-4**) and tert-butyl {trans-

3-cyclopropyl-3-hydroxy-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] cyclobutyl}carbamate (**62-5**)

Procedure similar to that for 2-{trans-3-hydroxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**16-6**) using cyclopropylmagnesium chloride gave 2-{trans-3-hydroxy-3-cyclopropyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}-1H-isoindole-1,3(2H)-dione (**62-4**) as a colorless solid. A mixture of **62-4** (288 mg) and hydrazine monohydrate (0.20 mL) in EtOH (5 mL) was stirred at 80°C for overnight. The resulting mixture was filtered and concentrated in vacuo. The residue was dissolved with MeOH (5 mL) and then added $BOC_2O$ (0.29 mL) and $Et_3N$ (0.21 mL). The mixture was stirred at 50 °C for overnight. The resulting mixture was diluted with EtOAc, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give tert-butyl {trans-3-cyclopropyl-3-hydroxy-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}carbamate (**62-5**) as a pale brown amorphous material.

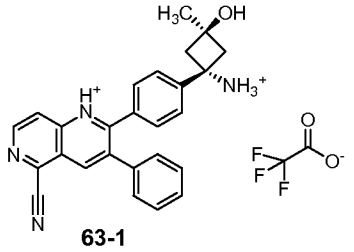
tert-butyl {trans-1-[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-3-cyclopropyl-3-hydroxycyclobutyl}carbamate (**62-6**)

A mixture of 2-chloro-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-3**) (44 mg), tert-butyl {trans-3-cyclopropyl-3-hydroxy-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}carbamate (**62-5**) (70 mg), $Pd(PPh_3)_4$ (35 mg) and 3 M $Na_2CO_3$ (0.15 mL) in 1,4-dioxane (1.5 mL) was heated under microwave irradiation at 140°C for 1 h. The reaction mixture was diluted with EtOAc, washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give tert-butyl {trans-1-[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-3-cyclopropyl-3-hydroxycyclobutyl} carbamate (**62-6**) as a colorless amorphous material.

2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-7**)

A mixture of {trans-1-[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-3-cyclopropyl-3-hydroxycyclobutyl}carbamate (**62-6**) (20 mg) in TFA (0.1 mL) was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with sat. sodium carbonate (aq) and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography to give 2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl) phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**62-7**) as a colorless solid. HRMS (M+H)+: observed = 433.2025, calculated = 433.2028

SCHEME 63

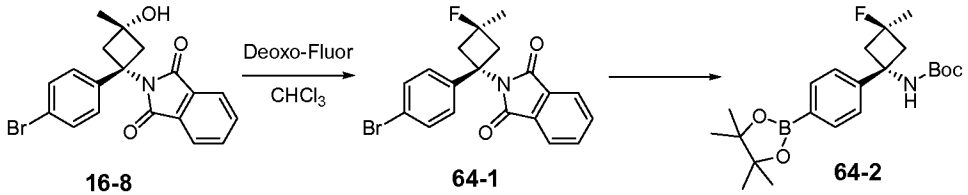


63-1

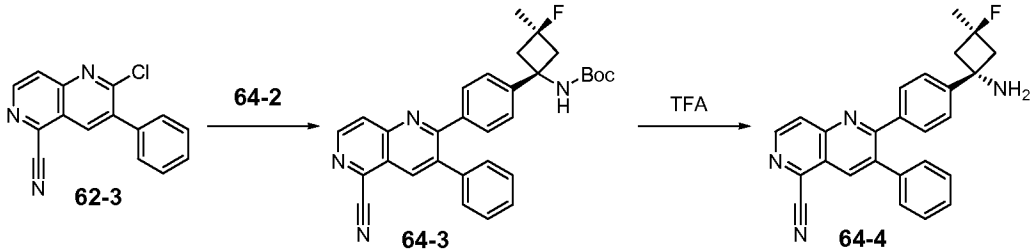
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**63-1**)

Procedure similar to that reported for Scheme 62 gave 2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**63-1**). HRMS (M+H)+: observed = 407.1863, calculated = 407.1872

SCHEME 64



16-8 64-1 64-2



62-3 64-3 64-4

2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**64-4**)

2-[trans-1-(4-bromophenyl)-3-fluoro-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**64-1**)

To a solution of 2-[cis-1-(4-bromophenyl)-3-hydroxy-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**16-8**) (360 mg) in $CHCl_3$ (10 mL) was added Deoxo-Fluor (0.375 mL) dropwise and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with $CHCl_3$, washed with water, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 2-[trans-1-(4-bromophenyl)-3-fluoro-3-methylcyclobutyl]-1H-isoindole-1,3(2H)-dione (**64-1**) as a colorless solid.

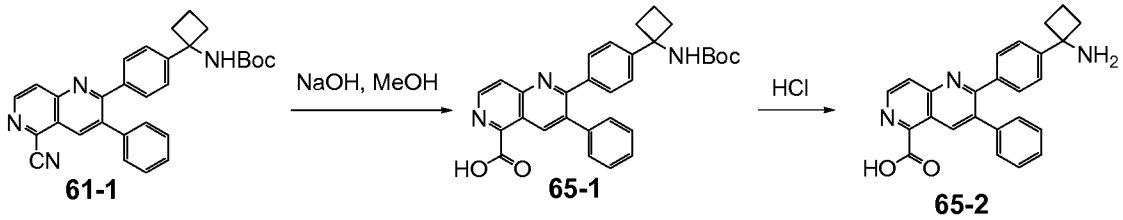
tert-butyl {trans-3-fluoro-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}carbamate (**64-2**)

Procedure similar to that reported for **62-5** using **62-1** gave tert-butyl {trans-3-fluoro-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl} carbamate (**64-3**) as a colorless solid.

2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**64-4**)

Procedure similar to that reported for Scheme 62 using **62-3** and **64-2** gave 2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile (**64-4**) as a colorless solid. HRMS (M+H)+: observed = 409.1827, calculated = 409.1829

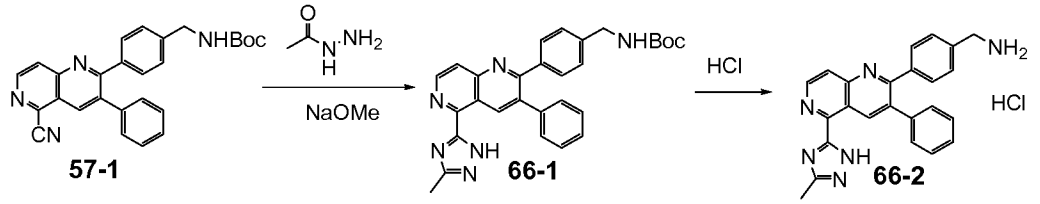
SCHEME 65




1-[4-(5-carboxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**65-2**)

Procedure similar to that reported for **80-1** using **61-1** gave 1-[4-(5-carboxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine (**65-2**) as a colorless solid. HRMS (M+H)+: observed = 396.1715, calculated = 396.1712

SCHEME 66




{4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-2**)

tert-butyl {4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**66-1**)

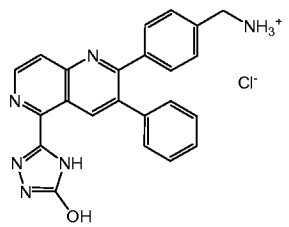
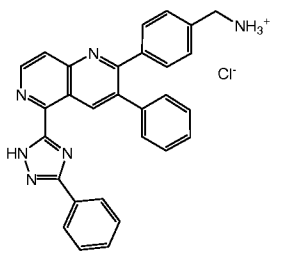
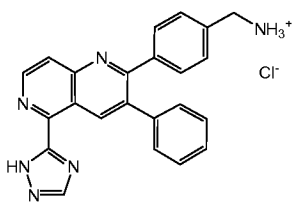
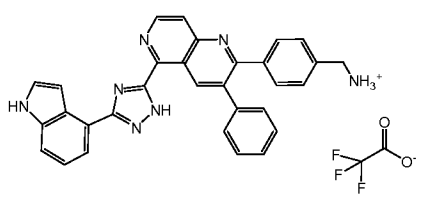
To a vial was added tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**57-1**) (38 mg, 0.087 mmol), 30% by weight solution of sodium methoxide in methanol (0.001 mg, 0.026 mmol), and n-BuOH (0.4 mL). The reaction mixture was then capped and heated to 70°C for 30 minutes. Then added acetohydrazide (19 mg, 0.26 mmol) and the reaction mixture was heated to 90°C for 3 days. The crude reaction mixture was then diluted with MeOH/NMP & purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl {4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**66-1**). HRMS (M+H)+: observed = 493.2326, calculated = 493.2347

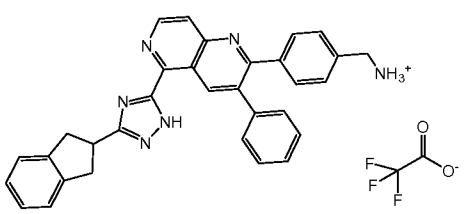
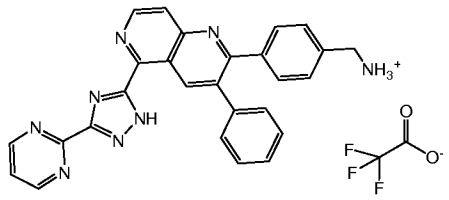
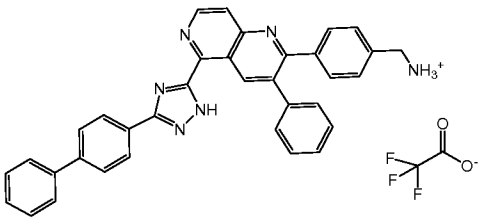
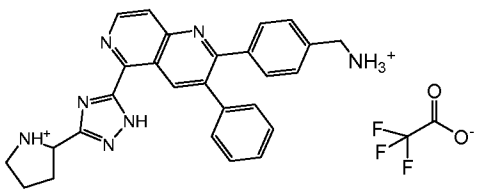
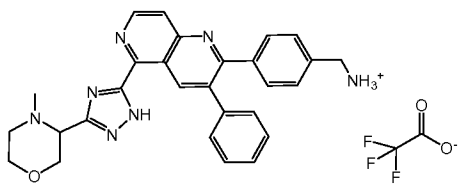
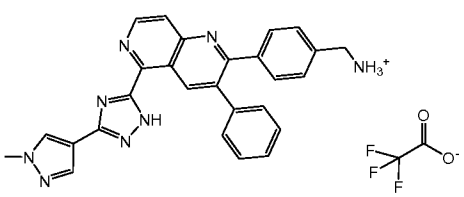
{4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-2**)

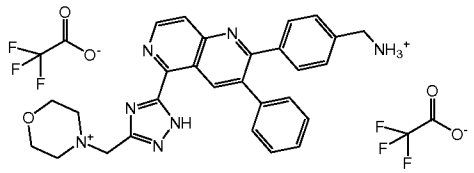
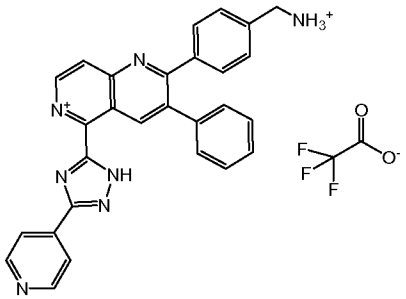
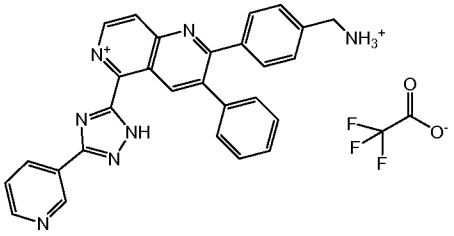
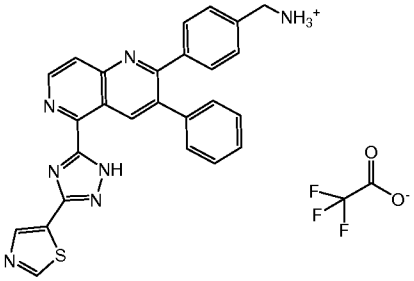
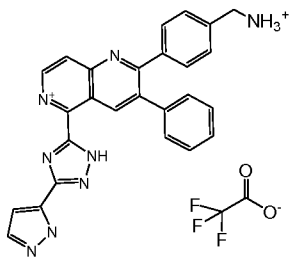
Procedure similar to that reported for **19-2** gave {4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**66-2**) as a tan solid. HRMS (M+H)+: observed = 393.1813, calculated = 393.1822

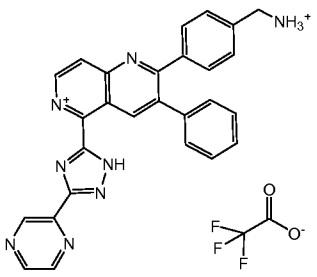
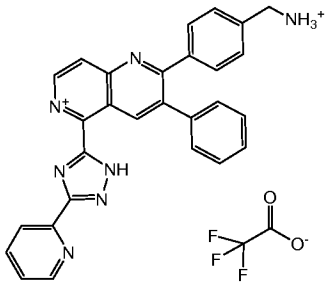
The compounds in Table 16 were prepared according to the Reaction Schemes and Scheme 66.

Table 16

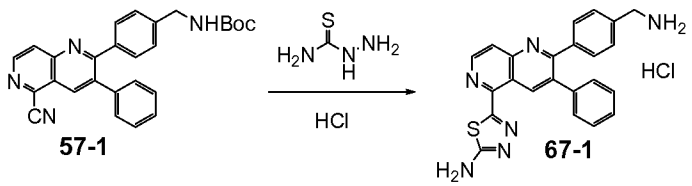
| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **66-3** |  | {4-[5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 395.1615 | 395.1609 |
| **66-4** |  | {4-[3-phenyl-5-(3-phenyl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 455.1979 | 455.1993 |
| **66-5** |  | {4-[3-phenyl-5-(1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride | 379.1666 | 379.1676 |
| **66-6** |  | (4-{5-[3-(1H-indol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate | 493.6 | 493.9 |

| | | | | |
|---|---|---|---|---|
| **66-7** |  | (4-{5-[3-(2,3-dihydro-1H-inden-2-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate | 495.2292 | 495.2313 |
| **66-8** |  | {4-[3-phenyl-5-(3-pyrimidin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 457.1884 | 457.1892 |
| **66-9** |  | {4-[5-(3-biphenyl-4-yl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium trifluoroacetate | 531.2292 | 531.2304 |
| **66-10** |  | 2-(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)pyrrolidinium bis(trifluoroacetate) | 448.2244 | 448.2251 |
| **66-11** |  | (4-{5-[3-(4-methylmorpholin-3-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium trifluoroacetate | 478.2350 | 478.2359 |
| **66-12** |  | (4-{5-[3-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate | 459.2040 | 459.2053 |

| | | | | |
|---|---|---|---|---|
| **66-13** |  | 4-[(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)methyl]morpholin-4-ium bis(trifluoroacetate) | 478.2350 | 478.2359 |
| **66-14** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-4-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 456.1931 | 456.1939 |
| **66-15** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-3-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 456.1931 | 456.1940 |
| **66-16** |  | (4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl)methanaminium trifluoroacetate | 462.1496 | 462.1505 |
| **66-17** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[3-(1H-pyrazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 445.1884 | 445.1871 |

| | | | | |
|---|---|---|---|---|
| **66-18** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 457.1884 | 457.1867 |
| **66-19** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 456.1931 | 456.1919 |

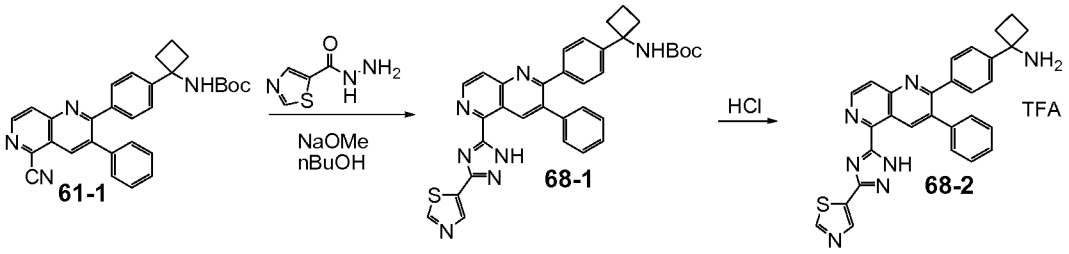
SCHEME 67




{4-[5-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl} methanaminium chloride (**67-1**)

To a vial was added tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**57-1**) (90 mg, 0.21 mmol), hydrazinecarbothioamide (38 mg, 0.41 mmol), and finally TFA (0.60 mL, 7.8 mmol). The reaction mixture was then capped and permitted to stir overnight at 60°C on a hot plate. The crude reaction mixture was then diluted with MeOH/NMP and purified directly (without work up) by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 50% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then concentratd in vacuo, then dissolved in MeOH/DCM, added a 4M solution of HCl in EtOAc (5 mL, 20 mmol) and concentrated to give {4-[5-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium chloride (**67-1**) as a yellow solid. HRMS (M+H)+: observed = 411.1390, calculated = 411.1387

SCHEME 68

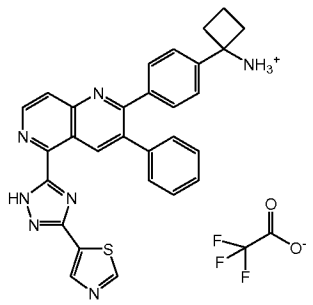
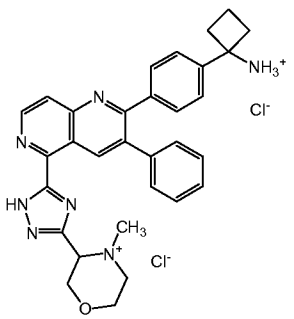



1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl)cyclobutanaminium trifluoroacetate (**68-2**)

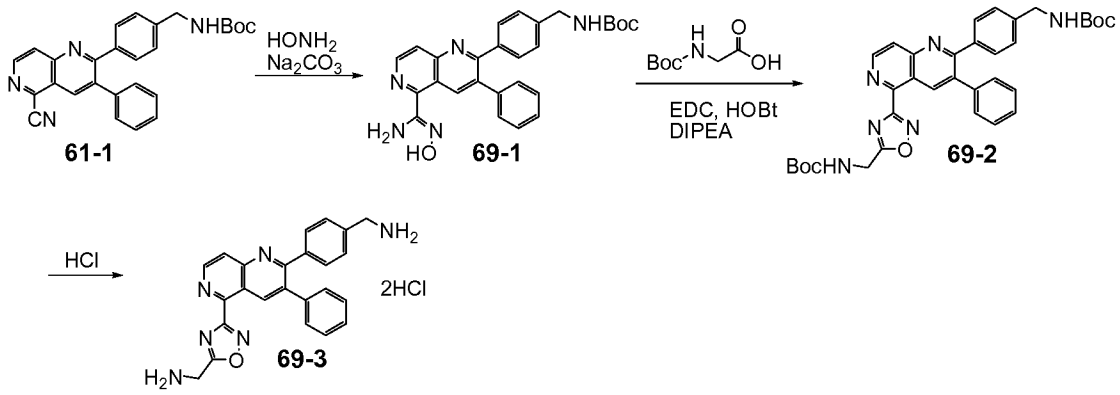
Procedures similar to that reported for Scheme 67 gave 1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanaminium trifluoroacetate (**68-2**) as a tan solid. HRMS (M+H)+: observed = 502.1836, calculated = 502.1809

The compounds in Table 17 were prepared according to the Reaction Schemes and Scheme 68.

Table 17

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **68-3** |  | 1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl)cyclobutanaminium trifluoroacetate | 502.1809 | 502.1836 |
| **68-4** |  | 3-(5-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)-4-methylmorpholin-4-ium dichloride | 518.2663 | 518.2712 |

SCHEME 69




1-(4-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**69-3**)

tert-butyl (4-{5-[(Z)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}benzyl)carbamate (**69-1**)

To a solution of tert-butyl [4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**41-1**) (2.0 g, 4.6 mmol) in ethanol (500 mL) and water (25 mL) was added sodium acetate (1.5 g, 14 mmol), and finally hydroxyl amine hydrochloride (1.0 g, 14 mmol). The reaction mixture was then heated to 90°C with a water cooled reflux condenser attached under an atmosphere of nitrogen while stirring. After 30 minutes, the crude reaction mixture was permitted to cool to room temperature, then suspended in ethyl acetate and washed with water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl (4-{5-[(Z)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}benzyl) carbamate (**69-1**) as a yellow solid. MS (M+H)+: observed = 470.2 , calculated = 470.6

tert-butyl {4-[5-(5-{[(tert-butoxycarbonyl)amino]methyl}-1,2,4-oxadiazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**69-2**)

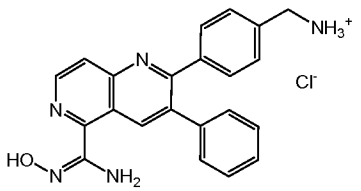
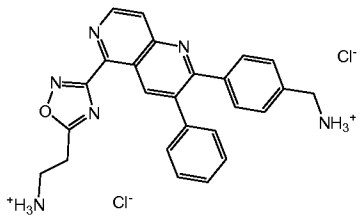
To a microwave vial was added tert-butyl (4-{5-[(Z)-amino(hydroxyimino) methyl]-3-phenyl-1,6-naphthyridin-2-yl}benzyl) carbamate (**69-1**), EDC, HOBt, DMF, DIPEA and Boc-glycine. The reaction mixture was then heated to 60°C for 5 minutes under microwave irradiation. The crude reaction mixture was then diluted with MeOH/NMP and purified by reverse phase chromatography (Waters Sunfire MSC18, 5% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl {4-[5-(5-{[(tert-butoxycarbonyl)amino]methyl}-1,2,4-oxadiazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl} carbamate (**69-2**) as a tan solid. HRMS (M+H)+: observed = 609.2867 , calculated = 609.2820

1-(4-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**69-3**)

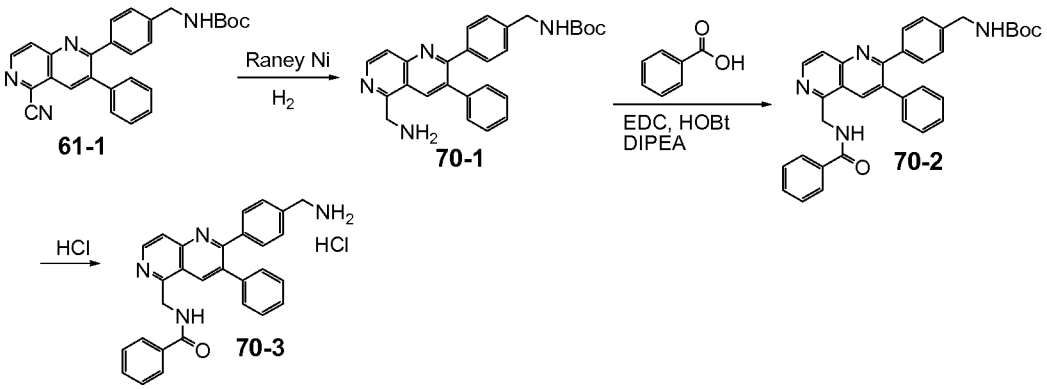
Procedure similar to that reported for **19-2** gave 1-(4-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine (**69-3**) as a tan solid. HRMS (M+H)+: observed = 409.1802 , calculated = 409.1772

The compound in Table 18 was prepared according to the Reaction Schemes and Scheme 69.

Table 18

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **69-4** |  | (4-{5-[(E)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 370.1663 | 370.1668 |
| **69-5** |  | 2-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1,2,4-oxadiazol-5-yl)ethanaminium dichloride | 423.1928 | 423.1953 |

SCHEME 70




(4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**70-3**)

tert-butyl {4-[5-(aminomethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**70-1**)

Procedure similar to that reported for **13-5** gave tert-butyl {4-[5-(aminomethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**70-1**) as a tan solid. MS (M+H)+: observed = 441.3 , calculated = 441.6

tert-butyl {4-[5-(aminomethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**70-2**)

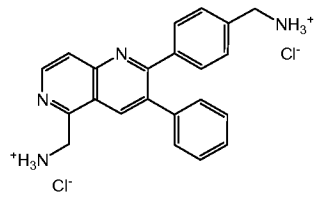
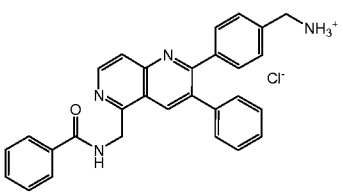
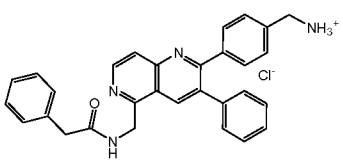
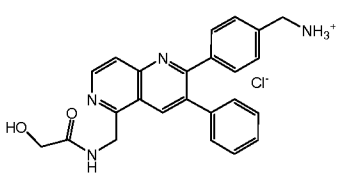
Procedure similar to that reported for **69-2** gave tert-butyl {4-[5-(aminomethyl)-3-phenyl-1,6-naphthyridin-2-yl]benzyl}carbamate (**70-2**). MS (M+H)+: observed = 545.3, calculated = 545.7

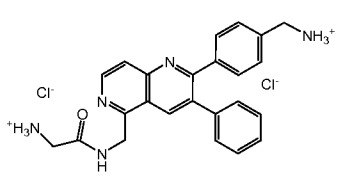
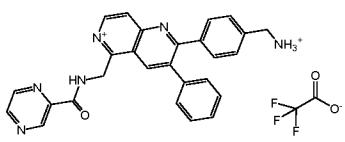
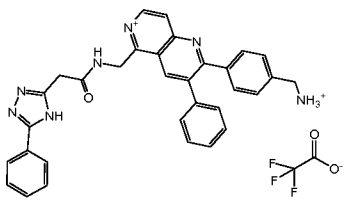
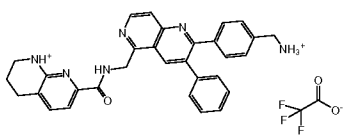
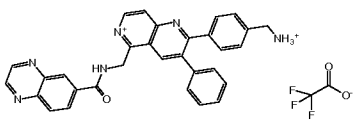
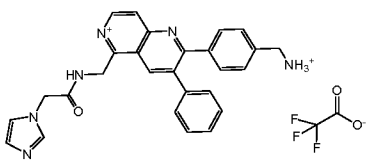
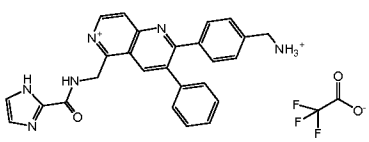
(4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanaminium chloride (**70-3**)

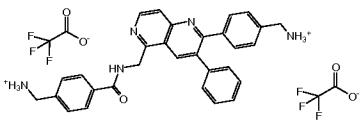
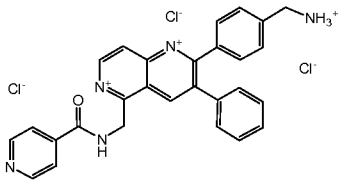
Procedure similar to that reported for **19-2** gave (4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride (**70-3**) as a green solid. HRMS (M+H)+: observed = 445.2046 , calculated = 445.2023

The compounds in Table 19 were prepared according to the Reaction Schemes and Scheme 70.

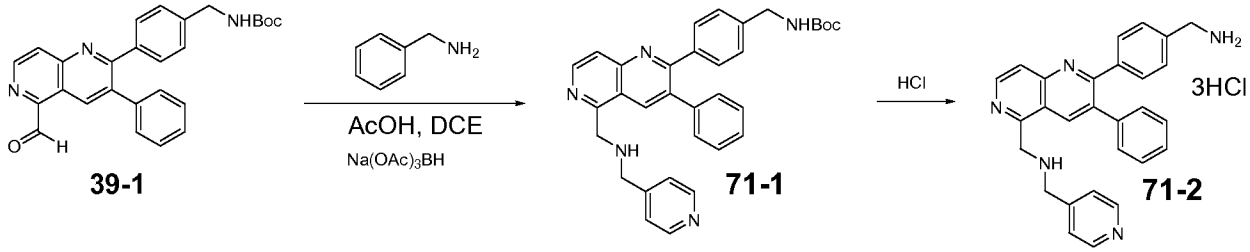
Table 19

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **70-4** |  | {4-[5-(ammoniomethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium dichloride | 341.1761 | 341.1757 |
| **70-5** |  | (4-{5-[(benzoylamino) methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 445.2023 | 445.2046 |
| **70-6** |  | [4-(3-phenyl-5-{[(phenylacetyl )amino]methyl}-1,6-naphthyridin-2-yl)phenyl]methanaminium chloride | 459.2180 | 459.2200 |
| **70-7** |  | (4-{5-[(glycoloylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanaminium chloride | 399.1816 | 399.1831 |

| | | | | |
|---|---|---|---|---|
| **70-8** |  | 2-[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)amino]-2-oxoethanaminium dichloride | 398.1976 | 398.1987 |
| **70-9** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(pyrazin-2-ylcarbonyl)amino]methyl}-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 447.5 | 447.0 |
| **70-10** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-({[(5-phenyl-4H-1,2,4-triazol-3-yl)acetyl]amino}methyl)-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 526.2350 | 526.2334 |
| **70-11** |  | 7-{[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) amino]carbonyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-1-ium bis(trifluoroacetate) | 501.2398 | 501.2384 |
| **70-12** |  | 2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(quinoxalin-6-ylcarbonyl)amino]methyl}-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 497.2085 | 497.2066 |
| **70-13** |  | 2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-1-ylacetyl)amino]methyl}-3-phenyl-1,6-naphthyridin-6-ium bis(trifluoroacetate) | 449.2085 | 449.2074 |
| **70-14** |  | 2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-2-ylcarbonyl)amino]methyl}-3-phenyl-1,6-naphthyridin-6-ium | 435.1928 | 435.1916 |

| | | | | |
|---|---|---|---|---|
| | | bis(trifluoroacetate) | | |
| **70-15** |  | {4-[5-({[4-(ammoniomethyl) benzoyl]amino}methyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanaminium bis(trifluoroacetate) | 474.2 | 474.0 |
| **70-16** |  | 2-[4-(ammoniomethyl) phenyl]-5-[(isonicotinoylamino)methyl]-3-phenyl-1,6-naphthyridinediium trichloride | 446.1976 | 446.1970 |

SCHEME 71




4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl}pyridinium trichloride (**71-2**)

tert-butyl [4-(3-phenyl-5-{[(pyridin-4-ylmethyl)amino]methyl}-1,6-naphthyridin-2-yl)benzyl]carbamate (**71-1**)

To a solution of tert-butyl [4-(5-formyl-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**39-1**) (100 mg, 0.23 mmol) and 1-phenylmethanamine (0.025 mL, 0.25 mmol) in anhydrous DCE (1 mL) was added acetic acid (0.026 mL, 0.46 mmol). The reaction mixture was permitted to stir for 30 minutes at room temperature (capped, but not under an atmosphere of nitrogen), then added sodium triacetoxyborohydride (48 mg, 0.23 mmol). After 4 hours the crude reaction mixture was then quenched by transferring into a saturated solution of sodium bicarbonate in water (20 mL), then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was then purified by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 100% acetonitrile / 0.1% trifluoroacetic acid / water). Desired fractions were then suspended in ethyl acetate and washed with a saturated solution of sodium bicarbonate, followed by water, then brine, dried over sodium sulfate, filtered, and concentrated to give tert-butyl [4-(3-phenyl-5-

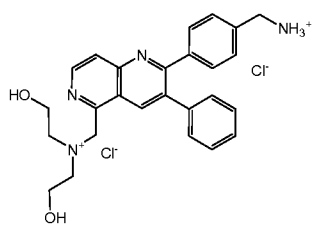
{[(pyridin-4-ylmethyl)amino]methyl}-1,6-naphthyridin-2-yl)benzyl]carbamate (**71-1**) as a solid. MS (M+H)+: observed = 532.3, calculated = 532.7

4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl}pyridinium trichloride (**71-2**)

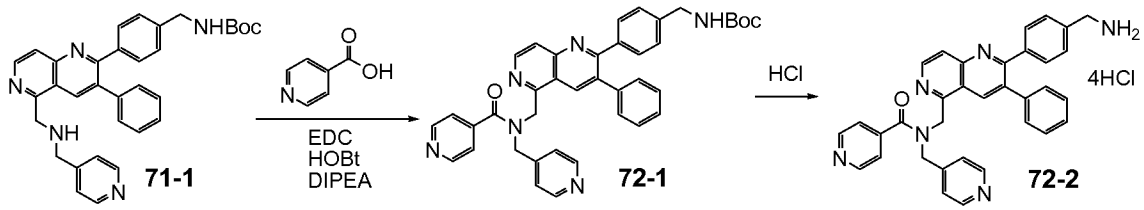
Procedure similar to that reported for **19-2** gave 4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl}pyridinium trichloride (**71-2**) as a green solid. HRMS (M+H)+: observed = 432.2176, calculated = 432.2183

The compound in Table 20 was prepared according to the Reaction Schemes and Scheme 77.

Table 20

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **71-3** |  | N-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)-2-hydroxy-N-(2-hydroxyethyl)ethanaminium dichloride | 429.2278 | 429.2285 |

SCHEME 72




2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[(pyridinium-4-ylcarbonyl)(pyridinium-4-ylmethyl)amino]methyl}-1,6-naphthyridin-6-ium tetrachloride (**72-2**)

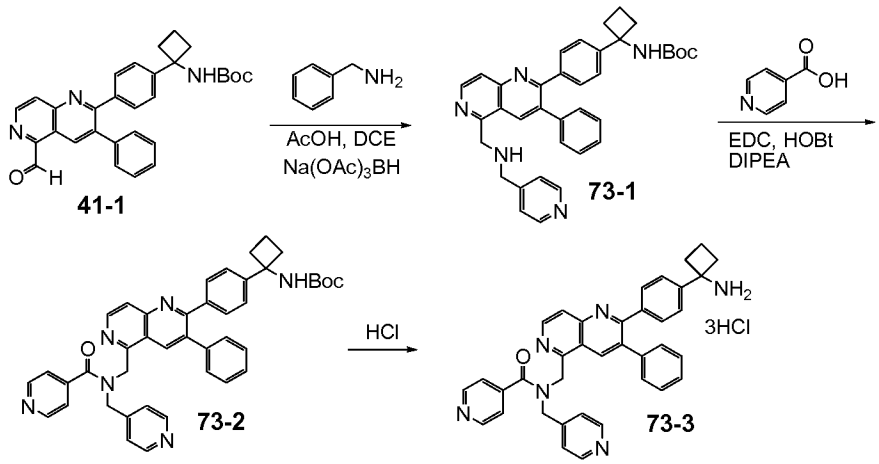
tert-butyl [4-(5-{[isonicotinoyl(pyridin-4-ylmethyl)amino]methyl}-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**72-1**)

Procedure similar to that reported for **69-2** gave tert-butyl [4-(5-{[isonicotinoyl(pyridin-4-ylmethyl)amino]methyl}-3-phenyl-1,6-naphthyridin-2-yl)benzyl]carbamate (**72-1**) as a solid. MS (M+H)+: observed = 637.4, calculated = 637.7

2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[(pyridinium-4-ylcarbonyl) (pyridinium-4-ylmethyl)amino]methyl}-1,6-naphthyridin-6-ium tetrachloride (**72-2**)

Procedure similar to that reported for **19-2** gave 2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[(pyridinium-4-ylcarbonyl)(pyridinium-4-ylmethyl)amino]methyl}-1,6-naphthyridin-6-ium tetrachloride (**72-2**) as an orange solid. HRMS (M+H)+: observed = 537.2388, calculated = 537.2398

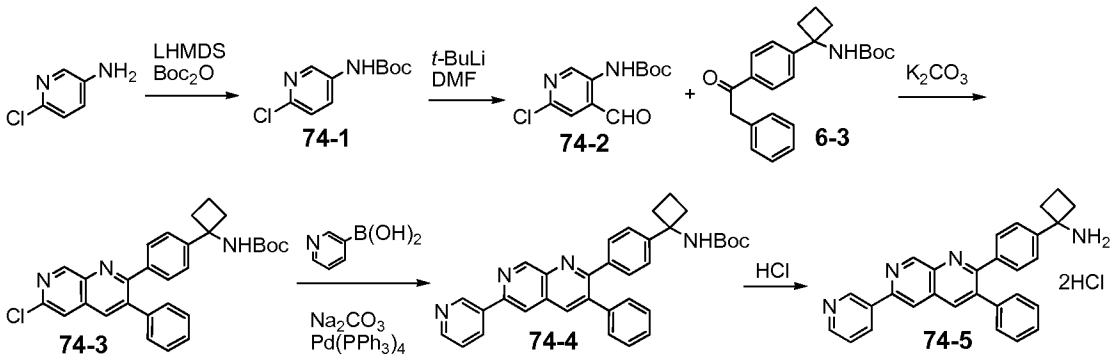
SCHEME 73




2-[4-(1-ammoniocyclobutyl)phenyl]-5-{[isonicotinoyl(pyridin-4-ylmethyl) amino]methyl}-3-phenyl-1,6-naphthyridinediium trichloride (**73-3**)

Procedures similar to that reported for Scheme 71 and Scheme 72 gave 2-[4-(1-ammoniocyclobutyl)phenyl]-5-{[isonicotinoyl(pyridin-4-ylmethyl)amino]methyl}-3-phenyl-1,6-naphthyridinediium trichloride (**73-3**) as a red solid. HRMS (M+H)+: observed = 577.2741, calculated = 577.2711

SCHEME 74




2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridin-1-ium dichloride (**74-5**)

1,1-dimethylethyl (6-chloro-3-pyridinyl)carbamate (**74-1**)

A stirred solution of 6-chloro-3-pyridinamine (5.0 g, 39 mmol) and BOC-Anhydride (9.0 mL, 39 mmol) in dry THF (200 mL) was cooled to -10°C. LHMDS (82 mL, 82 mmol) was added slowly trying to keep the reaction below 0°C. Reaction was complete within 5 minutes after addition. After quenching with aq. NH4Cl solution, most of the THF was removed

under reduced pressure. The mixture was diluted with EtOAc and washed with brine. The organic layer dried with $Na_2SO_4/MgSO_4$, filtered and then concentrated in vacuo. The crude residue was taken up in dichloromethane and was purified by silica gel chromatography (30% EtOAc in hexane) to yield 1,1-dimethylethyl (6-chloro-3-pyridinyl)carbamate (**74-1**). MS(M+1): observed = 229.0, calculated = 228.7

1,1-dimethylethyl (6-chloro-4-formyl-3-pyridinyl)carbamate (**74-2**)

Procedure similar to that reported for **1-5** gave 1,1-dimethylethyl (6-chloro-4-formyl-3-pyridinyl)carbamate (**74-2**). MS(M+1): observed = 257.0, calculated = 256.7

1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,7-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**74-3**)

Procedure similar to that reported for **6-4** gave 1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,7-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**74-3**). MS(M+1): observed = 486.0, calculated = 486.0

1,1-dimethylethyl(1-{4-[3-phenyl-6-(3-pyridinyl)-1,7-naphthyridin-2-yl]phenyl}cyclobutyl)carbamate (**74-4**)

1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,7-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**74-3**) (50 mg, 0.10 mmol), (14 mg, 0.11 mmol), PalladiumTetrakis (12 mg, 10 μmol), and $Na_2CO_3$ (22 mg, 0.21 mmol) were suspended in degassed 1,4-Dioxane (0.77 mL) and water (0.26 mL). The solution was flushed with nitrogen for 5 minutes. The reaction was heated to 120°C for 15 minutes in a microwave reactor. Upon cooling, the reaction was diluted with EtOAc, washed with water, followed by brine. The organic layer was separated, dried with Na2SO4/MgSO4, filtered then concentrated in vacuo. The crude residue was taken up in dichloromethane and purified by silica gel chromatography (70% EtOAc in hexane) to yield 1,1-dimethylethyl(1-{4-[3-phenyl-6-(3-pyridinyl)-1,7-naphthyridin-2-yl]phenyl}cyclobutyl) carbamate (**74-4**). MS(M+1): observed = 529.1, calculated = 528.7

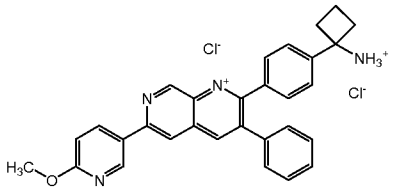
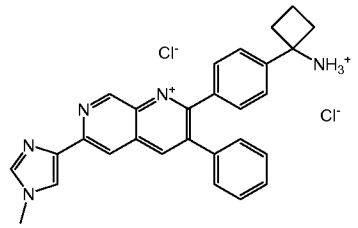
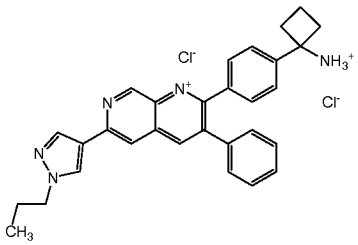
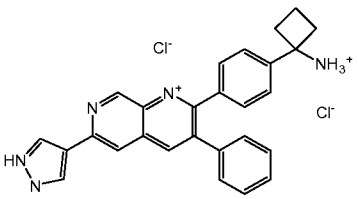
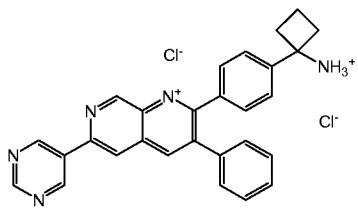
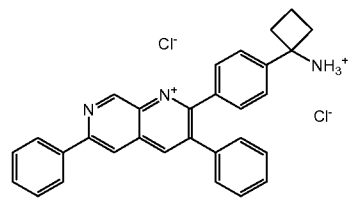
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridin-1-ium dichloride (**74-5**)

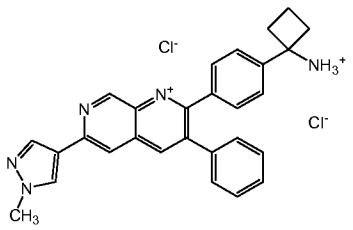
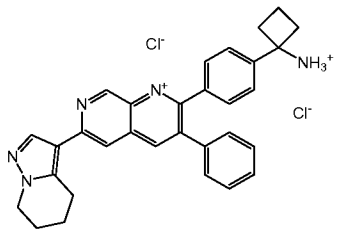
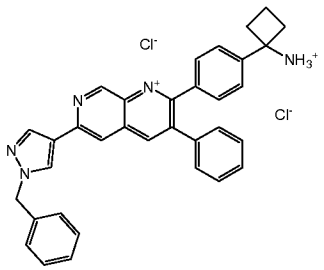
HCl gas was bubbled through 1mL of methanol for 5 minutes. To this was added 1,1-dimethylethyl(1-{4-[3-phenyl-6-(3-pyridinyl)-1,7-naphthyridin-2-yl]phenyl} cyclobutyl) carbamate (**74-4**) (50 mg, 0.09 mmol) as a solution in methanol (1 mL). The solution was heated to 80°C in a microwave reactor for 5 minutes. The solvent was removed in vacuo to yield 2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridin-1-ium dichloride (**74-5**). MS(M+1): observed = 429.1, calculated = 428.2

The compounds in Table 21 were prepared according to the Reaction Schemes and Scheme 50.

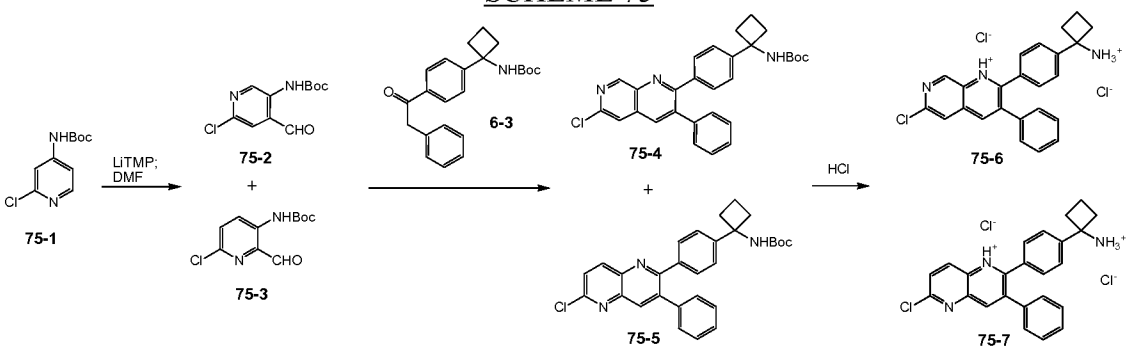
Table 21

| Cmp | Structure | Name | MS m/z | MS m/z |
|---|---|---|---|---|

| | | | (M+H): calc'd | (M+H): observed |
|---|---|---|---|---|
| **74-6** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-6-(6-methoxypyridin-3-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride | 459.6 | 459.1 |
| **74-7** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-imidazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride | 432.5 | 432.1 |
| **74-8** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1-propyl-1H-pyrazol-4-yl)-1,7-naphthyridin-1-ium dichloride | 460.6 | 460.1 |
| **74-9** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1H-pyrazol-4-yl)-1,7-naphthyridin-1-ium dichloride | 418.5 | 418.1 |
| **74-10** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-pyrimidin-5-yl-1,7-naphthyridin-1-ium dichloride | 430.5 | 430.19 |
| **74-11** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-3,6-diphenyl-1,7-naphthyridin-1-ium dichloride | 428.5 | 428.1 |

| | | | | |
|---|---|---|---|---|
| **74-12** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride | 432.5 | 432.1 |
| **74-13** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-1,7-naphthyridin-1-ium dichloride | 472.6 | 472.1 |
| **74-14** |  | 2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-benzyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridin-1-ium dichloride | 508.6 | 508.1 |

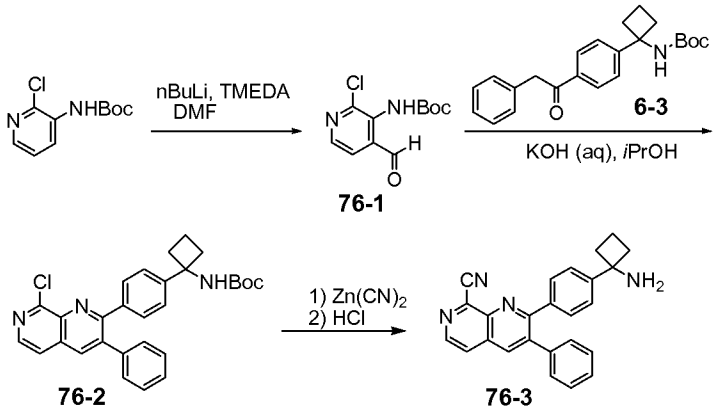
SCHEME 75




2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,7-naphthyridin-7-ium dichloride (**75-6**) and 2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,5-naphthyridin-1-ium dichloride (**75-7**)

Procedures similar to that reported for Scheme 74 gave 2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,7-naphthyridin-7-ium dichloride (**75-6**) and 2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,5-naphthyridin-1-ium dichloride (**75-7**) as colorless solids, respectively. **75-**6: HRMS (M+H)+: observed = 386.1425, calculated = 386.1424; **75-7**: HRMS (M+H)+: observed = 386.1426, calculated = 386.1424

SCHEME 76




2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile (**76-3**)

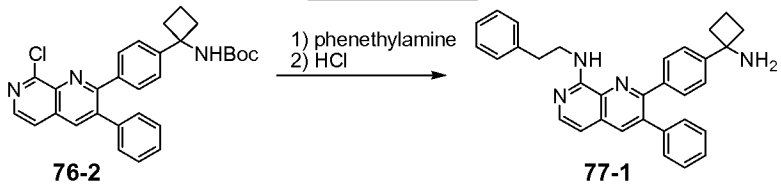
tert-butyl {1-[4-(8-chloro-3-phenyl-1,7-naphthyridin-2-yl)phenyl]cyclobutyl} carbamate (**76-2**)

Procedure similar to that reported for Scheme 74 using tert-butyl (2-chloropyridin-3-yl)carbamate (Ref: Synlett, (13), 2083-2086; 2006) gave tert-butyl {1-[4-(8-chloro-3-phenyl-1,7-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**76-2**) as a colorless solid.

2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile (**76-3**)

Procedure similar to that reported for Scheme 6 gave 2-[4-(1-aminocyclobutyl) phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile (**76-3**) as colorless solid. HRMS (M+H)+: observed = 377.1760, calculated = 377.1766

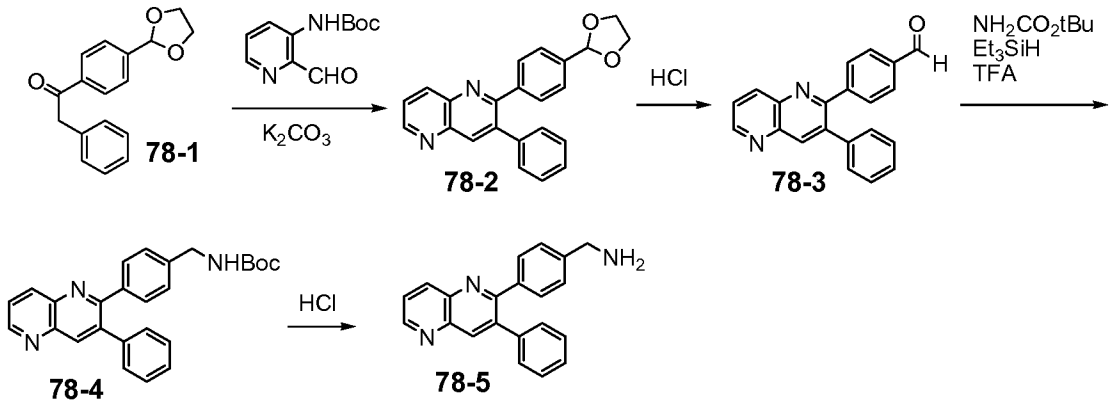
SCHEME 77




2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(2-phenylethyl)-1,7-naphthyridin-8-amine (**77-1**)

Procedure similar to that reported for Scheme 22 gave 2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(2-phenylethyl)-1,7-naphthyridin-8-amine (**77-1**) as colorless solid. HRMS (M+H)+: observed = 471.2538, calculated = 471.2549

SCHEME 78




1-[4-(3-phenyl-1,5-naphthyridin-2-yl)phenyl]methanamine (**78-5**)

2-[4-(1,3-dioxolan-2-yl)phenyl]-3-phenyl-1,5-naphthyridine (**78-2**)

Procedure similar to that reported for **6-4** gave 2-[4-(1,3-dioxolan-2-yl)phenyl]-3-phenyl-1,5-naphthyridine (**78-2**). MS(M+1): observed = 355.1, calculated = 354.4

4-(3-phenyl-1,5-naphthyridin-2-yl)benzaldehyde (**78-3**)

Procedure similar to that reported for **17-5** gave 4-(3-phenyl-1,5-naphthyridin-2-yl)benzaldehyde (**78-3**). MS(M+1): observed = 311.1, calculated = 310.4

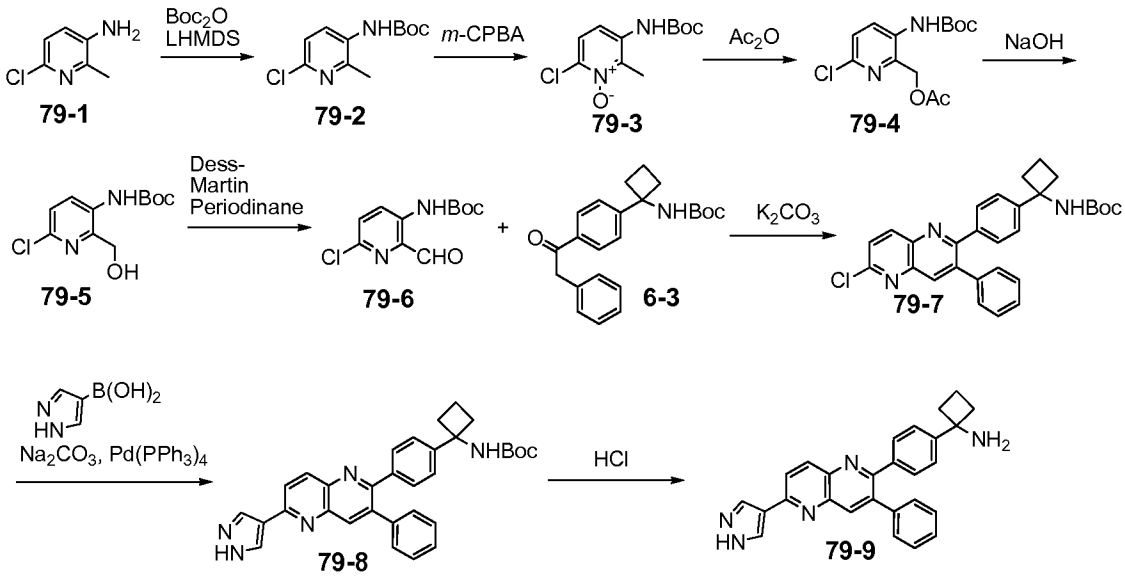
*tert*-butyl [4-(3-phenyl-1,5-naphthyridin-2-yl)benzyl]carbamate (**78-4**)

Procedure similar to that reported for **17-6** gave *tert*-butyl [4-(3-phenyl-1,5-naphthyridin-2-yl)benzyl]carbamate (**78-4**). MS(M+1): observed = 412.2, calculated = 411.5

1-[4-(3-phenyl-1,5-naphthyridin-2-yl)phenyl]methanamine (**78-5**)

Procedure similar to that reported for **19-2** gave 1-[4-(3-phenyl-1,5-naphthyridin-2-yl)phenyl]methanamine (**78-5**). MS(M+1): observed = 312.1, calculated = 311.4

SCHEME 79




1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl} cyclobutanamine (**79-9**)

1,1-dimethylethyl (6-chloro-2-methyl-3-pyridinyl)carbamate (**79-2**)

Procedure similar to that reported for **74-1** gave 1,1-dimethylethyl (6-chloro-2-methyl-3-pyridinyl)carbamate (**79-2**). MS(M+1): observed = 243.2, calculated = 242.7

1,1-dimethylethyl (6-chloro-2-methyl-1-oxido-3-pyridinyl)carbamate (**79-3**)

A solution of 1,1-dimethylethyl (6-chloro-2-methyl-3-pyridinyl)carbamate (**79-2**) (13.8 g, 56.8 mmol) and *m*-CPBA (14.7 g, 85 mmol) in chloroform (58 mL) was heated to 50°C. After stirring overnight, an additional 1.0 equivalent of mCPBA was added and the reaction was stirred again at 50°C overnight. Upon cooling to rt, the reaction was concentrated to dryness under reduced pressure. The crude residue was treated with acetonitrile, was poured into icy $NaHCO_3$ solution, and was filtered. The collected solid was dried azeotropically with toluene three times. The dried solid was triturated with ether and filtered to yield 1,1-dimethylethyl (6-chloro-2-methyl-1-oxido-3-pyridinyl)carbamate (**79-3**) as a white solid. MS(M+1): observed = 259.2, calculated = 258.7

[6-chloro-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-pyridinyl]methyl acetate (**79-4**)

Solid 1,1-dimethylethyl (6-chloro-2-methyl-1-oxido-3-pyridinyl)carbamate (**79-3**) (14.7 g, 56.8 mmol) was treated with acetic anhydride (250 mL). The mixture was heated at 120°C for 1.5 hours. Upon cooling to rt, the reaction was concentrated *in vacuo* and dried azeotropically with toluene three times. The crude residue was stirred at rt with MeOH for 30 minutes and upon removal of the solvent, was again dried azeotropically with toluene to yield [6-chloro-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-pyridinyl]methyl acetate (**79-4**). MS(M+1): observed = 301.0, calculated = 300.7

1,1-dimethylethyl [6-chloro-2-(hydroxymethyl)-3-pyridinyl]carbamate (**79-5**)

To a stirred solution of [6-chloro-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-pyridinyl]methyl acetate (**79-4**) (17.0 g, 56.5 mmol) in 1,4-Dioxane (90 mL) was added 1N NaOH (62.2 ml, 62.2 mmol). After stirring at rt for 30 minutes, the reaction was diluted with water and was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine, dried with $Na_2SO_4/MgSO_4$, filtered and concentrated *in vacuo* to yield 1,1-dimethylethyl [6-chloro-2-(hydroxymethyl)-3-pyridinyl]carbamate (**79-5**). MS(M+1): observed = 259.2, calculated = 258.7

1,1-dimethylethyl (6-chloro-2-formyl-3-pyridinyl)carbamate (**79-6**)

To a stirred solution of 1,1-dimethylethyl [6-chloro-2-(hydroxymethyl)-3-pyridinyl]carbamate (**79-5**) (14 g, 54 mmol) in dry $CH_2Cl_2$ (300 mL) was added Dess-Martin periodinane (32 g, 76 mmol). After stirring at rt for 15 minutes, the reaction was complete and some $CH_2Cl_2$ was removed *in vacuo*. Ether was added along with 1N NaOH and water. The resulting suspension was filtered and the filtrate was separated into layers. The organic layer

was washed with water followed by brine. The organic layer was then dried, filtered, and concentrated *in vacuo*. The crude residue was taken up in $CH_2Cl_2$ and was purified using normal phase flash chromatography (20% EtOAc in hexane) to yield 1,1-dimethylethyl (6-chloro-2-formyl-3-pyridinyl)carbamate (**79-6**) as a solid. $^1$H NMR (500MHz, $CDCl_3$): δ 10.19 (s, 1H), 10.0 (s, 1H), 8.90-8.88 (m, 1H), 7.49-7.47 (m, 1H), 1.55 (s, 9H).

1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,5-naphthyridin-2-yl)phenyl] cyclobutyl}carbamate (**79-7**)

Procedure similar to that reported for **6-4** gave 1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,5-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**79-7**). MS(M+1): observed = 486.2, calculated = 486.0

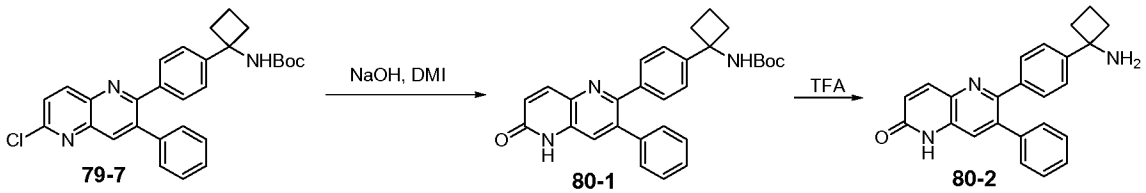
*tert*-butyl (1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl}cyclobutyl)carbamate (**79-8**)

Procedure similar to that reported for **74-4** gave *tert*-butyl (1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl}cyclobutyl)carbamate (**79-8**). MS(M+1): observed = 518.1, calculated = 517.6

1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl} cyclobutanamine (**79-9**)

Procedure similar to that reported for **74-5** gave 1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl}cyclobutanamine (**79-9**). MS(M+1): observed = 418.1, calculated = 417.5

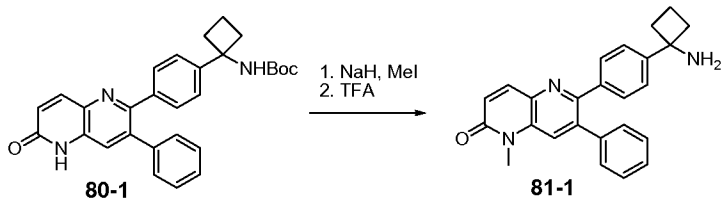
SCHEME 80




6-[4-(1-aminocyclobutyl)phenyl]-7-phenyl-1,5-naphthyridin-2(1H)-one (**80-2**)

A mixture of tert-butyl {1-[4-(6-chloro-3-phenyl-1,5-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**79-7**) (100 mg) and aqueous NaOH (5.0M, 400 μL) in 1,3-dimethyl-2-imidazolidinone (2 mL) was stirred at 100°C for overnight. The resulting mixture was neutralized with 1N HCl (aq), extracted with AcOEt, washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo to give crude **80-1**. The residue was dissolved with TFA (0.1 mL) and stirred for 1h. The mixture was neutralized with 1N NaOH (aq), extracted with AcOEt, washed with water and brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography to give 6-[4-(1-aminocyclobutyl)phenyl]-7-phenyl-1,5-naphthyridin-2(1H)-one (**80-2**) as a colorless solid. HRMS (M+H)+: observed = 368.1757, calculated = 368.1763

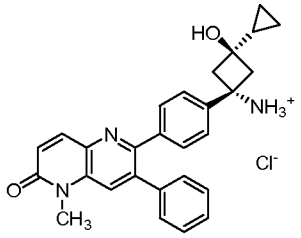
SCHEME 81




6-[4-(1-aminocyclobutyl)phenyl]-1-methyl-7-phenyl-1,5-naphthyridin-2(1H)-one (**81-1**)

Procedure similar to that reported for Scheme 8 gave 6-[4-(1-aminocyclobutyl)phenyl]-1-methyl-7-phenyl-1,5-naphthyridin-2(1H)-one (**81-1**). HRMS (M+H)+: observed = 382.1917, calculated = 382.1919

SCHEME 82

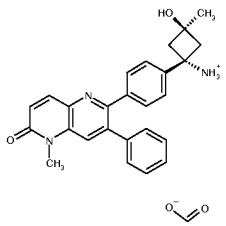
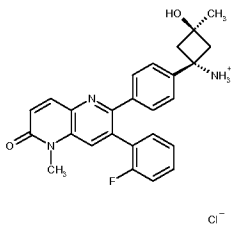



6-trans-3-cyclopropyl-3-hydroxy-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanaminium chloride (**82-1**)

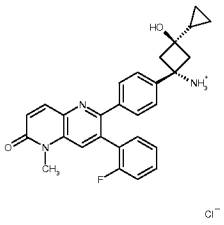
Procedure similar to that reported for Scheme 16 gave 6trans-3-cyclopropyl-3-hydroxy-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl] cyclobutanaminium chloride (**82-1**). HRMS (M+H)+: observed = 438.2175, calculated = 438.2182

The compounds in Table 22 were prepared according to the Reaction Schemes and Scheme 82.

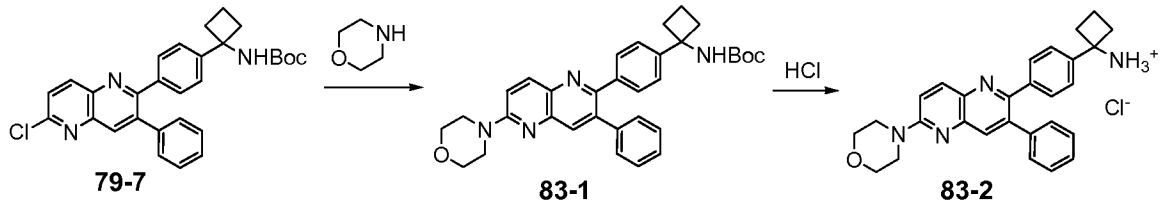
Table 22

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **82-2** |  | trans-3-hydroxy-3-methyl-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanaminium formate | 412.2025 | 412.2032 |
| **82-3** |  | trans-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy-3-methyl | 430.1931 | 430.1939 |

cyclobutanaminium chloride

| | | | | |
|---|---|---|---|---|
| **82-4** |  | trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy cyclobutanaminium chloride | 456.2087 | 456.2091 |

SCHEME 83



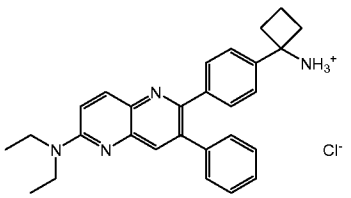
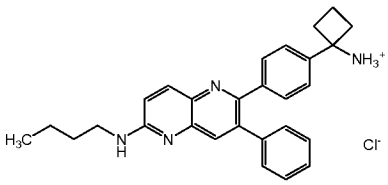

1-[4-(6-morpholin-4-yl-3-phenyl-1,5-naphthyridin-2-yl)phenyl] cyclobutanaminium chloride (**83-2**)

To a stirred solution of 1,1-dimethylethyl{1-[4-(6-chloro-3-phenyl-1,5-naphthyridin-2-yl)phenyl]cyclobutyl}carbamate (**79-7**) (20 mg, 0.041 mmol) in DMSO (0.5 mL) was added morpholine (0.054 mL, 0.62 mmol). The reaction was heated to 150°C overnight to give crude **83-1**; MS(M+1): observed = 537.2, calculated = 536.9. Upon cooling, TFA (0.20 mL) was added and the reaction was heated to 60°C. Upon completion, some TFA was removed under reduced pressure. The reaction was purified using reverse phase chromatography (C18) to yield 1-[4-(6-morpholin-4-yl-3-phenyl-1,5-naphthyridin-2-yl)phenyl]cyclobutanaminium chloride (**83-2**). MS(M+1): observed = 437.1, calculated = 437.6

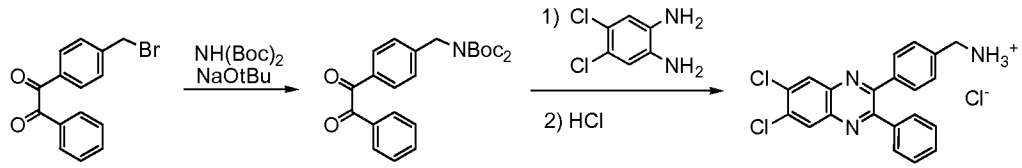
The compounds in Table 23 were prepared according to the Reaction Schemes and Scheme 83.

Table 23

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|

| | | | |
|---|---|---|---|
| **83-3** |  | 1-{4-[6-(diethylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride | 423.6 423.2 |
| **83-4** |  | 1-{4-[6-(butylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanaminium chloride | 423.6 423.1 |

SCHEME 84




**84-1** **84-2**

[4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanaminium chloride (**84-2**)

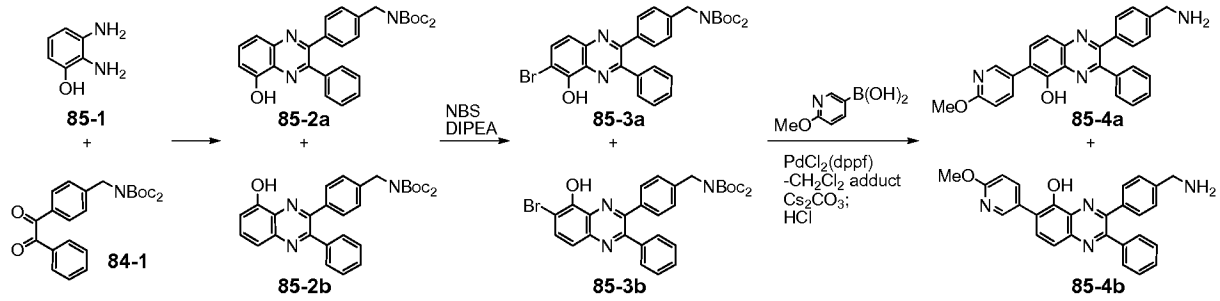
di-*tert*-butyl {4-[oxo(phenyl)acetyl]benzyl}imidodicarbonate (**84-1**)

To a stirred solution of 1-[4-(bromomethyl)phenyl]-2-phenylethane-1,2-dione (15 g, 50 mmol) and di-*tert*-butyl imidodicarbonate (11 g, 50 mmol) in anhydrous THF (210 mL) was added sodium tert-butoxide (4.8 g, 50 mmol). The mixture was stirred at room temperature for 2 hours. Upon completion, the solvent was removed under reduced pressure and the residue was treated with 500 mL water. The product was extracted into EtOAc three times, dried with $MgSO_4/Na_2SO_4$, filtered and concentrated in vacuo to yield di-tert-butyl {4-[oxo(phenyl)acetyl] benzyl}imidodicarbonate (**84-1**) as a yellow solid. MS(M+1): observed = 340.2 (M+1-boc), calculated = 439.5

[4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanaminium chloride (**84-2**)

A solution of 4,5-dichlorobenzene-1,2-diamine (0.92 g, 5.2 mmol) and di-*tert*-butyl {4-[oxo(phenyl)acetyl]benzyl}imidodicarbonate (**84-1**) (2.3 g, 5.2 mmol) in MeOH (75 mL) was allowed to stir overnight at rt. Upon completion, the solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (20% EtOAc in Hexane). The isolated material was treated with a solution of HCl in methanol (1 mL). The solution was heated to 80°C in a microwave reactor for 5 minutes. The solvent was removed *in vacuo* to yield [4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanaminium chloride (**84-2**). MS(M+1): caculated = 380.27, observed = 381.2

SCHEME 85




2-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-3-phenylquinoxalin-5-ol (**85-4a**) and 3-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-2-phenylquinoxalin-5-ol (**85-4b**)

di-*tert*-butyl [4-(5-hydroxy-3-phenylquinoxalin-2-yl)benzyl] imidodicarbonate (**85-2a**) and di-tert-butyl [4-(8-hydroxy-3-phenylquinoxalin-2-yl)benzyl] imidodicarbonate (**85-2b**)

Procedure similar to that reported for **84-2** gave **85-2a** and **85-2b** as a mixture of regioisomers. MS(M+1): observed = 528.3 , calculated = 527.6

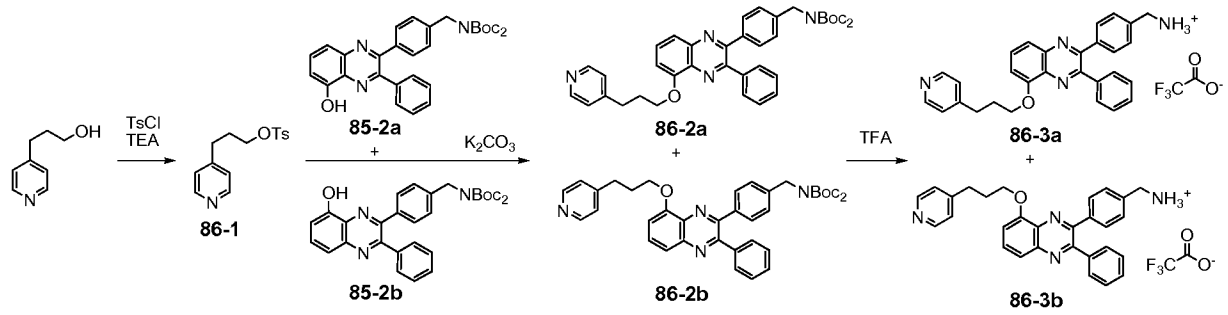
di-*tert*-butyl [4-(6-bromo-5-hydroxy-3-phenylquinoxalin-2-yl)benzyl] imidodicarbonate (**85-3a**) and di-*tert*-butyl [4-(7-bromo-8-hydroxy-3-phenylquinoxalin-2-yl)benzyl]imidodicarbonate (**85-3b**)

To a stirred solution of di-*tert*-butyl [4-(5-hydroxy-3-phenylquinoxalin-2-yl)benzyl]malonate (**85-2**) (3.0 g, 5.7 mmol) and diisopropylamine (0.081 mL, 0.57 mmol) in $CH_2Cl_2$ (40 mL) was added NBS (1.0 g, 5.7 mmol). The reaction was stirred at room temperature and was followed by LC-MS. Upon completion, the solvent was removed *in vacuo*. The crude residue was purified using silica gel chromatography (1-100% EtOAc in Hexane) to yield di-*tert*-butyl [4-(6-bromo-5-hydroxy-3-phenylquinoxalin-2-yl)benzyl]malonate (**85-3a**) and and di-*tert*-butyl [4-(7-bromo-8-hydroxy-3-phenylquinoxalin-2-yl)benzyl]imidodicarbonate (**85-3b**) as a mixture of regioisomers. MS(M+1): observed = 608.3, calculated = 606.5

2-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-3-phenylquinoxalin-5-ol (**85-4a**) and 3-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-2-phenylquinoxalin-5-ol (**85-4b**)

Procedure similar to that reported for Scheme 24 gave **85-4a** and **85-4b** as a mixture of regioisomers. MS(M+1): observed = 435.2, calculated = 434.5

SCHEME 86




(4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3a**) and (4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3b**)

3-pyridin-4-ylpropyl 4-methylbenzenesulfonate (**86-1**)

To a stirred solution of 3-pyridin-4-ylpropan-1-ol (1g, 7.29 mmol) and triethylamine (1.1 mL, 8.0 mmol) in $CH_2Cl_2$ (25mL) was added Tosyl-Cl (1.5 g, 8.0 mmol). After stirring at rt overnight the solvent was removed *in vacuo*. The crude residue was taken up in dichloromethane and purified by silica gel chromatography (90% EtOAc in Hexane) to yield 3-pyridin-4-ylpropyl 4-methylbenzenesulfonate (**86-1**). MS(M+1): observed = 292.1, calculated = 291.4

di-*tert*-butyl (4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2a**) and di-*tert*-butyl (4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2b**)

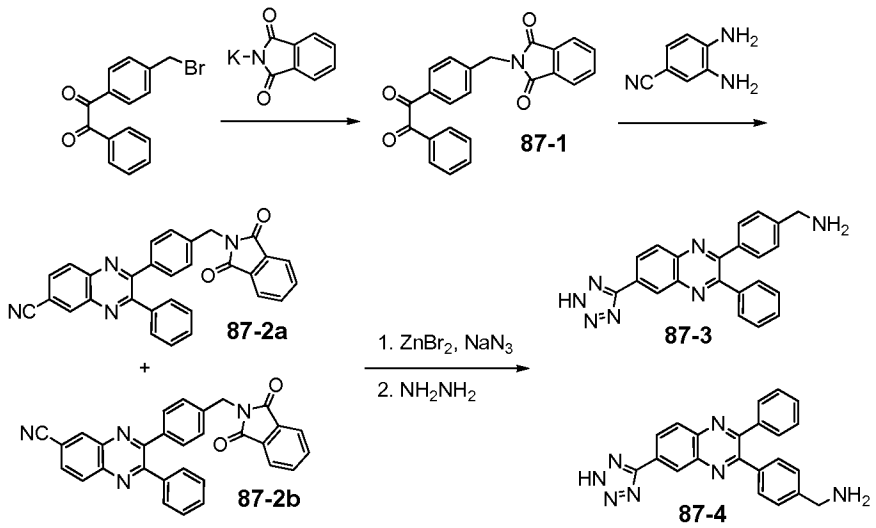
A solution of a mixture of di-*tert*-butyl [4-(5-hydroxy-3-phenylquinoxalin-2-yl)benzyl] imidodicarbonate (**85-2a**) and di-tert-butyl [4-(8-hydroxy-3-phenylquinoxalin-2-yl)benzyl] imidodicarbonate (**85-2b**) (163 mg, 0.309 mmol), 3-pyridin-4-ylpropyl 4-methylbenzenesulfonate (**55-1**) (180 mg, 0.618 mmol), and potassium carbonate (171 mg, 1.24 mmol) was stirred at rt over a period of around 72 hours. Upon completion, the reaction was treated with aq. $NaHCO_3$ solution and was extracted into EtOAc three times. The combined organic layers were concentrated in vacuo. The crude residue was purified by silica gel chromatography (60% EtOAc in hexane) to yield di-*tert*-butyl (4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2a**) and di-*tert*-butyl (4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2b**) as a mixture of regioisomers. MS(M+1): observed = 647.4, calculated = 646.8

(4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3a**) and (4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanaminium trifluoroacetate (**86-3b**)

Di-*tert*-butyl (4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2a**) and di-*tert*-butyl (4-{3-phenyl-8-[3-(pyridin-4-

yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2b**) was treated with 2mL of 30% TFA in $CH_2Cl_2$. After stirring at rt for 15 minutes, the solvent was removed under reduced pressure to yield di-*tert*-butyl (4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2a**) and di-*tert*-butyl (4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}benzyl)imidodicarbonate (**86-2b**) as a mixture of regioisomers. MS(M+1): observed = 447.3, calculated = 446.5

SCHEME 87




1-{4-[3-phenyl-6-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-3**) and 1-{4-[3-phenyl-7-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-4**)

2-{4-[oxo(phenyl)acetyl]benzyl}-1*H*-isoindole-1,3(2*H*)-dione (**87-1**)

A mixture of 1-[4-(bromomethyl)phenyl]-2-phenylethane-1,2-dione (1.0 g, 3.3 mmol) and potassium phthalimide (0.6 g, 3.3 mmol) in 15 mL anhydrous DMF was stirred at rt for overnight. The mixture was concentrated to provide the desired product (**87-1**) as a yellow solid, which was used for next step without further purification. LC/MS: cal. 369.38; found 370.0

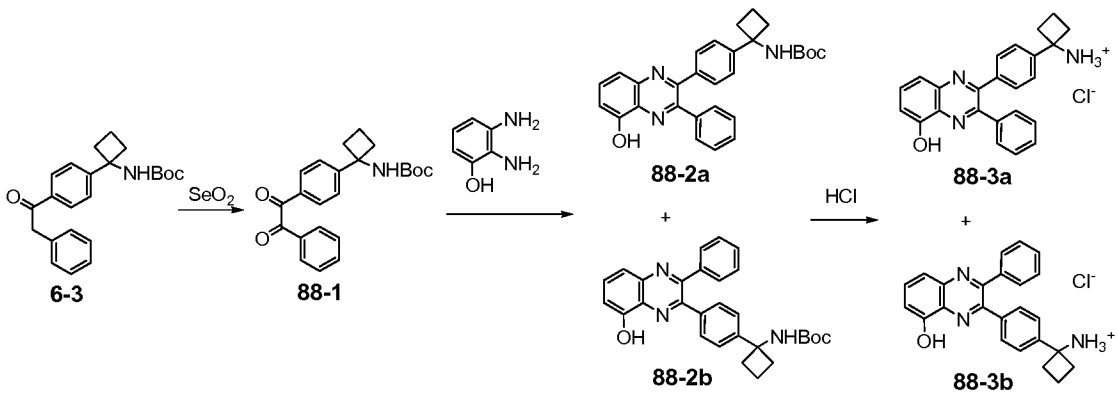
2-{4-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl}-3-phenylquinoxaline-6-carbonitrile (**87-2a**) and 3-{4-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl}-2-phenylquinoxaline-6-carbonitrile (**87-2b**)

A mixture of **87-1** (2.2 g, 6.0 mmol) and 3,4-diaminobenzonitrile (0.8 g, 6.0 mmol) and acetic acid (1.0 mL, 18 mmol) in EtOH (20 mL) was stirred at rt overnight. The reaction mixture was concentrated and treated with 10 mL ethyl ether. The solid was collected by filtration to give the desired products (**87-2a**) and (**87-2b**) as a 1:1 mixture. LC/MS: cal. 466.50; found 467.1

1-{4-[3-phenyl-6-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-3**) and 1-{4-[3-phenyl-7-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-4**)

To a suspension of a 1:1 mixture of (**87-2a**) and (**87-2b**) (0.20 g, 0.43 mmol) in *i*-PrOH (1 mL) was added aqueous zinc bromide (0.43 mL, 2M) and aqueous sodium azide (0.64 mL, 2M). The mixture was heated at 150$^0$C in a microwave reactor for 20 mins. The reaction was subsequently treated with hydrazine (0.14 mL, 4.3 mmol) and stirred at rt for 1hr. It was quenched with 3N HCl until pH=5. The suspension was filtered. The filtrate was collected and purified on reverse-phase HPLC to provide the desired products 1-{4-[3-phenyl-6-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-3**) and 1-{4-[3-phenyl-7-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine (**87-4**) separately. LC/MS: cal. 379.43; found 380.1

SCHEME 88




1-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3a**) and 1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3b**)

*tert*-butyl (1-{4-[oxo(phenyl)acetyl]phenyl}cyclobutyl)carbamate (**88-1**)

A mixture of **6-3** (0.50 g, 1.4 mmol) and selenium dioxide (0.30 g, 2.7 mmol) in DMSO (3 mL) was heated in a microwave reactor for 45 mins at 120$^0$C. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to give desired product (**88-1**) as a solid, which was used for the next step without further purification. LC/MS: cal. 379.45; found 381.2

*tert*-butyl {1-[4-(5-hydroxy-3-phenylquinoxalin-2- yl)phenyl]cyclobutyl} carbamate (**88-2a**) and *tert*-butyl {1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutyl}carbamate (**88-2b**)

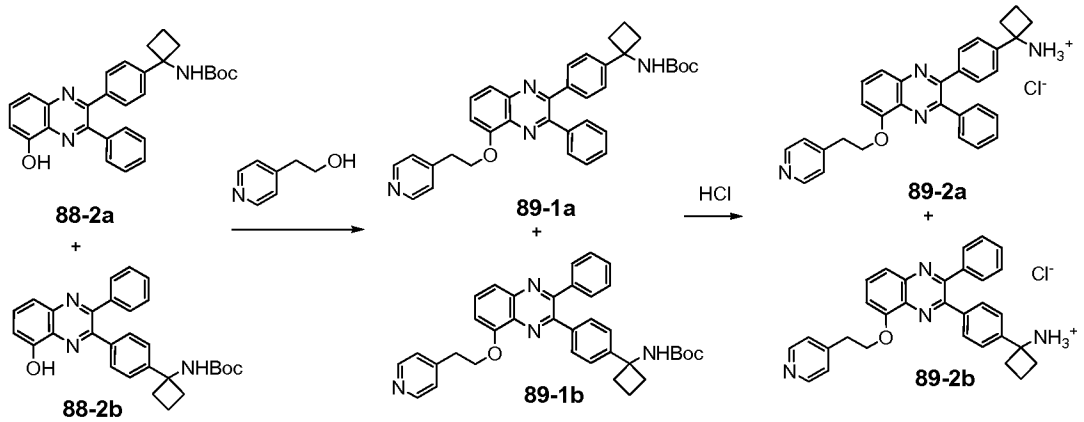
A mixture of **88-1** (0.30 g, 0.80 mmol) and 2,3-diaminophenol in 1,4-dioxane (5 mL) was stirred at rt for 1 hr. Upon removal of the solvent, the residue was purified by silica gel chromatography (20-80% EtOAc in hexane) to afford the desired product as an inseparable (1:1) mixture of *tert*-butyl {1-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutyl} carbamate

(**88-2a**) and *tert*-butyl {1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutyl}carbamate (**88-2b**). LC/MS: cal. 467.56; found 468.21

21-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3a**) and 1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanaminium chloride (**88-3b**)

A 1:1 mixture of **88-2a** and **88-2b** (30 mg, 0.06 mmol) was dissolved in a saturated solution of HCl in MeOH (1 mL). The mixture was heated at 80$^0$C for 5mins and concentrated to give clean desired products **88-3a** and **88-3b** as a 1:1 mixture. LC/MS: cal. 368.4; found 369.2

SCHEME 89




1-(4-{3-phenyl-5-[2-(pyridin-4-yl)ethoxy]quinoxalin-2-yl}phenyl) cyclobutanaminium chloride (**89-2a**) and 1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**89-2b**)

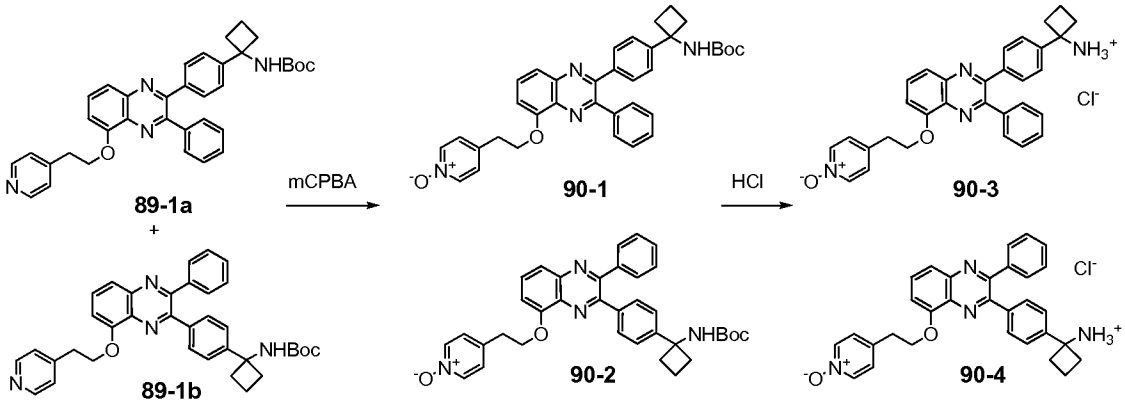
*tert*-butyl (1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl}cyclobutyl)carbamate (**89-1a**) and *tert*-butyl (1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl}cyclobutyl)carbamate (**89-1b**)

To a 1:1 mixture of **88-2a** and **88-2b** (80 mg, 0.17 mmol), 2-pyridin-4-ylethanol (27 mg, 0.22 mmol) and triphenylphosphine (63 mg, 0.24 mmol) in anhydrous THF (1.5 mL) was added diisopropyl azodicarboxylate (43 uL, 0.22 mmol) at rt overnight. Upon removal of the solvent, the residue was purified by silica gel chromatography (10%-80% EtOAc in hexane) to provide the desired products **89-1a** and **89-1b** as a 1:1 mixture. LC/MS: cal. 573.7; found 573.3

1-(4-{3-phenyl-5-[2-(pyridin-4-yl)ethoxy]quinoxalin-2-yl}phenyl) cyclobutanaminium chloride (**89-2a**) and 1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**89-2b**)

A 1:1 mixture of **89-1a** and **89-1b** (60 mg, 0.10 mmol) was dissolved in a saturated solution of HCl in MeOH (1 mL). The mixture was heated at 80 $^0$C for 5mins in a microwave reactor. Upon removal of the solvent, the mixture provided desired products **89-2a** and **89-2b** as a 1:1 mixture. LC/MS: cal. 473.6; found 473.2

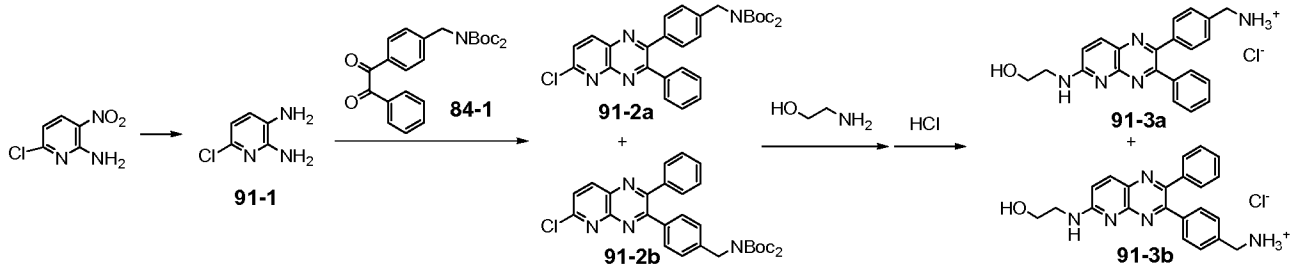
SCHEME 90




1-{4-[3-phenyl-5-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**90-3**) and 1-{4-[3-phenyl-8-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**90-4**)

To a solution of a 1:1 mixture of **89-1a** and **89-1b** (60 mg, 0.11 mmol) in $CH_2Cl_2$ (1 mL) was added *m*-CPBA (35 mg, 0.16 mmol). The reaction mixture was stirred at rt overnight. The mixture was separated via silica gel chromatography to provide the two regioisomers, **90-1** and **90-2**. Each regioisomer was dissolved in a saturated solution of HCl in MeOH (1 mL) and heated in a microwave reactor at 80 $^0$C for 5mins. The two reaction mixtures were then concentrated and purified on reverse phase HPLC to afford 1-{4-[3-phenyl-5-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl}_cyclobutanaminium chloride (**90-3**) and 1-{4-[3-phenyl-8-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl} cyclobutanaminium chloride (**90-4**). LC/MS: cal. 488.58; found 489.24

SCHEME 91




(4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanaminium chloride (**91-3a**) and (4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanaminium chloride (**91-3b**)

6-chloropyridine-2,3-diamine (**91-1**)

6-chloro-3-nitropyridin-2-amine (7.2 g, 42 mmol) and tin(II) chloride (40.0 g, 210 mmol) were dissolved in ethyl acetate (160 mL) and t-butanol (18 mL). The reaction mixture was stirred at 60°C for 1 hour. Sodium borohydride (0.79 g, 21 mmol) was added and the resulting mixture was stirred at 60°C for 3 hours. The mixture was cooled, concentrated,

suspended in water, neutralized with potassium carbonate and extracted with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered and reduced in vacuo to give 6-chloropyridine-2,3-diamine (**60-1**) as a green solid; Reference: Oguchi, et. al. J. Med. Chem. (**2000**), 43, 3052-3066.

di-*tert*-butyl [4-(6-chloro-3-phenylpyrido[2,3-b]pyrazin-2-yl)benzyl] imidodicarbonate (**91-2a**) and di-*tert*-butyl [4-(6-chloro-2-phenylpyrido[2,3-b] pyrazin-3-yl)benzyl]imidodicarbonate (**91-2b**)

To a solution of **84-1** (3.3 g, 7.5 mmol) and **91-1** (1.1 g, 7.5 mmol) dissolved in ethanol (15 mL) was added acetic acid (32 mL) and the mixture was stirred at 60°C for 1 hour. The reaction mixture was cooled to room temperature then poured into ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried over $Na_2SO_4$, filtered and reduced in vacuo. The crude intermediate was purified by silica gel chromatography (7-60% EtOAc/Hexane) to give the desired products **91-2a** and **91-2b** as a 1:1 mixture as an oil. LCMS 547.2 (M+1).

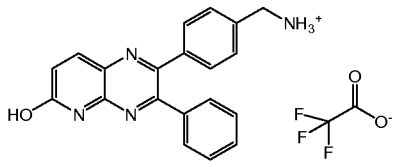
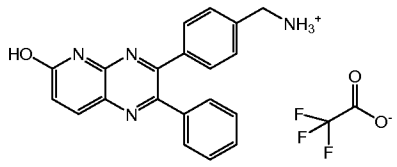
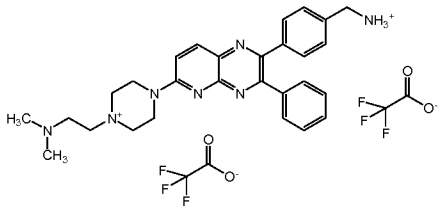
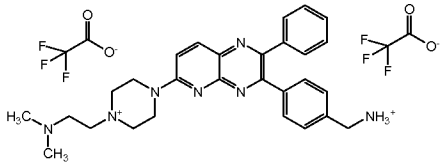
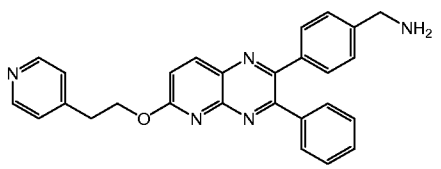
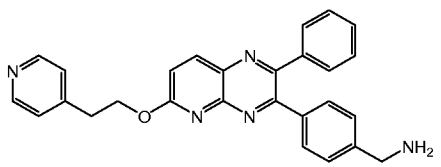
(4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanaminium chloride (**91-3a**) and (4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanaminium chloride (**91-3b**)

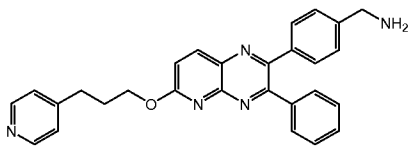
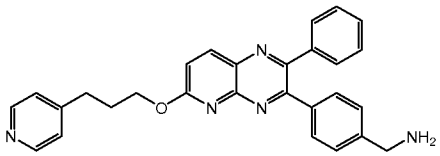
A 1:1 mixure of **91-2a** and **91-2b** (0.20 g, 0.37 mmol) and 2-aminoethanol (0.022 g, 0.37 mmol) were dissolved in dioxane (1 mL). The reaction mixture was then heated under microwave irradiation at 100°C for 15 minutes. The crude reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate, then washed with saturated aqueous sodium bicarobonate followed by water then brine. The organic layer was dried over sodium sulfate, filtered and reduced in vacuo to give the crude intermediate, LCMS: 572.2 (M+1). To a solution of the crude mixture in ethyl acetate (1 mL) was added a saturated solution of HCl in EtOAc (5 mL). The reaction mixture was then permitted to stir at room temperature under an atmosphere of nitrogen for 10 minutes. The solution was reduced in vacuo and the residual oil was purified by reverse chromatography to give (4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanaminium chloride (**91-3a**) and (4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanaminium chloride (**91-3b**). LCMS(M+1): 372.1

The compounds in Table 23 were prepared according to the Reaction Schemes and Scheme 91.

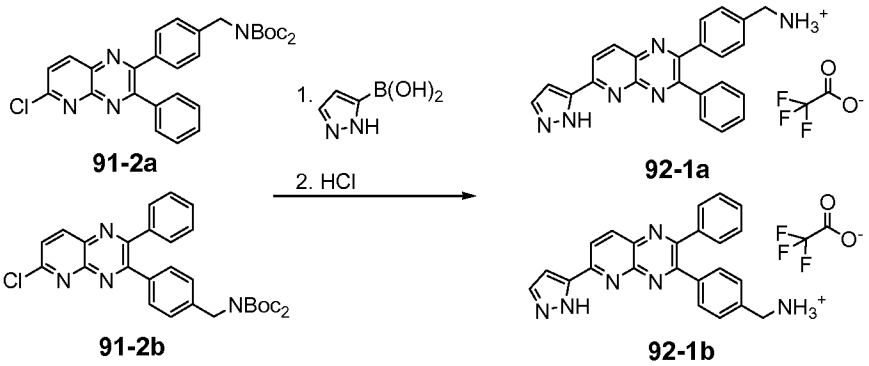
Table 23

| Cmp | Structure | Name | MS m/z | MS m/z |
|---|---|---|---|---|

| | | | (M+H): calc'd | (M+H): observed |
|---|---|---|---|---|
| **91-4a** |  | [4-(6-hydroxy-3-phenylpyrido[2,3-b] pyrazin-2-yl)phenyl] methanaminium trifluoroacetate | 329.1397 | 329.1407 |
| **91-4b** |  | [4-(6-hydroxy-2-phenylpyrido[2,3-b] pyrazin-3-yl)phenyl] methanaminium trifluoroacetate | 329.1397 | 329.1407 |
| **91-5a** |  | 4-{2-[4-(ammonio methyl) phenyl]-3-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl] piperazin-1-ium bis(trifluoroacetate) | 468.6 | 468.2 |
| **91-5b** |  | 4-{3-[4-(ammoniomethyl) phenyl]-2-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]pip erazin-1-ium bis(trifluoroacetate) | 468.6 | 468.2 |
| **91-6a** |  | 1-{4-[3-phenyl-6-(2-pyridin-4-ylethoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine | 434.5 | 434.0 |
| **91-6b** |  | 1-(4-{2-phenyl-6-[2-(pyridin-4-yl)ethoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine | 434.5 | 434.0 |

| | | | | |
|---|---|---|---|---|
| **91-7a** |  | 1-{4-[3-phenyl-6-(3-pyridin-4-ylpropoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine | 448.5 | 448.3 |
| **91-7b** |  | 1-(4-{2-phenyl-6-[3-(pyridin-4-yl)propoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine | 448.5 | 448.3 |

SCHEME 92

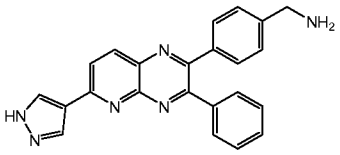
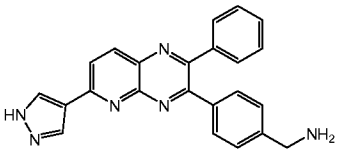



{4-[3-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**92-1a**) and {4-[2-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**92-1b**)

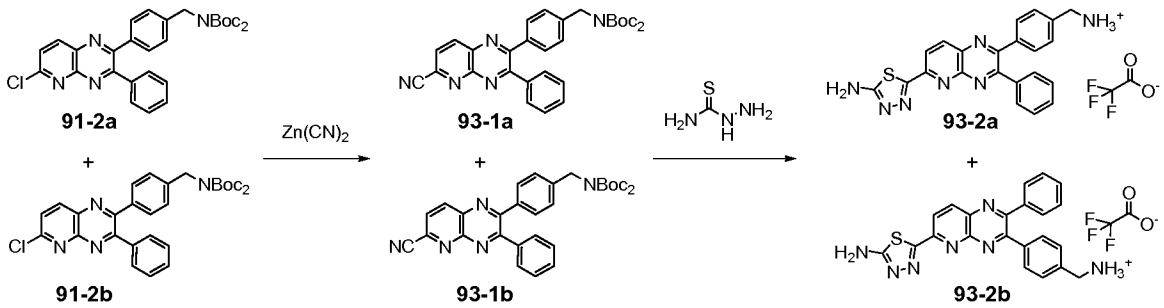
A 1:1 mixture of **91-2a** and **91-2b** (0.10 g, 0.18 mmol), 1H-pyrazole-5-boronic acid (0.041 g, 0.37 mmol) and cesium carbonate (0.18 g, 0.55 mmol) were dissolved in DMF (1 mL). The reaction mixture was then heated under microwave irradiation at 100°C for 10 minutes. The crude reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate, washed with water and brine. The organic layer was dried over sodium sulfate, filtered and reduced in vacuo to give the crude intermediate, LCMS 579.2 (M+1). To a solution of the crude mixture in ethyl acetate (1 mL) was added a saturated solution of HCl in EtOAc (5 mL). The reaction mixture was then permitted to stir at room temperature under an atmosphere of nitrogen for 10 minutes. The solution was reduced in vacuo and the residual oil was purified by reverse chromatography to give {4-[3-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate (**92-1a**) and {4-[2-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**92-1b**) as a 1:1 mixture. LCMS: 379.1 (M+1)

The compounds in Table 24 were prepared according to the Reaction Schemes and Scheme 92.

Table 24.

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **92-2a** |  | 1-{4-[3-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine | 379.1666 | 379.1677 |
| **92-2b** |  | 1-{4-[2-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanamine | 379.1666 | 379.1677 |

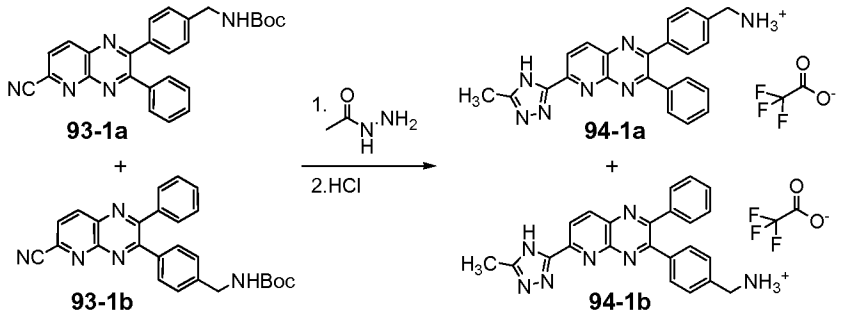
SCHEME 93




{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl}methanaminium trifluoroacetate (**93-2a**) and {4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**93-2b**)

Procedure similar to that reported for **67-1** gave {4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl}methanaminium trifluoroacetate (**93-2a**) and {4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**93-2b**) as a 1:1 mixture. LCMS (M+1): 412.1

SCHEME 94

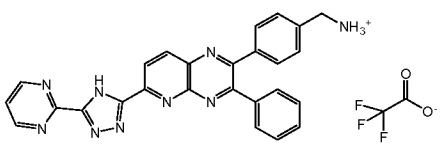


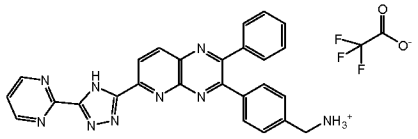

{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl}methanaminium trifluoroacetate (**94-1a**) and {4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl}methanaminium trifluoroacetate (**94-1b**)

A 1:1 mixture of **93-1a** and **93-1b** (0.10 g, 0.23 mmol) and acetic acid hydrazide (0.017 g, 0.23 mmol) were dissolved in n-butanol and heated to reflux overnight. Reduced in vacuo to give the crude intermediate, LCMS: 494.2 (M+1). To a solution of the crude mixture in ethyl acetate (1 mL) was added a saturated solution of HCl in EtOAc (5 mL). The reaction mixture was then permitted to stir at room temperature under an atmosphere of nitrogen for 10 minutes. The solution was reduced in vacuo and the residual oil was purified by reverse chromatography to give the desired products (**94-1a**) and (**94-1b**) as a 1:1 mixture. LCMS (M+1): 394.1

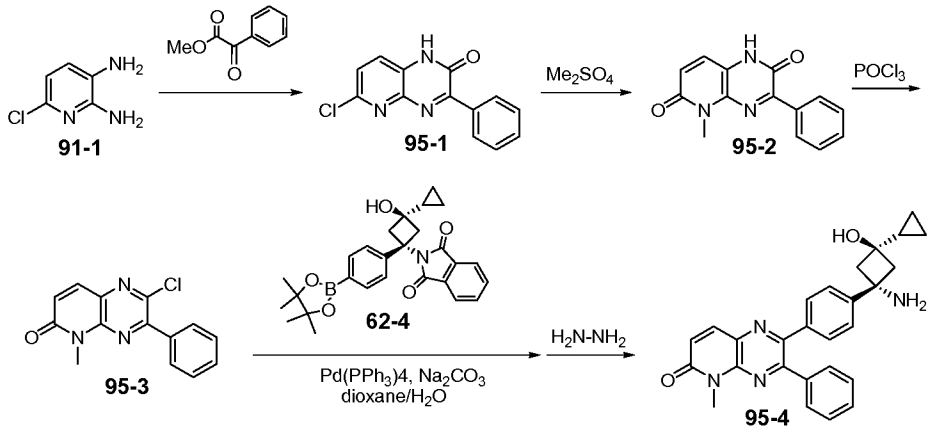
The compounds in Table 25 were prepared according to the Reaction Schemes and Scheme 94.

Table 25.

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **94-2a** |  | {4-[3-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanaminium trifluoroacetate | 458.5 | 458.1 |

| | | | |
|---|---|---|---|
| **94-2b** |  | {4-[2-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl} methanaminium trifluoroacetate | 458.5 458.1 |

SCHEME 95




2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-4**)

6-chloro-3-phenylpyrido[2,3-b]pyrazin-2(1H)-one (**95-1**)

To a stirred solution of 6-chloropyridine-2,3-diamine (**91-1**, 15 g, 110 mmol) in DMF (53 mL) was added methyl oxo(phenyl)acetate (23 mL, 160 mmol) and DIPEA (37 mL, 210 mmol). After 72 hours, the reaction was concentrated to dryness. The resulting material was suspended in ethyl acetate / water and filtered to give 6-chloro-3-phenylpyrido[2,3-b]pyrazin-2(1H)-one (**95-1**) as a solid. The organic phase was washed with water, $NaHCO_3$ and brine, dried over sodium sulfate, filtered and concentrated. The crude mixture was suspended in DCM (200 mL) and filtered to give another batch of **95-1** as a solid.

5-methyl-3-phenyl-1,5-dihydropyrido[2,3-b]pyrazine-2,6-dione (**95-2**)

A mixture of 6-chloro-3-phenylpyrido[2,3-b]pyrazin-2(1H)-one (**95-1**) (31mg) and dimethyl sulfate (17 mg) in DCE (1 mL) was placed in a sealed tube and heated in a microwave oven at 150°C for 10 min. $H_2O$ (0.2 mL) was added to the reaction mixture and then heated in a microwave oven at 150°C for 10min. The precipitate was collected by filtration to give 5-methyl-3-phenyl-1,5-dihydropyrido[2,3-b]pyrazine-2,6-dione (**95-2**) as a orange solid.

2-chloro-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-3**)

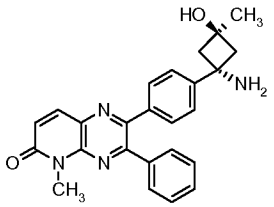
A mixture of 5-methyl-3-phenyl-1,5-dihydropyrido[2,3-b]pyrazine-2,6-dione (**95-2**) (130 mg), diethylaniline (75 mg) and $POCl_3$ (2 mL) was stirred at 60°C for 3 h. The reaction mixture was poured into aq. $NaHCO_3$ and extracted by EtOAc. Tha combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced

pressure. The residue was purified by silica gel column chromatography to give 2-chloro-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-3**) as a orange solid.

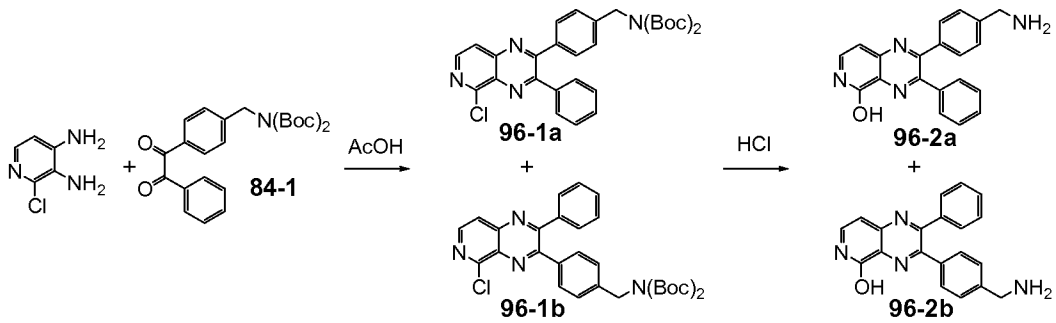
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-4**)

Procedure similar to that reported for **16-9** gave 2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one (**95-4**) as a colorless solid. HRMS (M+H)+: observed = 413.1971, calculated = 413.1978

Table 26.

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **95-5** |  | 2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one | 413.1978 | 413.1971 |

SCHEME 96




2-[4-(aminomethyl)phenyl]-3-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2a**) and 3-[4-(aminomethyl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2b**)

di-*tert*-butyl [4-(5-chloro-3-phenylpyrido[3,4-*b*]pyrazin-2-yl)benzyl] imidodicarbonate (**96-1a**) and di-*tert*-butyl [4-(5-chloro-2-phenylpyrido[3,4-*b*]pyrazin-3-yl)benzyl]imidodicarbonate (**96-1b**)

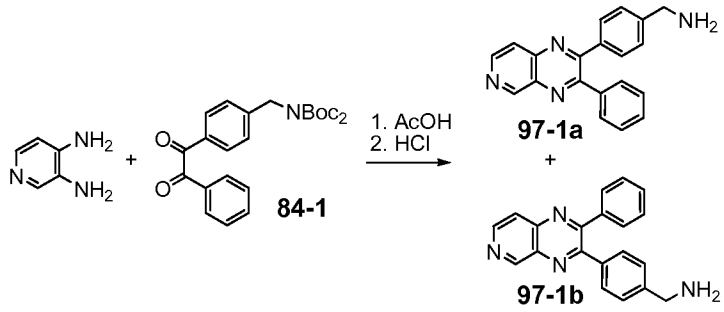
To a solution of 2-chloropyridine-3,4-diamine (0.99 g, 6.9 mmol) in anhydrous ethanol (30 mL) was added di-*tert*-butyl {4-[oxo(phenyl)acetyl]benzyl} imidodicarbonate (**84-1**) (3.0 g, 6.9 mmol) and glacial acetic acid (1.6 mL, 27 mmol) and the resulting solution was heated to 60°C in a sealed tube with stirring in a hot oil bath. After 20 hours, the reaction mixture was quenched by slow addition of a saturated solution of sodium bicarbonate, extracted with ethyl acetate, and the organic layer was washed with water, then brine, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure gave the title compounds

(**96-1a** and **96-1b**) as a solid (1:1 mixture of regioisomers). MS(M+): calculated = 547.1, observed = 547.1

2-[4-(aminomethyl)phenyl]-3-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2a**) and 3-[4-(aminomethyl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2b**)

Procedure similar to that reported for **19-2** gave 2-[4-(aminomethyl)phenyl]-3-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2a**) and 3-[4-(aminomethyl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-5-ol (**96-2b**). HRMS $(M+H)^+$: observed = 329.1397, calculated = 329.1400

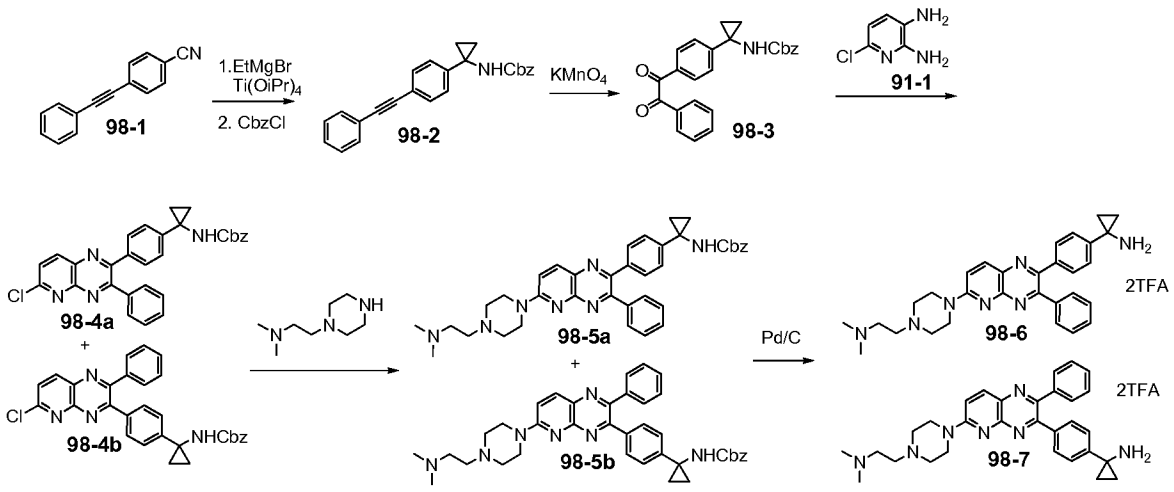
SCHEME 97




1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)phenyl]methanamine (**97-1a**) and 1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)phenyl]methanamine (**97-1b**)

Procedure similar to that reported for Scheme 96 gave 1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)phenyl]methanamine (**97-1a**) and 1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)phenyl]methanamine (**97-1b**). HRMS $(M+H)^+$: observed = 313.1459, calculated = 313.1448

SCHEME 98




4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6a**) and 4-{2-[4-(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-

(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6b**)

benzyl {1-[4-(phenylethynyl)phenyl]cyclopropyl}carbamate (**98-2**)

Procedure similar to that reported for **5-1** using 4-(phenylethynyl)benzonitrile (**98-1**) gave benzyl {1-[4-(phenylethynyl)phenyl]cyclopropyl}carbamate (**98-2**).

benzyl (1-{4-[oxo(phenyl)acetyl]phenyl}cyclopropyl)carbamate (**98-3**)

A solution of benzyl {1-[4-(phenylethynyl)phenyl]cyclopropyl}carbamate (**98-2**) (1.5 g, 4.1 mmol) in acetone (40 mL) was treated with sodium bicarbonate (0.34 g, 4.1 mmol) and potassium permanganate (2.6 g, 16 mmol). The reaction mixture was then heated at 35°C for 4 hours. Added additional 1 equivalent potassium permanganate and stirred overnight. The reaction mixture was concentrated, suspended in ethyl acetate and water and filtered. The organic layer washed with water, brine, dried over sodium sulfate, filtered and reduced in vacuo to give crude benzyl (1-{4-[oxo(phenyl)acetyl]phenyl}cyclopropyl)carbamate (**98-3**) as a yellow foam. LCMS (M+1): 400.1

benzyl {1-[4-(6-chloro-3-phenylpyrido[2,3-b]pyrazin-2-yl)phenyl]cyclopropyl} carbamate (**98-4a**) and benzyl {1-[4-(6-chloro-2-phenylpyrido[2,3-b]pyrazin-3-yl)phenyl]cyclopropyl}carbamate (**98-4b**)

Procedure similar to that reported for **96-1** gave benzyl {1-[4-(6-chloro-3-phenylpyrido[2,3-b]pyrazin-2-yl)phenyl]cyclopropyl}carbamate (**98-4a**) and benzyl {1-[4-(6-chloro-2-phenylpyrido[2,3-b]pyrazin-3-yl)phenyl]cyclopropyl}carbamate (**98-4b**). LCMS (M+1): 507.0

Benzyl {1-[4-(6-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-3-phenylpyrido[2,3-b]pyrazin-2-yl)phenyl]cyclopropyl}carbamate (**98-5a**) and benzyl {1-[4-(6-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-2-phenylpyrido[2,3-b]pyrazin-3-yl)phenyl]cyclopropyl}carbamate (**98-5b**)

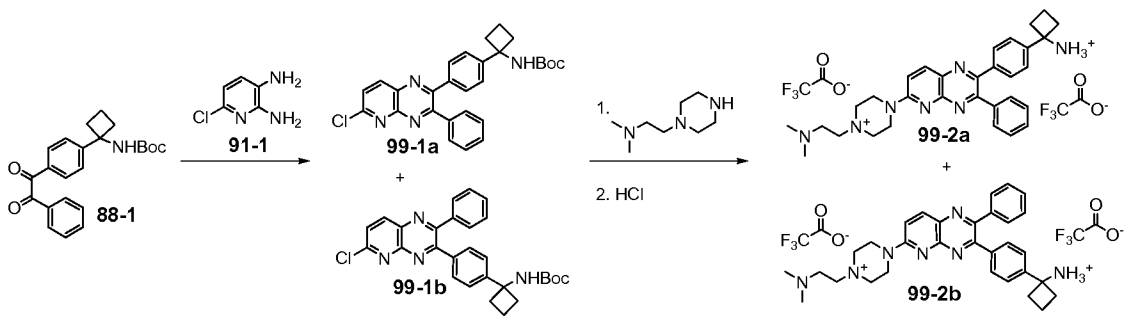
A 1:1 mixture of **98-4a** and **98-4b** (100 mg, 0.20 mmol) and 1-(2-dimethylaminoethyl)-piperazine (46 mg, 0.30 mmol) were dissolved in dioxane (2.5 mL). The reaction mixture was then heated under microwave irradiation at 100°C for 15 minutes. The crude reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate, then washed with saturated aqueous sodium bicarbonate then water followed by brine. The organic layer was dried over sodium sulfate, filtered and reduced in vacuo to give the crude **98-5a** and **98-5b** as a brown solid. LCMS (M+1): 628.3

4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6**) and 4-{2-[4-

(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-7**)

To a solution of a 1:1 mixture of **98-5a** and **98-5b** (120 mg, 0.19 mmol) in ethanol (5 mL) was added 10% Pd/C (41 mg, 0.38 mmol). The reaction mixture was hydrogenated under atmospheric pressure of hydrogen for 2 hours. The palladium was removed by filtration through celite and the filtrate was reduced in vacuo. The residual oil was purified by reverse chromatography to give 4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-6**), 1st off reverse phase, LCMS: 494.2 (M+1), and 4-{2-[4-(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**98-7**), 2nd off reverse phase. LCMS: 494.2 (M+1)

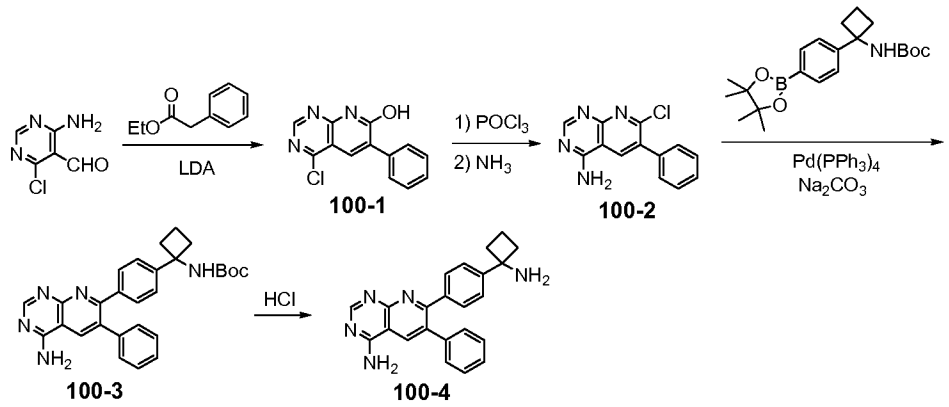
SCHEME 99




4-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(methylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**99-2a**) and 4-{3-[4-(1-ammoniocyclobutyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazin-1-ium bis(trifluoroacetate) (**99-2b**)

Procedure similar to that reported for Scheme 98 gave **99-2a** and **99-2b**. LCMS: 508.6 (M+1)

SCHEME 100




7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-4**)

4-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-7-ol (**100-1**)

To a solution of ethyl phenylacetate (14 mL, 86 mmol) in THF (100 mL) cooled to -78°C was added LDA (1.8M in heptane/THF/ethylbenzene) (48 mL, 86 mmol). After stirring for 10 minutes, the solution was allowed to reach rt. Upon reaching ambient temperature, 4-amino-6-chloropyrimidine-5-carbaldehyde (9.0 g, 57 mmol) was added as a solution in THF (150 mL). The reaction was allowed to stir at rt overnight. The reaction was quenched with aq. $NaHCO_3$ solution and some of the THF was removed under reduced pressure. The reaction was extracted with EtOAc and the combined organic layers were washed with brine. Upon standing in EtOAc some material crystallized out and was collected by filtration. The filtrate was concentrated in vacuo and the solid residue was triturated in diethyl ether, filtered and dried to yield the remainder of 4-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-7-ol (**100-1**) as a solid. MS(M+1): observed = 258.0, calculated = 257.7

7-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-2**)

To a stirred solution of 4-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-7-ol (**100-1**) (500 mg, 1.9 mmol) in dry acetonitrile (5 mL) was added phosphorus oxychloride (10 mL, 110 mmol) and 1 drop of DMF. The reaction was heated to 120°C in a microwave reactor for 15 minutes. Upon cooling to rt, the solvent was removed *in vacuo* and the residue was dried azeotropically with toluene. 5% $NH_3$ in acetonitrile (5 mL) was added and reaction was stirred overnight at rt. The solvent was removed under reduced pressure and the reaction was purified by silica gel chromatography (EtOAc in Hexane) to yield 7-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-2**). MS(M+1): observed = 257.0, calculated = 256.7

*tert*-butyl {1-[4-(4-amino-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl)phenyl] cyclobutyl}carbamate (**100-3**)

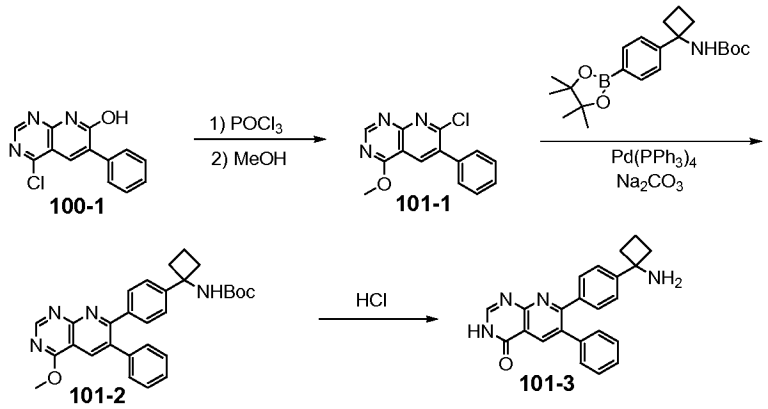
7-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-2**) (32 mg, 0.12 mmol), *tert*-butyl {1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl} carbamate (Reference: US2007/024722) (49 mg, 0.13 mmol), palladiumtetrakis (14 mg, 0.012 mmol), and sodium carbonate (26 mg, 0.25 mmol) were suspended in degassed 1,4-Dioxane (1

mL) and water (0.33 mL). The flask was flushed with nitrogen for 5 minutes. The reaction was heated to 100°C for 15 minutes in a microwave reactor. Upon cooling, the reaction was diluted with EtOAc, washed with water twice, followed by brine. The organic layer was separated, dried with $Na_2SO_4/MgSO_4$ , filtered then concentrated in vacuo to yield tert-butyl {1-[4-(4-amino-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]cyclobutyl}carbamate (**100-3**). MS (M+1): observed = 368.1, calculated = 367.5

7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-4**)

Procedure similar to that reported for **19-2** gave 7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**100-4**). MS (M+1): observed = 368.1, calculated = 367.5

SCHEME 101




7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**101-3**)

7-chloro-4-methoxy-6-phenylpyrido[2,3-*d*]pyrimidine (**101-1**)

To a stirred solution of 4-chloro-6-phenylpyrido[2,3-*d*]pyrimidin-7-ol (**100-1**) (500 mg, 1.9 mmol) in dry acetonitrile (5 mL) was added phosphorus oxychloride (10 mL, 110 mmol) and 1 drop of DMF. The reaction was heated to 120°C in a microwave reactor for 15 minutes. Upon cooling to rt, the solvent was removed *in vacuo* and the residue was dried azeotropically with toluene. Acetonitrile (5 mL) was added and the reaction was cooled to 0°C in an ice bath. Methanol (5 mL) was then added and the reaction was allowed to reach rt. The solvent was removed in vacuo and the crude residue was diluted with EtOAc then washed with $NaHCO_3$ solution, water then brine. The organic layer was dried with $Na_2SO_4/MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified using silica gel chromatography (0-35% EtOAc in hexane) to yield 7-chloro-4-methoxy-6-phenylpyrido[2,3-d]pyrimidine (**101-1**) as a solid. MS (M+1): calculated = 271.7, observed = 272.0

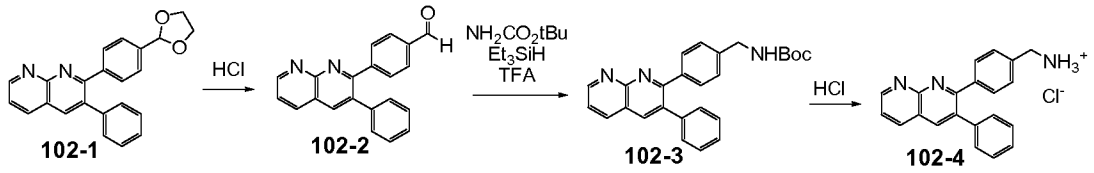
tert-butyl {1-[4-(4-methoxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]cyclobutyl}carbamate (**101-2**)

Procedure similar to that reported for **100-3** gave tert-butyl {1-[4-(4-methoxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]cyclobutyl}carbamate (**101-2**). MS (M+1): calculated = 482.6, observed =483.3

7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine (**101-3**)

Procedure similar to that reported for **19-2** gave MS (M+1): calculated = 368.4, observed = 369.1.

SCHEME 102




[4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanaminium chloride (**102-4**)

4-(3-phenyl-1,8-naphthyridin-2-yl)benzaldehyde (**102-2**)

A suspension of 2-[4-(1,3-dioxolan-2-yl)phenyl]-3-phenyl-1,8-naphthyridine (**102-1**; prepared in a manner similar to **78-2** from tert-butyl (3-formylpyridin-2-yl)carbamate) (1.8 g, 5.1 mmol) in 1,4-Dioxane (10 mL) was cooled to 0°C in an ice bath. The suspension was then treated with 3M HCl (3.4 mL, 10 mmol) and was allowed to reach room temperature. The reaction mixture stirred at room temperature for 2.5 hours. Upon completion, the reaction mixture was treated with a saturated $NaHCO_3$ solution until pH = 8 and was then extracted with EtOAc. The combined organic layers were washed with water followed by brine, dried over $Na_2SO_4/MgSO_4$, filtered and concentrated. The yellow foam was dried azeotropically with toluene to give 4-(3-phenyl-1,8-naphthyridin-2-yl)benzaldehyde (**102-2**) as a yellow solid. MS calculated M+H: 311.4; found 311.1

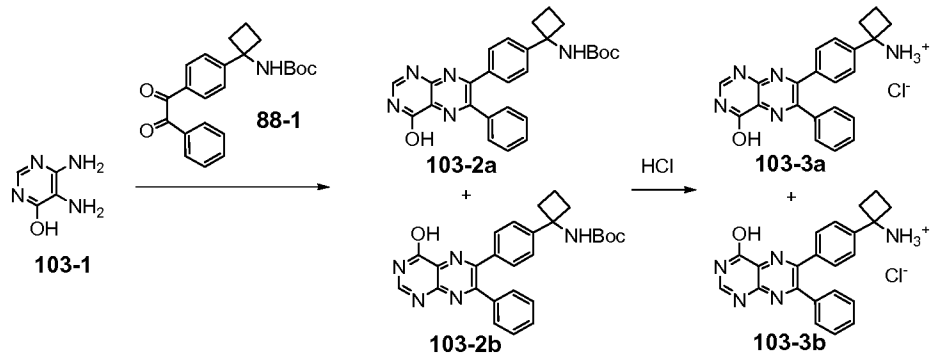
tert-butyl [4-(3-phenyl-1,8-naphthyridin-2-yl)benzyl]carbamate (**102-3**)

Procedure similar to that reported for **17-6** gave tert-butyl [4-(3-phenyl-1,8-naphthyridin-2-yl)benzyl]carbamate (**102-3**) as a yellow oil. MS calculated M+H: 412.5; found 412.2

[4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanaminium chloride (**102-4**)

Procedure similar to that reported for **19-2** gave [4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanaminium chloride (**102-4**). MS M+H: calculated 312.4; found 312.2

SCHEME 103

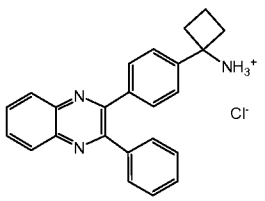
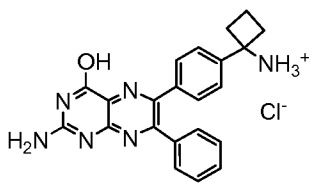



1-[4-(4-hydroxy-6-phenylpteridin-7-yl)phenyl]cyclobutanaminium chloride (**103-3a**) and 1-[4-(4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanaminium chloride (**103-3b**)

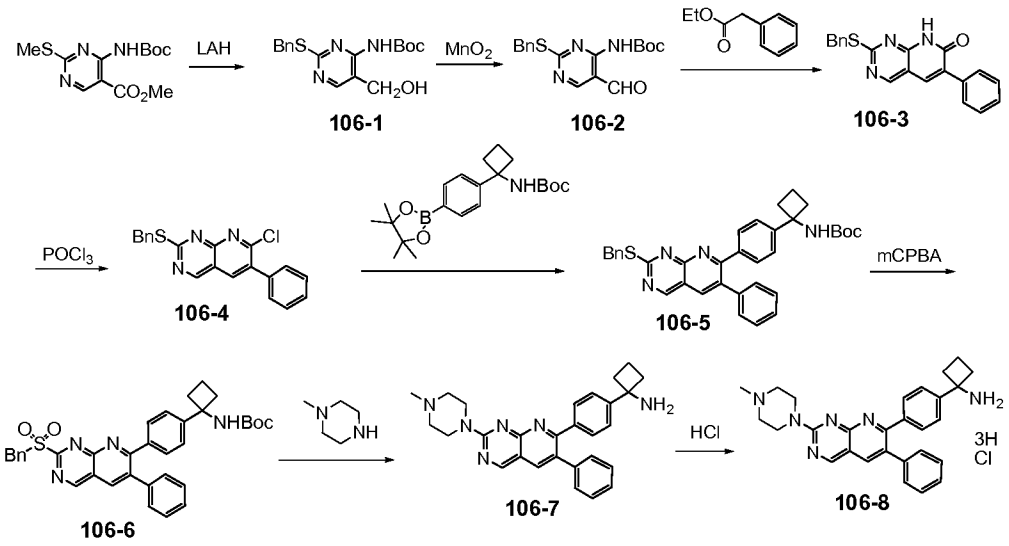
Procedure similar to that reported for Scheme 84 gave 1-[4-(4-hydroxy-6-phenylpteridin-7-yl)phenyl]cyclobutanaminium chloride (**103-3a**) and 1-[4-(4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanaminium chloride (**103-3b**) as a 1:1 mixture. LCMS: calc'd = 370.4, observed = 371.2

The compounds in Table 27 were prepared according to the Reaction Schemes and Scheme 103.

Table 27

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **103-4** |  | 1-[4-(3-phenylquinoxalin-2-yl)phenyl] cyclobutanaminium chloride | 353.5 | 353.2 |
| **103-5b** |  | 1-[4-(2-amino-4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanaminium chloride | 385.4 | 385.2 |

SCHEME 106




7-[4-(1-ammoniocyclobutyl)phenyl]-2-(4-methylpiperazin-4-ium-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-8-ium trichloride (**106-8**)

[4-amino-2-(benzylthio)pyrimidin-5-yl]methanol (**106-1**)

To a solution of 1M LAH (350 mL, 350 mmol) in THF (300 mL) at 0°C was added dropwise a solution of methyl 4-[(tert-butoxycarbonyl)amino]-2-(methylsulfanyl)pyrimidine-5-carboxylate (50 g, 230 mmol) in THF (150 mL). The resulting solution was stirred overnight at room temperature. The reaction mixture was quenched with water followed by addition of 15% NaOH then additional water. The resulting suspension was filtered and the filtrate was reduced in vacuo, to give [4-amino-2-(methylthio)pyrimidin-5-yl]methanol (**106-1**) as a yellow solid.

4-amino-2-(benzylthio)pyrimidine-5-carbaldehyde (**106-2**)

To a solution of [4-amino-2-(benzylthio)pyrimidin-5-yl]methanol (**106-1**) (7.9 g, 32 mmol) in $CHCl_3$ (100 mL) was added manganese dioxide (8.3 g, 96 mmol) and the reaction mixture was heated to 60°C for 2 hours. Another equivalent of manganese dioxide was added and heated for 45 minutes. The reaction mixture was allowed to cool and was then filtered through celite, rinsing with $CHCl_3$ and EtOAc. The filtrate was concentrated in vacuo to afford 4-amino-2-(benzylthio)pyrimidine-5-carbaldehyde (**106-2**) as a white solid.

2-(benzylthio)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**106-3**)

To a solution of ethyl phenylacetate (3.7 mL, 23 mmol) in THF (25 mL) at -78°C was added LDA (1.8M in heptane/THF/ethylbenzene (9.5 mL, 17 mmol). After stirring for 10 minutes, the solution was allowed to warm to room temperature. Once at room temperature, 4-amino-2-(benzylthio)pyrimidine-5-carbaldehyde (**106-2**) (3.8 g, 15 mmol) was added as a solution in THF (85 mL). The reaction mixture was allowed to stir at room temperature for 2 days. Another 1.2 eq of the enolate was added and the reaction mixture was warmed up to 50°C for 1.5 hours. The reaction was quenched with a saturated solution of $NaHCO_3$, partially concentrated, extracted with EtOAc and the combined organic layers were washed with brine.

To the organic layer was added hexane and the mixture was allowed to sit overnight. The mixture was filtered to give 2-(benzylthio)-6-phenylpyrido[2,3-d]pyrimidin-7(8H)-one (**106-3**) as a yellow solid. MS calculated M+H: 346.4; found 346.0

2-(benzylthio)-7-chloro-6-phenylpyrido[2,3-*d*]pyrimidine (**106-4**)

To a mixture of 2-(benzylthio)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**106-3**) (2.1 g, 6.1 mmol) in MeCN (40 mL) was added phosphorus oxychloride (3.4 mL, 37 mmol) and the reaction mixture was stirred at 80°C for 3 hours. Another 6eq of $POCl_3$ were added and heated for 6 hours. The solvent was removed in vacuo, the residue was dissolved in EtOAc, washed with $NaHCO_3$ solution, water, then brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford 2-(benzylthio)-7-chloro-6-phenylpyrido[2,3-*d*]pyrimidine (**106-4**) as a brown solid. MS calculated M+H: 364.8; found 364.1

*tert*-butyl (1-{4-[2-(benzylthio)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-5**)

Into a dried microwave tube was weighed 2-(benzylthio)-7-chloro-6-phenylpyrido[2,3-*d*]pyrimidine (**106-4**) (3.0 g, 8.2 mmol), 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutanamine (US2007/024722) (3.2 g, 8.7 mmol), and sodium carbonate (1.7 g, 16 mmol). To this was then added 1,4-dioxane (62 mL) and water (21 mL). The reaction mixture was purged with $N_2$ for 10 minutes. To this was added palladium tetrakis (0.95 g, 0.82 mmol) and the reaction mixture was bubbled with $N_2$ for 5 minutes. The reaction mixture was then heated at 100°C in the microwave for 20 minutes. Upon completion, the reaction mixture was diluted with EtOAc, water, and a saturated solution of $NaHCO_3$. The layers were separated and the organic layer was washed with brine. The organic layer was then dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (0-100% EtOAc in DCM) to give tert-butyl (1-{4-[2-(benzylthio)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-5**) as a solid. MS calculated M+H: 575.7; found 575.3

*tert*-butyl (1-{4-[2-(benzylsulfonyl)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-6**)

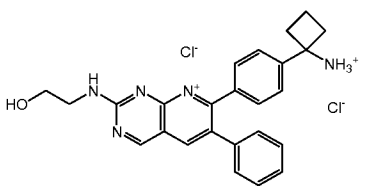
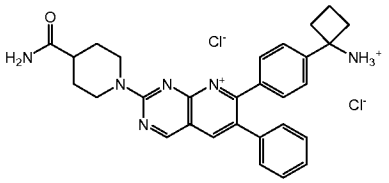
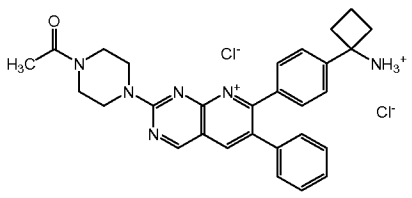
To a mixture of *tert*-butyl (1-{4-[2-(benzylthio)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-5**) (1.1 g, 1.9 mmol) in $CHCl_3$ (15 mL) was added mCPBA (0.66 g, 3.8 mmol) in portions. The reaction mixture was allowed to stir at room temperature for 1 hour before adding another 1.5 eq of mCPBA. After 2.5 hours, the solvent was removed in vacuo and a saturated solution of $NaHCO_3$ was added. Extraction with EtOAc followed by washing the organic with water, concentrating, and drying azeotropically with toluene afforded tert-butyl (1-{4-[2-(benzylsulfonyl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutyl)carbamate (**106-6**) as a solid. MS calculated M+H: 607.7; found 607.3

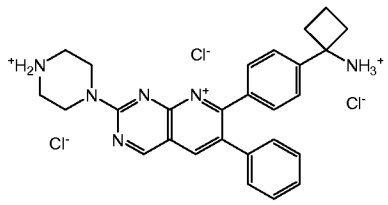
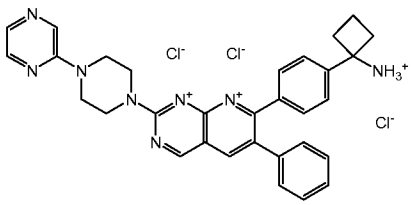
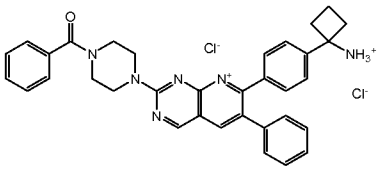
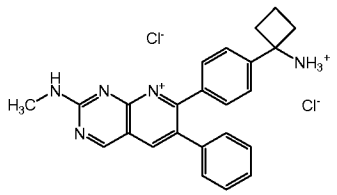
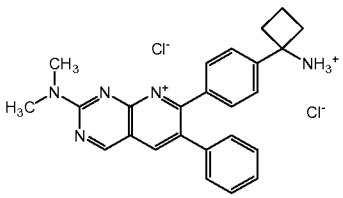
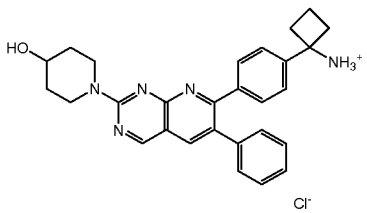
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(4-methylpiperazin-4-ium-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-8-ium trichloride (**106-8**)

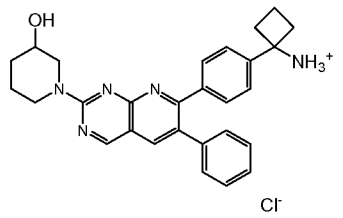
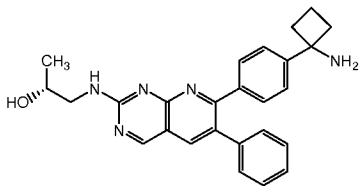
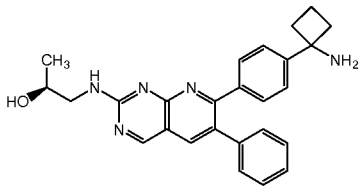
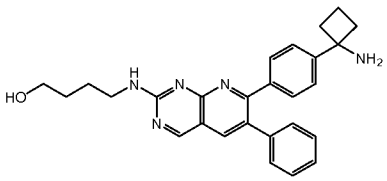
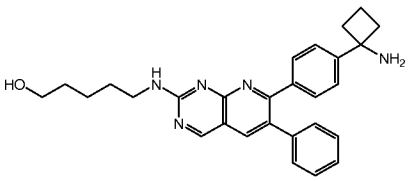
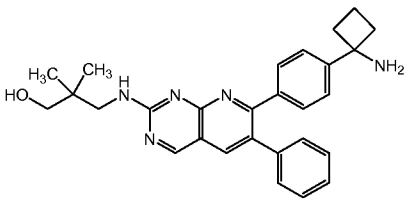
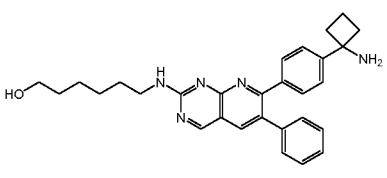
To a mixture of *tert*-butyl (1-{4-[2-(benzylsulfonyl)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-6**) (20 mg, 0.033 mmol) in 1,4-dioxane (0.5 mL) was added 1-methylpiperazine (0.037 mL, 0.33 mmol). The reaction mixture was heated at 100°C for 40 minutes to give *tert*-butyl (1-{4-[2-(4-methylpiperazin-1-yl)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutyl)carbamate (**106-7**). The reaction mixture was then treated with a saturated solution of HCl in MeOH (1 mL) and heated at 80°C in the microwave for 5 minutes. The solvent was removed in vacuo and the residue was taken up in MeOH/DMSO, neutralized and purified on the reverse phase to give 1-{4-[2-(4-methylpiperazin-1-yl)-6-phenylpyrido[2,3-*d*]pyrimidin-7-yl]phenyl}cyclobutanamine (**106-8**) as a yellow solid. MS calculated M+H: 451.6; found 451.2

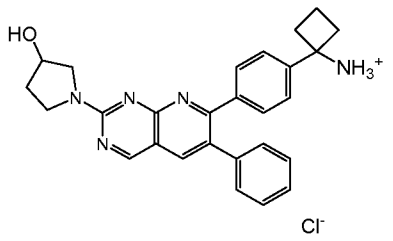
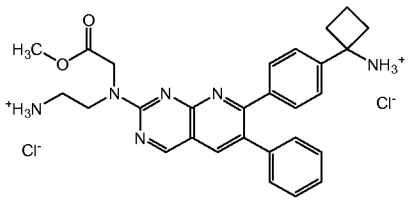
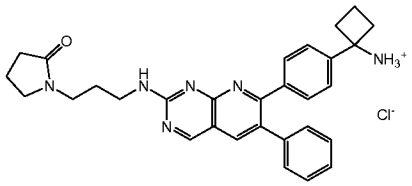
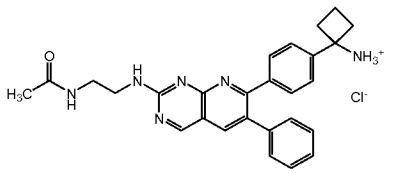
The compounds in Table 28 were prepared according to the Reaction Schemes and Scheme 106.

Table 28.

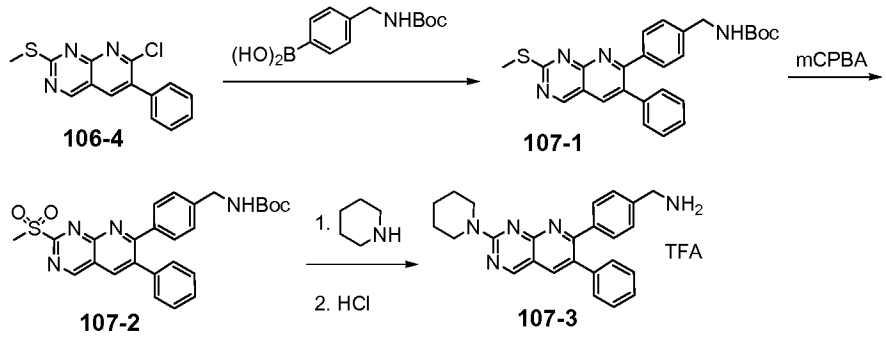
| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **106-9** |  | 7-[4-(1-ammonio cyclobutyl)phenyl]-2-[(2-hydroxyethyl)amino]-6-phenylpyrido[2,3-d] pyrimidin-8-ium dichloride | 412.5 | 412.2 |
| **106-10** |  | 2-[4-(aminocarbonyl) piperidin-1-yl]-7-[4-(1-ammoniocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride | 479.6 | 479.2 |
| **106-11** |  | 2-(4-acetylpiperazin-1-yl)-7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride | 479.6 | 479.2 |

| | | | | |
|---|---|---|---|---|
| **106-12** |  | 7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-piperazin-4-ium-1-ylpyrido[2,3-d]pyrimidin-8-ium trichloride | 437.6 | 437.2 |
| **106-13** |  | 7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-(4-pyrazin-2-ylpiperazin-1-yl) pyrido [2,3-d]pyrimidine-1,8-diium trichloride | 515.6 | 515.2 |
| **106-14** |  | 7-[4-(1-ammonio cyclobutyl)phenyl]-2-(4-benzoylpiperazin-1-yl)-6-phenylpyrido[2,3-d] pyrimidin-8-ium dichloride | 541.7 | 541.3 |
| **106-15** |  | 7-[4-(1-ammoniocyclobutyl)phenyl]-2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride | 382.5 | 382.2 |
| **106-16** |  | 7-[4-(1-ammoniocyclobutyl)phenyl]-2-(dimethylamino)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride | 396.5 | 396.2 |
| **106-17** |  | 1-{4-[2-(4-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}cyclobutanaminium chloride | 452.6 | 452.1 |

| | | | | |
|---|---|---|---|---|
| **106-18** |  | 1-{4-[2-(3-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}cyclobutanaminium chloride | 452.6 | 452.1 |
| **106-19** |  | (2R)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol | 426.5 | 426.1 |
| **106-20** |  | (2S)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol | 426.5 | 426.1 |
| **106-21** |  | 4-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)butan-1-ol | 440.6 | 440.1 |
| **106-22** |  | 5-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)pentan-1-ol | 454.6 | 454.2 |
| **106-23** |  | 3-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)-2,2-dimethylpropan-1-ol | 454.6 | 454.2 |
| **106-24** |  | 6-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)hexan-1-ol | 468.6 | 468.2 |

| | | | | |
|---|---|---|---|---|
| **106-25** |  | 1-{4-[2-(3-hydroxypyrrolidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanaminium chloride | 438.5 | 438.1 |
| **106-26** |  | 1-(4-{2-[(2-ammonioethyl)(2-methoxy-2-oxoethyl)amino]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) cyclobutanaminium dichloride | 483.6 | 483.2 |
| **106-27** |  | 1-[4-(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanaminium chloride | 493.6 | 493.2 |
| **106-28** |  | 1-[4-(2-{[2-(acetylamino) ethyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanaminium chloride | 453.6 | 453.2 |

SCHEME 107




[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-3**)

tert-butyl {4-[2-(methylthio)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]benzyl}carbamate (**107-1**)

A solution of **106-4** (1.3 g, 4.5 mmol), cesium carbonate (5.9 g, 18 mmol), (4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)boronic acid (2.3 g, 9.1 mmol), ethanol (10 mL), dioxane (15 mL) and dichloro-bis(tri-t-butylphosphine)palladium(0) (0.48 g, 0.68 mmol) was heated for 1 hour at 125°C. The reaction mixture was then filtered and concentrated in vacuo. The resulting residue was then purified by silica gel chromatography (10-30% ethyl acetate in hexane with 5% dichloromethane) to give tert-butyl {4-[2-(methylthio)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]benzyl}carbamate (**107-1**) as a yellow glass.

tert-butyl {4-[2-(methylsulfonyl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]benzyl}carbamate (**107-2**)

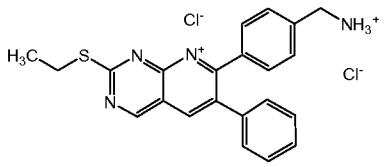
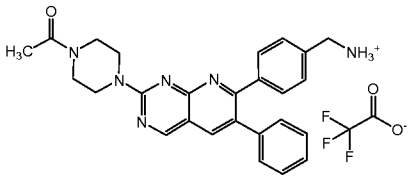
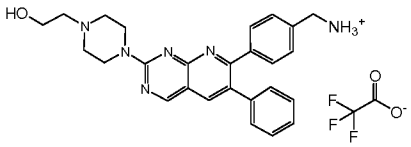
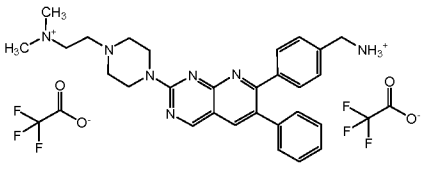
To a solution of **107-1** (100 mg, 0.22 mmol) in dry DCM (2 mL) at 0°C was added a solution of mCPBA (83 mg, 0.48 mmol) in DCM (2 mL) dropwise and the reaction was warmed to warm temperature. After 6 hours at room temperature, the solution was washed with saturated sodium bicarbonate then brine, and the organic layer was dried over sodium sulfate, filtered and reduced in vacuo to give tert-butyl {4-[2-(methylsulfonyl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]benzyl}carbamate (**107-2**) as a yellow foam.

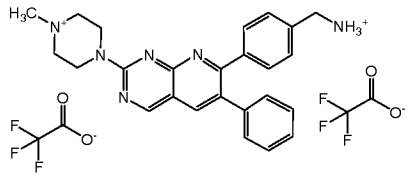
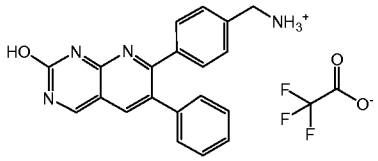
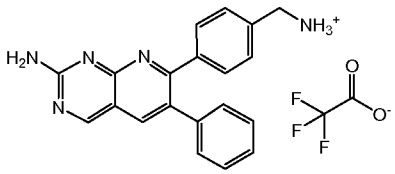
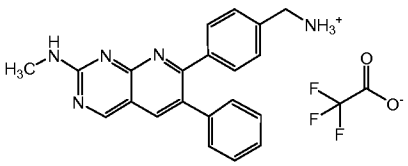
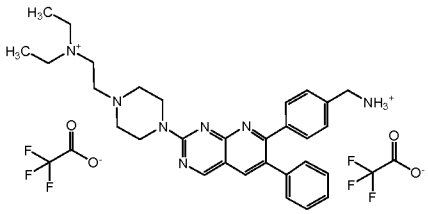
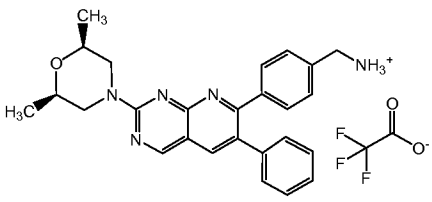
[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-3**)

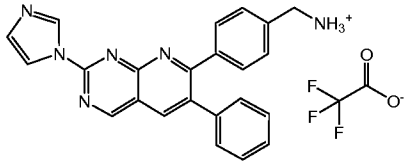
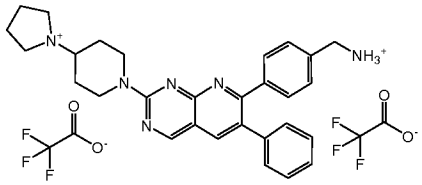
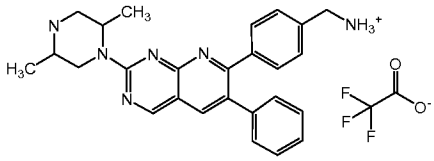
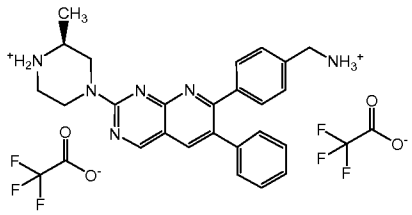
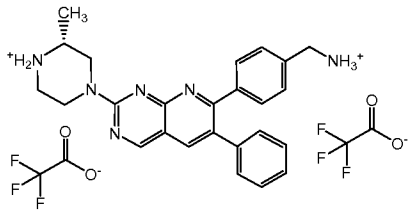
To a solution of **107-2** (0.043 g, 0.091 mmol) in dioxane (1 mL) was added piperidine (0.009 mL, 0.091 mmol). The reaction mixture was then heated under microwave irradiation at 130°C for 10 minutes. The reaction mixture was cooled to room temperature and treated with 6N HCl (1mL). The solution was capped and stirred overnight at room temperature. The crude reaction mixture was purified by reverse phase chromatography to give [4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate (**107-3**) as a yellow glass. MS calculated M+H: 396.5; found 396.3

The compounds in Table 29 were prepared according to the Reaction Schemes and Scheme 107.

Table 29.

| Cmp | Structure | Name | MS m/z (M+H): calc'd | MS m/z (M+H): observed |
|---|---|---|---|---|
| **107-4** |  | 7-[4-(ammoniomethyl) phenyl]-2-(ethylthio)-6-phenylpyrido[2,3-d]pyrimidin-8-ium dichloride | 373.5 | 373.2 |
| **107-5** |  | {4-[2-(4-acetylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate | 439.5 | 439.3 |
| **107-6** |  | (4-{2-[4-(2-hydroxy ethyl) piperazin-1-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl} phenyl) methanaminium trifluoroacetate | 441.5 | 441.3 |
| **107-7** |  | 2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperazin-1-yl)-N,N-dimethylethanaminium bis(trifluoroacetate) | 468.6 | 468.4 |

| | | | | |
|---|---|---|---|---|
| **107-8** |  | 4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-1-methylpiperazin-1-ium bis(trifluoroacetate) | 411.5 | 411.3 |
| **107-9** |  | [4-(2-hydroxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate | 329.4 | 329.2 |
| **107-10** |  | [4-(2-amino-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanaminium trifluoroacetate | 328.4 | 328.2 |
| **107-11** |  | {4-[2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate | 342.4 | 342.2 |
| **107-12** |  | 2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}piperazin-1-yl)-N,N-diethylethanaminium bis(trifluoroacetate) | 496.7 | 496.3 |
| **107-13** |  | (4-{2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl)methanamini | 426.5 | 426.3 |

| | | | | |
|---|---|---|---|---|
| | | um trifluoroacetate | | |
| **107-14** |  | {4-[2-(1H-imidazol-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate | 379.4 | 379.2 |
| **107-15** |  | 1-(1-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}piperidin-4-yl)pyrrolidinium bis(trifluoroacetate) | 465.6 | 465.5 |
| **107-16** |  | {4-[2-(2,5-dimethylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanaminium trifluoroacetate | 425.5 | 425.3 |
| **107-17** |  | (2S)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium bis(trifluoroacetate) | 411.5 | 411.3 |
| **107-18** |  | (2R)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium bis(trifluoroacetate) | 411.5 | 411.3 |

## EXAMPLE 1

Cloning of the human Akt isoforms and ΔPH-Akt1

The pS2neo vector (deposited in the ATCC on April 3, 2001 as ATCC PTA-3253) was prepared as follows: The pRmHA3 vector (prepared as described in *Nucl. Acid Res.* 16:1043-1061 (1988)) was cut with BglII and a 2734 bp fragment was isolated. The pUChsneo vector (prepared as described in *EMBO J.* 4:167-171 (1985)) was also cut with BglII and a 4029 bp band was isolated. These two isolated fragments were ligated together to generate a vector termed pS2neo-1. This plasmid contains a polylinker between a metallothionine promoter and an alcohol dehydrogenase poly A addition site. It also has a neo resistance gene driven by a heat shock promoter. The pS2neo-1 vector was cut with Psp5II and BsiWI. Two complementary oligonucleotides were synthesized and then annealed (CTGCGGCCGC (SEQ.ID.NO.: 1) and GTACGCGGCCGCAG (SEQ.ID.NO.: 2)). The cut pS2neo-1 and the annealed oligonucleotides were ligated together to generate a second vector, pS2neo. Added in this conversion was a NotI site to aid in the linearization prior to transfection into S2 cells.

Human Akt1 gene was amplified by PCR (Clontech) out of a human spleen cDNA (Clontech) using the 5' primer:
5'CGCGAATTCAGATCTACCATGAGCGACGTGGCTATTGTG 3' (SEQ.ID.NO.: 3), and the 3' primer: 5'CGCTCTAGAGGATCCTCAGGCCGTGCTGCTGGC3' (SEQ.ID.NO.: 4). The 5' primer included an EcoRI and BglII site. The 3' primer included an XbaI and BamHI site for cloning purposes. The resultant PCR product was subcloned into pGEM3Z (Promega) as an EcoRI/Xba I fragment. For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt1 gene using the PCR primer:
5'GTACGATGCTGAACGATATCTTCG 3' (SEQ.ID.NO.: 5). The resulting PCR product encompassed a 5' KpnI site and a 3' BamHI site which were used to subclone the fragment in frame with a biotin tag containing insect cell expression vector, pS2neo.

For the expression of a pleckstrin homology domain ( PH ) deleted (Δaa 4-129, which includes deletion of a portion of the Akt1 hinge region) version of Akt1, PCR deletion mutagenesis was done using the full length Akt1 gene in the pS2neo vector as template. The PCR was carried out in 2 steps using overlapping internal primers (5'GAATACATGCCGATGGAAAGCGACGGGGCTGAAGAGATGGAGGTG 3' (SEQ.ID.NO.: 6), and 5'CCCCTCCATCTCTTCAGCCCCGTCGCTTTCCATCGGCATG TATTC 3' (SEQ.ID.NO.: 7)) which encompassed the deletion and 5' and 3' flanking primers which encompassed the KpnI site and middle T tag on the 5' end. The final PCR product was digested with KpnI and SmaI and ligated into the pS2neo full length Akt1 KpnI/SmaI cut vector, effectively replacing the 5' end of the clone with the deleted version.

Human Akt3 gene was amplified by PCR of adult brain cDNA (Clontech) using the amino terminal oligo primer:
5' GAATTCAGATCTACCATGAGCGATGTTACCATTGTG 3' (SEQ.ID.NO.: 8); and the carboxy terminal oligo primer :
5' TCTAGATCTTATTCTCGTCCACTTGCAGAG 3'(SEQ.ID.NO.: 9).

These primers included a 5' EcoRI/BglII site and a 3' XbaI/BglII site for cloning purposes. The resultant PCR product was cloned into the EcoRI and XbaI sites of pGEM4Z (Promega). For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt3 clone using the PCR primer:

5'GGTACCATGGAATACATGCCGATGGAAAGCGATGTTACCATTGTGAAG 3'(SEQ.ID.NO.: 10). The resultant PCR product encompassed a 5' KpnI site which allowed in frame cloning with the biotin tag containing insect cell expression vector, pS2neo.

Human Akt2 gene was amplified by PCR from human thymus cDNA (Clontech) using the amino terminal oligo primer:

5' AAGCTTAGATCTACCATGAATGAGGTGTCTGTC 3' (SEQ.ID.NO.: 11); and the carboxy terminal oligo primer: 5'GAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.NO.: 12). These primers included a 5' HindIII/BglII site and a 3' EcoRI/BamHI site for cloning purposes. The resultant PCR product was subcloned into the HindIII/EcoRI sites of pGem3Z (Promega). For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt2 using the PCR primer:

5'GGTACCATGGAATACATGCCGATGGAAAATGAGGTGTCTGTCATCAAAG 3' (SEQ.ID.NO.: 13). The resultant PCR product was subcloned into the pS2neo vector as described above.

## EXAMPLE 2

### Expression of human Akt isoforms and ΔPH-Akt1

The DNA containing the cloned Akt1, Akt2, Akt3 and ΔPH-Akt1 genes in the pS2neo expression vector was purified and used to transfect *Drosophila* S2 cells (ATCC) by the calcium phosphate method. Pools of antibiotic (G418, 500 μg/ml) resistant cells were selected. Cell were expanded to a 1.0 L volume (~7.0 x $10^6$ / ml), biotin and $CuSO_4$ were added to a final concentration of 50 μM and 50 mM respectively. Cells were grown for 72 h at 27°C and harvested by centrifugation. The cell paste was frozen at –70°C until needed.

## EXAMPLE 3

### Purification of human Akt isoforms and ΔPH-Akt1

Cell paste from one liter of S2 cells, described in Example 2, was lysed by sonication with 50 mls 1% CHAPS in buffer A: (50mM Tris pH 7.4, 1mM EDTA, 1mM EGTA, 0.2mM AEBSF, 10μg/ml benzamidine, 5μg/ml of leupeptin, aprotinin and pepstatin each, 10% glycerol and 1mM DTT). The soluble fraction was purified on a Protein G Sepharose fast flow (Pharmacia) column loaded with 9mg/ml anti-middle T monoclonal antibody and eluted with 75 μM EYMPME (SEQ.ID.NO.: 14) peptide in buffer A containing 25% glycerol. Akt/PKB containing fractions were pooled and the protein purity evaluated by SDS-PAGE. The purified protein was quantitated using a standard Bradford protocol. Purified protein was flash frozen on liquid nitrogen and stored at -70°C.

Akt and Akt pleckstrin homology domain deletions purified from S2 cells required activation. Akt and Akt pleckstrin homology domain deletions were activated (Alessi

et al. *Current Biology* 7:261-269) in a reaction containing 10 nM PDK1 (Upstate Biotechnology, Inc.), lipid vesicles (10 μM phosphatidylinositol-3,4,5-trisphosphate – Metreya, Inc, 100 μM phosphatidylcholine and 100 μM phosphatidylserine – Avanti Polar lipids, Inc.) and activation buffer (50 mM Tris pH7.4, 1.0 mM DTT, 0.1 mM EGTA, 1.0 μM Microcystin–LR, 0.1 mM ATP, 10 mM $MgCl_2$, 333 μg/ml BSA and 0.1mM EDTA). The reaction was incubated at 22°C for 4 hours. Aliquots were flash frozen in liquid nitrogen.

EXAMPLE 4

Akt Kinase Assays

Activated Akt isoforms and pleckstrin homology domain deletion constructs were assayed utilizing a GSK-derived biotinylated peptide substrate. The extent of peptide phosphorylation was determined by Homogeneous Time Resolved Fluorescence (HTRF) using a lanthanide chelate(Lance)-coupled monoclonal antibody specific for the phosphopeptide in combination with a streptavidin-linked allophycocyanin (SA-APC) fluorophore which will bind to the biotin moiety on the peptide. When the Lance and APC are in proximity (i.e. bound to the same phosphopeptide molecule), a non-radiative energy transfer takes place from the Lance to the APC, followed by emission of light from APC at 665 nm.

Materials required for the assay:

A. Activated Akt isozyme or pleckstrin homology domain deleted construct

B. Akt peptide substrate: GSK3α (S21) Peptide #3928 biotin-GGRARTSSFAEPG (SEQ.ID.NO.:15), Macromolecular Resources.

C. Lance labeled anti-phospho GSK3α monoclonal antibody (Cell Signaling Technology, clone # 27).

D. SA-APC (Prozyme catalog no. PJ25S lot # 896067).

E. Microfluor®B U Bottom Microtiter Plates (Dynex Technologies, Catalog no. 7205).

F. Discovery® HTRF Microplate Analyzer, Packard Instrument Company.

G. 100 X Protease Inhibitor Cocktail (PIC): 1 mg/ml benzamidine, 0.5 mg/ml pepstatin, 0.5 mg/ml leupeptin, 0.5 mg/ml aprotinin.

H. 10X Assay Buffer: 500 mM HEPES, pH 7.5, 1% PEG, mM EDTA, 1 mM EGTA, 1% BSA, 20 mM ϑ-Glycerol phosphate.

I. Quench Buffer: 50 mM HEPES pH 7.3, 16.6 mM EDTA, 0.1% BSA, 0.1% Triton X-100, 0.17 nM Lance labeled monoclonal antibody clone # 27, 0.0067 mg/ml SA-APC

J. ATP/$MgCl_2$ working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 125 mM KCl, 5% Glycerol, 25 mM $MgCl_2$, 375 TM ATP

K. Enzyme working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, active Akt. The final enzyme concentrations were selected so that the assay was in a linear response range.

L. Peptide working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, 2 TM GSK3 biotinylated peptide # 3928

The reaction is assembled by adding 16 TL of the ATP/$MgCl_2$ working solution to the appropriate wells of a 96-well microtiter plate. Inhibitor or vehicle (1.0 Tl ) is added followed by 10 Tl of peptide working solution. The reaction is started by adding 13 Tl of the enzyme working solution and mixing. The reaction is allowed to proceed for 50 min and then stopped by the addition of 60 Tl HTRF quench buffer. The stopped reactions were incubated at room temperature for at least 30 min and then read on the Discovery instrument.

Procedure for Streptavidin Flash Plate Assay:

Step 1:

A 1 µl solution of the test compound in 100% DMSO was added to 20 µl of 2X substrate solution (20 uM GSK3 Peptide, 300 µM ATP, 20 mM $MgCl_2$, 20 µCi / ml [$\gamma^{33}$P] ATP, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC, 0.1% BSA and 100 mM KCl). Phosphorylation reactions were initiated by adding 19 µl of 2X Enzyme solution (6.4 nM active Akt/PKB, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC and 0.1% BSA). The reactions were then incubated at room temperature for 45 minutes.

Step 2:

The reaction was stopped by adding 170 µl of 125 mM EDTA. 200 µl of stopped reaction was transferred to a Streptavidin Flashplate® PLUS (NEN Life Sciences, catalog no. SMP103). The plate was incubated for ≥10 minutes at room temperature on a plate shaker. The contents of each well was aspirated, and the wells rinsed 2 times with 200 µl TBS per well. The wells were then washed 3 times for 5 minutes with 200 µl TBS per well with the plates incubated at room temperature on a platform shaker during wash steps.

The plates were covered with sealing tape and counted using the Packard TopCount with the appropriate settings for counting [$^{33}$P] in Flashplates.

Procedure for Streptavidin Filter Plate Assay:

Step 1:

The enzymatic reactions as described in Step 1 of the Streptavidin Flash Plate Assay above were performed.

Step 2:

The reaction was stopped by adding 20 µl of 7.5M Guanidine Hydrochloride. 50 µl of the stopped reaction was transferred to the Streptavidin filter plate (SAM$^{2™}$ Biotin Capture Plate, Promega, catalog no. V7542) and the reaction was incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 4 x 200 µl/well of 2M NaCl; 2) 6 x 200 µl/well of 2M NaCl with 1% $H_3PO_4$; 3) 2 x 200 µl/well of di$H_20$; and 4) 2 x 100 µl/well of 95% Ethanol. The membranes were then allowed to air dry completely before adding scintillant.

The bottom of the plate was sealed with white backing tape, 30 µl/well of Microscint 20 (Packard Instruments, catalog no. 6013621) was added. The top of the plate was

sealed with clear sealing tape, and the plate then counted using the Packard TopCount with the appropriate settings for [$^{33}$P] with liquid scintillant.

Procedure for Phosphocellulose Filter Plate Assay:

Step 1:

The enzymatic reactions were performed as described in Step 1 of the Streptavidin Flash Plate Assay (above) utilizing KKGGRARTSSFAEPG (SEQ.ID.NO.: 16) as the substrate in place of biotin-GGRARTSSFAEPG.

Step 2:

The reaction was stopped by adding 20 µl of 0.75% $H_3PO_4$. 50 µl of stopped reaction was transferred to the filter plate (UNIFILTER™, Whatman P81 Strong Cation Exchanger, White Polystyrene 96 Well Plates, Polyfiltronics, catalog no. 7700-3312) and the reaction incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 9 x 200 µl/well of 0.75% $H_3PO_4$; and 2) 2 x 200 µl/well of di$H_20$. The bottom of the plate was sealed with white backing tape, then 30 µl/well of Microscint 20 was added. The top of the plate was sealed with clear sealing tape, and the plate counted using the Packard TopCount with the appropriate settings for [$^{33}$P] and liquid scintillant.

PKA assay:

Each individual PKA assay consists of the following components:

A. 5X PKA assay buffer (200 mM Tris pH7.5, 100 mM $MgCl_2$, 5mM ϑ-mercaptoethanol, 0.5 mM EDTA)

B. 50 µM stock of Kemptide (Sigma) diluted in water

C. $^{33}$P-ATP prepared by diluting 1.0 µl $^{33}$P-ATP [10 mCi/ml] into 200 Tl of a 50 µM stock of unlabeled ATP

D. 10 µl of a 70 nM stock of PKA catalytic subunit (UBI catalog # 14-114) diluted in 0.5 mg/ml BSA

E. PKA/Kemptide working solution: equal volumes of 5X PKA assay buffer, Kemptide solution and PKA catalytic subunit.

The reaction is assembled in a 96 deep-well assay plate. The inhibitor or vehicle (10 Tl) is added to 10 Tl of the $^{33}$P-ATP solution. The reaction is initiated by adding 30 Tl of the PKA/Kemptide working solution to each well. The reactions were mixed and incubated at room temperature for 20 min. The reactions were stopped by adding 50 Tl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing.

The enzyme reaction product (phosphorylated Kemptide) was collected on p81 phosphocellulose 96 well filter plates (Millipore). To prepare the plate, each well of a p81 filter plate was filled with 75 mM phosphoric acid. The wells were emptied through the filter by applying a vacuum to the bottom of the plate. Phosphoric acid (75 mM, 170 µl) was added to each well. A 30 µl aliquot from each stopped PKA reaction was added to corresponding wells on the filter plate containing the phosphoric acid. The peptide was trapped on the filter following

the application of a vacuum and the filters were washed 5 times with 75 mM phosphoric acid. After the final wash, the filters were allowed to air dry. Scintillation fluid (30 µl) was added to each well and the filters counted on a TopCount (Packard).

PKC assay:

Each PKC assay consists of the following components:

A. 10X PKC co-activation buffer: 2.5 mM EGTA, 4mM $CaCl_2$

B. 5X PKC activation buffer: 1.6 mg/ml phosphatidylserine, 0.16 mg/ml diacylglycerol, 100 mM Tris pH 7.5, 50 mM $MgCl_2$, 5 mM ϑ-mercaptoethanol

C. $^{33}$P-ATP prepared by diluting 1.0 µl $^{33}$P-ATP [10 mCi/ml] into 100µl of a 100 µM stock of unlabeled ATP

D. Myelin basic protein (350 µg/ml, UBI) diluted in water

E. PKC (50ng/ml, UBI catalog # 14-115) diluted into 0.5 mg/ml BSA

F. PKC/Myelin Basic Protein working solution: Prepared by mixing 5 volumes each of PKC co-activation buffer and Myelin Basic protein with 10 volumes each of PKC activation buffer and PKC.

The assays were assembled in 96 deep-well assay plates. Inhibitor or vehicle (10 Tl) was added to 5.0 ul of $^{33}$P-ATP. Reactions were initiated with the addition of the PKC/Myelin Basic Protein working solution and mixing. Reactions were incubated at 30$^{O}$C for 20 min. The reactions were stopped by adding 50 Tl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing. Phosphorylated Mylein Basic Protein was collected on PVDF membranes in 96 well filter plates and quantitated by scintillation counting.

Compounds of the instant invention described in Schemes and Tables above were tested in the assay described above and were found to have $IC_{50}$ of ≤ 50 µM against one or more of Akt1, Akt2 and Akt3.

## EXAMPLE 5

Cell based Assays to Determine Inhibition of Akt/PKB

Cells (for example LnCaP or a PTEN$^{(-/-)}$tumor cell line with activated Akt/PKB) were plated in 100 mM dishes. When the cells were approximately 70 to 80% confluent, the cells were refed with 5 mls of fresh media and the test compound added in solution. Controls included untreated cells, vehicle treated cells and cells treated with either LY294002 (Sigma) or wortmanin (Sigma) at 20 µM or 200 nM, respectively. The cells were incubated for 2, 4 or 6 hrs, and the media removed, The cells were washed with PBS, scraped and transferred to a centrifuge tube. They were pelleted and washed again with PBS. Finally, the cell pellet was resuspended in lysis buffer (20 mM Tris pH8, 140 mM NaCl, 2 mM EDTA, 1% Triton, 1 mM Na Pyrophosphate, 10 mM ϑ-Glycerol Phosphate, 10 mM NaF, 0.5 mm $NaVO_4$, 1 µM Microsystine, and 1x Protease Inhibitor Cocktail), placed on ice for 15 minutes and gently vortexed to lyse the cells. The lysate was spun in a Beckman tabletop ultra centrifuge at 100,000 x g at 4°C for 20min. The supernatant protein was quantitated by a standard Bradford protocol (BioRad) and stored at –70° C until needed.

Proteins were immunoprecipitated (IP) from cleared lysates as follows: For Akt1/PKBI, lysates are mixed with Santa Cruz sc-7126 (D-17) in NETN (100mM NaCl, 20mM Tris pH 8.0, 1mM EDTA, 0.5% NP-40) and Protein A/G Agarose (Santa Cruz sc-2003) was added. For Akt2/PKBϑ, lysates were mixed in NETN with anti-Akt2 agarose (Upstate Biotechnology #16-174) and for Akt3/PKBK, lysates were mixed in NETN with anti-Akt3 agarose (Upstate Biotechnology #16-175). The IPs were incubated overnight at 4° C, washed and seperated by SDS-PAGE.

Western blots were used to analyze total Akt, pThr308 Akt1, pSer473 Akt1, and corresponding phosphorylation sites on Akt2 and Akt3, and downstream targets of Akt using specific antibodies (Cell Signaling Technology): Anti-Total Akt (cat. no. 9272), Anti-Phopho Akt Serine 473 (cat. no. 9271), and Anti-Phospho Akt Threonine 308 (cat. no. 9275). After incubating with the appropriate primary antibody diluted in PBS + 0.5% non-fat dry milk (NFDM) at 4 °C overnight, blots were washed, incubated with Horseradish peroxidase (HRP)-tagged secondary antibody in PBS + 0.5% NFDM for 1 hour at room temperature. Proteins were detected with ECL Reagents (Amersham/Pharmacia Biotech RPN2134).

## EXAMPLE 6

### Heregulin Stimulated Akt Activation

MCF7 cells (a human breast cancer line that is $PTEN^{+/+}$) were plated at $1x10^6$ cells per 100mM plate. When the cells were 70 – 80% confluent, they were refed with 5 ml of serum free media and incubated overnight. The following morning, compound was added and the cells were incubated for 1 – 2 hrs, after which time heregulin was added (to induce the activation of Akt) for 30 minutes and the cells were analyzed as described above.

## EXAMPLE 7

### Inhibition Of Tumor Growth

In vivo efficacy of an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art.

Human tumor cell lines which exhibit a deregulation of the PI3K pathway (such as LnCaP, PC3, C33a, OVCAR-3, MDA-MB-468, A2780 or the like) are injected subcutaneously into the left flank of 6-10 week old female nude (also male mice [age 10-14 weeks] are used for prostate tumor xenografts [LnCaP and PC3]) mice (Harlan) on day 0. The mice are randomly assigned to a vehicle, compound or combination treatment group. Daily subcutaneous administration begins on day 1 and continues for the duration of the experiment. Alternatively, the inhibitor test compound may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.2 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 4 to 5.5 weeks after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

## EXAMPLE 8

### Spot Multiplex Assay

This procedure describes a sandwich immunoassay used to detect multiple phosphorylated proteins in the same well of a 96 well format plate. Cell lysates are incubated in 96-well plates on which different capture antibodies are placed on spatially distinct spots in the same well. Phoshorylation-specific rabbit polyclonal antibodies are added and the complex is detected by an anti-rabbit antibody labeled with an electrochemiluminescent tag.

96-Well LNCaP plates +/- Compounds:

Spin in Beckman J6 1200 rpm 10 min, aspirate media. Add 50µl/well: TBS (Pierce #28376-20mM Tris pH 7.5, 150mM NaCl) + 1% Triton X-100 + Protease and Phosphatase Inhibitors. Wrap in plastic wrap, place in -70°C freezer until completely frozen. Block Multiplex Plates (Meso Scale Discovery, Gaithersburg, MD) with 3% Blocker A in 1X Tris Wash Buffer, 150µl/well. Cover with plate sealer, incubate on Micromix shaker RT 2h (minimum). Wash with 1X RCM 51 (TTBS). Thaw cell lysate plates on ice, add 40µl lysate/well into blocked plates. Cover with plate sealer, incubate on Micromix shaker 4°C O/N, Wash with 1X RCM 51. Dilute Secondary Antibodies in 1% Blocker A in 1X Tris Wash Buffer: Anti phospho AKT (T308), Anti phospho Tuberin (T1462), alone or in combination. Add 25µl/well, cover with plate sealer, incubate on Micromix shaker RT 3h. Wash with 1X RCM 51. Dilute Ru-GAR in 1% Blocker A in 1X Tris Wash Buffer. Add 25µl/well, cover with plate sealer, incubate on Micromix shaker RT 1h. Wash with 1X RCM 51. Dilute 4X Read Buffer T to 1X with Water, add 200µl diluted Read Buffer/well

Read on Sector 6000 Imager.

Protease and Phosphatase Inhibitors:

Microcystin-LR, Calbiochem # 475815 to 1 µM final concentration (stock=500µM)

Calbiochem # 524624, 100X Set I

Calbiochem # 524625, 100X Set II

Calbiochem # 539134, 100X Set III

Anti Phospho AKT (T308):

Cell Signaling Technologies # 9275

Anti Phospho Tuberin (T1462):

Covance Affinity Purified (Rabbits MS 2731/2732)

Ru-GAR = Ruthenylated Goat anti Rabbit

10X Tris Wash Buffer, Blocker A and 4X Read Buffer T

10X RCM 51 (10X TTBS, RCM 51)

1X = 20mM Tris pH 7.5, 140mM NaCl, 0.1% Tween-20

EXAMPLE 9

Cell-Based (In-vivo) Assay

This procedure describes a cell-based (in vivo) activity assay for the Akt serine/threonine kinase. Activated endogenous Akt is capable of phosphorylatinga specific Akt substrate (GSK3β) peptide which is biotinylated. Detection is performed by Homogeneous Time Resolved Fluorescence (HTRF) using a Europium Kryptate [Eu(K)] coupled antibody specific

for the phosphopeptide and streptavidin linked XL665 fluorophore which will bind to the biotin moiety on the peptide. When the [Eu(K)] and XL665 are in proximity (i.e. bound to the same phosphopeptide molecule) a non-radiative energy transfer takes place from the Eu(K) to the XL665, followed by emission of light from XL665 at 665 nm.

The assay can be used to detect inhibitors of all three Akt isozymes (Akt1, Akt2, and Akt3) from multiple different species if specific antibodies to each exist.

MATERIALS AND REAGENTS

A. Cell Culture Microtiter Flat Bottom 96 well plates, Corning Costar, Catalog no. 3598

B. Reacti-Bind Protein A Coated 96-well plates, Pierce, Catalog no 15130.

C. Reacti-Bind Protein G Coated 96-well plates, Pierce, Catalog no 15131.

D. Micromix 5 Shaker.

E. Microfluor®B U Bottom Microtiter Plates, Dynex Technologies, Catalog no. 7205.

F. 96 Well Plate Washer, Bio-Tek Instruments, Catalog no. EL 404.

G. Discovery® HTRF Microplate Analyzer, Packard Instrument Company.

BUFFER SOLUTIONS

A. IP Kinase Cell Lysis Buffer: 1X TBS; 0.2% Tween 20; 1X Protease Inhibitor Cocktail III (Stock is 100X, Calbiochem, 539134); 1X Phosphatase Inhibitor Cocktail I (Stock is 100X, Calbiochem, 524624); and 1X Phosphatase Inhibitor Cocktail II (Stock is 100X, Calbiochem, 524625).

B. 10X Assay Buffer: 500 mM Hepes pH 7.5; 1% PEG; 1 mM EDTA; 1 mM EGTA; and 20 mM β-glycerophosphate.

C. IP Kinase Assay Buffer: 1X Assay Buffer; 50 mM KCl; 150 μM ATP; 10 mM $MgCl_2$; 5% Glycerol; 1 mM DTT; 1 Tablet Protease Inhibitor Cocktail per 50 ml Assay Buffer; and 0.1% BSA

D. GSK3β Substrate Solution: IP Kinase Assay Buffer; and 500 nM Biotinylated GSK3β peptide.

E. Lance Buffer: 50 mM Hepes pH 7.5; 0.1% BSA; and 0.1%Triton X-100.

F. Lance Stop Buffer: Lance Buffer; and 33.3 mM EDTA.

G. Lance Detection Buffer: Lance Buffer; 13.3 μg/ml SA-APC; and 0.665 nM EuK Ab a-phospho (Ser-21) GSK3ß

Multi-Step Immunoprecipitation Akt Kinase Assay

Day1

A. Seed C33a cells Step: Plate 60,000 C33a cells/well in 96 well microtiter plate.

B. Incubate cells overnight at 37°C.

Day 2

D. Compound Addition Step: Add compounds in fresh media (alpha-MEM/10% FBS, room temp) to 96 well plate from above and incubate for 5 hrs in tissue culture incubator.

E. Cell Lysis Step: Aspirate media and add 100 μl of IP Kinase Cell Lysis Buffer.

F. Freeze 96 well microtiter plate at -70°C (NOTE: This step can be done for a minimum of 1 hour or overnight.)

Day 3

G. Coat Protein A/G 96 well plate Step: Add appropriate concentration of α-Akt antibody (Akt1, Akt2, or Akt3) in a 100 µl of PBS to the following wells:

| | |
|---|---|
| α-Akt 1 (20 ng/well/100ul) | B2 >>>>>> B10 / rows B – G / Akt1 plate |
| α-Akt 2 (50 ng/well/100ul) | B2 >>>>>> B10 / rows B – G / Akt2 plate |
| Rabbit-IgG (150 ng/well/100 ul): | B11 – G11 on every plate (Akt1 and Akt2) |

H. Incubate in the cold room (+4°C) for 4 hours on the Micromix 5 (Form 20; Attitude 2) (NOTE: Attitude depends on which Micromix 5 machine).

I. Aspirate off α-Akt antibody solution and add 100 µl of PBS to each well.

J. Akt Immunoprecipitation Step: To the 100 µl of PBS from Step(I) add 5 µl of thawed cell lystate for Akt1 plates and 10 µl of thawed cell lysate for Akt2 plates. NOTE: Thaw cell lysate on ice. Mix thawed lysate by pipetting up & down 10X before transferring to antibody plates. Keep the cell lysate plates on ice. After transfer of cell lysate to the antibody plates refreeze the cell lysate plates at -70°C.

K. Incubate in the cold room (+4°C) overnight on Micromix 5 shaker (form 20, attitude 3).

Day 4

L. Immunoprecipitation Plate Wash Step: Wash 96 well plates 1X with TTBS (RCM 51, 1X = 2 cycles) using the 96-Well Plate Washer. Fill wells with TTBS and incubate for 10 minutes. Wash 96 well plates 2X with TTBS. (NOTE: Prime plate washer before use: 1. Check buffer reservoirs, making sure they are full and 2. empty waste containers.

M. Manual Plate Wash Step: Add 180 µl of IP Kinase Assay buffer.

N. Start Akt Enzyme Reaction: Aspirate supernatant. Add 60 µl of GSK3β Substrate Solution.

O. Incubate for 2.5 hours on Micromix 5 shaker @ RT. NOTE: Time of incubation should be adjusted so that the ratio of Column 10 /Column 11 is not >10.

P. Combine 30 µl of Lance Detection Buffer with 30 µl of Lance Stop Buffer (60 µl total/well) and add to Microfluor U bottom 96 well black plates.

Q. Stop Akt Enzyme Reaction: Transfer 40 µl of Akt Enzyme Reaction Mix from Protein A/G 96 well plate from Step (O) to Microfluor U bottom 96 well black plates from Step (P).

U. Incubate at room temperature for 1-2 hrs on Micromix 5 shaker (form 20, attitude 3), then read with the Discovery HTRF Microplate Analyzer using Akt program.

IP Kinase Cell Lysis Buffer

100 µl per well

| | | | |
|---|---|---|---|
| | 8 ml<br>(1 Plate) | | 45 ml<br>(6 Plates) |

| | | | |
|---|---|---|---|
| 1X TBS | 7744 µl | | NA |
| Tween 20 | 20 µl | | NA |
| 1X Protease Inhibitor Cocktail III | 80 µl | | NA |
| 1X Phosphatase Inhibitor | | | 450 µl |
| Cocktail I | 80 µl | | 450 µl |
| 1X Phosphatase Inhibitor | | | 450 µl |
| Cocktail II | 80 µl | | |
| Microcystin LR (500X) | | | 90 µl |

IP Kinase Assay Buffer

100 µl per well

| | 8 ml (1 Plate) | | 50 ml (3 Plates) |
|---|---|---|---|
| 10X Assay Buffer | 800 µl | | 5 ml |
| 1 M KCl | 400 µl | | 2.5 ml |
| 250 mM ATP | 4.8 µl | | 30 µl |
| 1M $MgCl_2$ | 80 µl | | 500 µl |
| Glycerol | 400 µl | | 2.5 ml |
| 1M DTT | 8 µl | | 50 µl |
| Protease Inhibitor Cocktail | 1 tablet/50 ml | | 1 |
| 10% BSA | 80 µl | | 500 µl |
| di $dH_20$ | 6227.2 µl | | 38.9 ml |

GSK3ß Substrate Solution

60 µl per well

| | 5 ml (1 Plate) | | 7 ml |
|---|---|---|---|
| IP Kinase Assay Buffer | 5 ml | | - |
| 1 mM GSK3ß peptide | 2.5 µl | | 3.5 µl |

Lance Stop Buffer

30 µl per well

| | 3 ml (1 Plate) | 5 ml | 5 ml |
|---|---|---|---|
| 1X Lance Buffer | 2800.2 µl | | |
| EDTA 0.5 M | 199.8 µl | | |

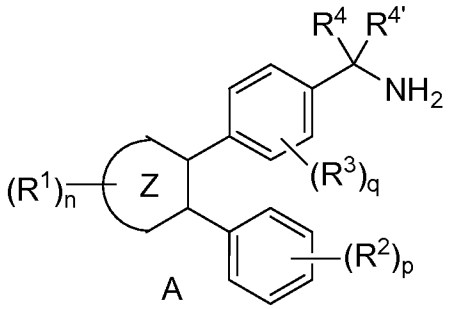
Lance Detection Buffer

30 µl per well

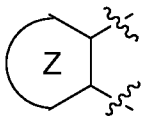
| | | | |
|---|---|---|---|
| | 3 ml<br>(1 Plate) | | 5 ml |
| SA-APC (1 mg/ml in ddH2O, dilute 1/75.2 in Lance Buffer)<br>EuK Ab a-phospho (Ser 21)GSK3ß (680 nM, dilute 1/1133 in Lance Buffer) | 40 µl<br><br>2.7 µl | | 66.7 µl<br><br>4.5 µl |

WHAT IS CLAIMED IS:

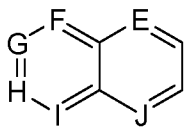
1. A compound according to the Formula A:




wherein:



is selected from:




and wherein E, F, G, H, I and J are independently selected from CH or N;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; n is 1, 2, 3, 4, 5 or 6; p is 0, 1, 2, 3, 4 or 5 and q is 0, 1, 2, 3 or 4;

$R^1$ can be found on either ring of the bicyclic moiety and is independently selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^2$ is independently selected from: $(C_1\text{-}C_6)$alkyl, halo and OH, wherein said alkyl is optionally substituted with halo;

$R^3$ is independently selected from: $(C_1\text{-}C_6)$alkyl, halo and OH, wherein said alkyl is optionally substituted with halo;

$R^4$ and $R^{4'}$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)NR^7R^8$, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$, or $R^4$ and $R^{4'}$ can be taken together to form a $(C_3\text{-}C_8)$cycloalkyl or a monocyclic heterocycle optionally containing one to four heteroatoms selected from N, O and S, said cycloalkyl and monocyclic heterocycle optionally substituted with one or more substituents selected from $R^6$, wherein the $R^6$ substituent is optionally a spirocyclic moiety;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one to three substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

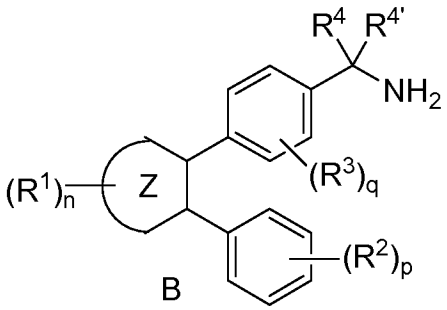
$R^7$ and $R^8$ are independently selected from: H, $(C=O)O_bC_1\text{-}C_{10}$ alkyl, $(C=O)O_bC_3\text{-}C_8$ cycloalkyl, $(C=O)O_b$aryl, $(C=O)O_b$heterocyclyl, $C_1\text{-}C_{10}$ alkyl, aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, heterocyclyl, $C_3\text{-}C_8$ cycloalkyl, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one to three substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one to three substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

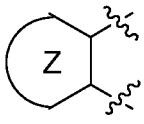
$R^b$ is H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)_aO_b(C_1\text{-}C_6)$alkyl, or $S(O)_2R^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

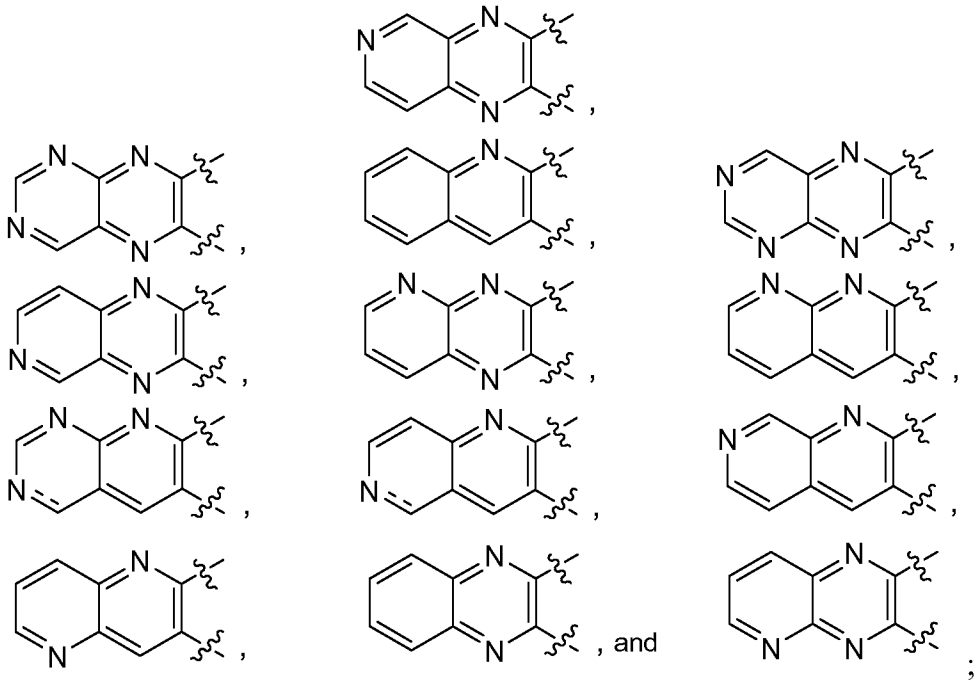
2. A compound according to Claim 1 of the Formula B:




wherein:




is selected from:

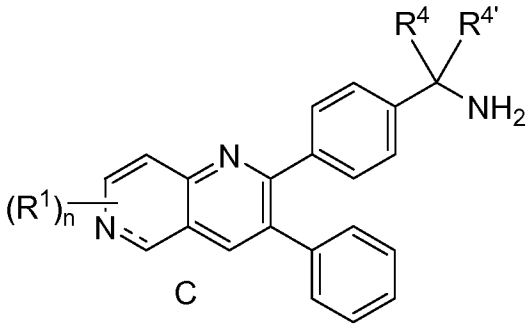



and wherein the dashed line is an optional double bond,

and all other substituents and variables are as defined in Claim 1,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

3. A compound according to Claim 1 of the Formula C:



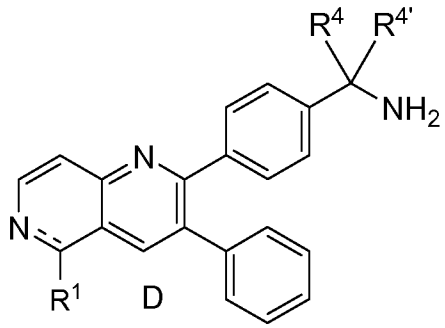

C

wherein the dashed line is an optional double bond,

and wherein all other substituents and variables are as defined in Claim 1,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

4. A compound according to Claim 1 of the Formula D:




D

wherein the dashed line is an optional double bond,

and wherein all other substituents and variables are as defined in Claim 1,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

5. A compound which is selected from:

2-[4-(1-amino-1-methylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6H)-one;
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine;
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine;
2-methyl-1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]propan-1-amine;
2-[4-(1-amino-2-phenylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6*H*)-one;
2-[4-(1,2-diammonioethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine;
2-[4-(1-ammonio-2-fluoroethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine;
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopropanamine;

1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclopentanamine;
1-[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]cyclohexanamine;
[4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(6-benzyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-oxo-3-phenyl-6-propyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(6-ethyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
2-[4-(1-aminocyclobutyl)phenyl]-6-(difluoromethyl)-3-phenyl-1,6-naphthyridin-5(6H)-one;
{4-[8-(2-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(2-methoxy-1,3-thiazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[5-hydroxy-3-phenyl-8-(1,3-thiazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(3-furyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(1-benzofuran-2-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin -2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(5-methyl-2-furyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(4-methylthien-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(1-benzothien-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(1-benzothien-7-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(1-benzofuran-5-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
[4-(5-hydroxy-3-phenyl-8-thien-3-yl-1,6-naphthyridin-2-yl)phenyl] methanamine;
{4-[5-hydroxy-8-(3-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanamine;
{4-[5-hydroxy-8-(2-methylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(2-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(2-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(3-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(3-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
(4-{5-hydroxy-3-phenyl-8-[3-(trifluoromethyl)phenyl]-1,6-naphthyridin-2-yl}phenyl) methanamine;
{4-[5-hydroxy-8-(3-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(3-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(4-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(4-fluorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[8-(4-chlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(4-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(3,5-dimethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;

{4-[8-(3,5-dichlorophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(3-ethoxyphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
[4-(8-cyclohex-1-en-1-yl-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
{4-[5-hydroxy-8-(3-mercaptophenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[5-hydroxy-8-(2-hydroxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
(4-{5-hydroxy-8-[3-(hydroxymethyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl);
{4-[8-(3-cyanophenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(3-isopropylphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(1,1'-biphenyl-3-yl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
2-[4-(ammoniomethyl)phenyl]-8-[3-(dimethylamino)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridine;
{4-[8-(3-acetylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
(4-{5-hydroxy-8-[3-(methoxycarbonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
8-(3-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-5-hydroxy-3-phenyl-1,6-naphthyridine;
[4-(5-hydroxy-8-{3-[(methylamino)carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
(4-{5-hydroxy-8-[3-(methylsulfonyl)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
{4-[8-(3-ethylphenyl)-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-hydroxy-8-(3-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
6-[4-(ammoniomethyl)phenyl]-1-hydroxy-4-isobutyl-7-phenylisoquinoline;
{4-[5-oxo-3-phenyl-8-(1-propyl-1*H*-pyrazol-4-yl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(4-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[5-oxo-3-phenyl-8-(2-thienyl)-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine;
[4-(5-oxo-3-phenyl-8-pyridin-3-yl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-oxo-3,8-diphenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
{4-[8-(2-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(6-methoxypyridin-3-yl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(3-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(4-nitrophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[8-(2-cyanophenyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[6-methyl-8-(4-methyl-2-thienyl)-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine;

{4-[8-(4-fluoro-3-methylphenyl)-6-methyl-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine;
[4-(8-cyano-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(8-chloro-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(8-bromo-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
1-{4-[5-hydroxy-8-(4-methylthien-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine;
1-[4-(8-cyano-5-hydroxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
[3-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl]methanamine;
[5-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)pyridin-2-yl] methanamine;
[2,3-difluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanamine;
[2-fluoro-4-(5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridin-2-yl)phenyl] methanamine;
{4-[3-(4-chlorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}methanamine;
1-{4-[3-(4-fluorophenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;

2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-(2-fluorophenyl)-6-methyl-1,6-naphthyridin-5(6H)-one;
2-[4-(aminomethyl)phenyl]-5-oxo-3-phenyl-5,6-dihydro-1,6-naphthyridine-4-carbonitrile;
(1*R*)-1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}ethanamine;
1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclopropanamine;
1-{4-[3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[5-(2-oxopyrrolidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-(4-{3-phenyl-5-[(2-pyridin-4-ylethyl)thio]-1,6-naphthyridin-2-yl}phenyl)cyclobutanamine;
2-[4-(1-ammoniocyclobutyl) phenyl]-5-diazan-2-iumyl-3-phenyl-1,6-naphthyridine;
1-(4-{5-[2,2-difluoro-2-(pyridin-4-yl)ethoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine;
1-(4-{5-[2-methyl-2-(pyridin-4-yl)propoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine;
1-(4-{5-[(2-fluoropyridin-4-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine;
1-{4-[3-phenyl-5-(pyridin-3-yloxy)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(1,3,4-thiadiazol-2-yl)-1,6-naphthyridin-5-amine;
2-[4-(1-aminocyclobutyl)phenyl]-N-(3-methyl-1H-pyrazol-5-yl)-3-phenyl-1,6-naphthyridin-5-amine;
1-{4-[3-phenyl-5-(piperidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[5-(3,3-difluoroazetidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[5-(3,3-difluoropiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[5-(4-hydroxypiperidin-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
2-[4-(1-aminocyclobutyl)phenyl]-N-(benzyloxy)-3-phenyl-1,6-naphthyridin-5-amine;

2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine;
5-amino-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-2-ylethyl)amino]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl)phenyl]-5-[methyl(2-pyridin-4-ylethyl)amino]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(2- pyridine-2-ylethyl) amino]-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-piperidin-1-yl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-(benzylamino) -3-phenyl-1,6-naphthyridine;
2-({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}amino) ethanamine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrrolidin-1-yl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-(diethylamino) -3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-(methylamino) -3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-[bis(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-[(2-hydroxyethyl)(methyl) amino]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-[ethyl(2-hydroxyethyl)amino]-3-phenyl-1,6-naphthyridine;
5-[4-(aminocarbonyl)piperidin-1-yl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[(2-pyridin-4-ylethyl)amino]-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-morpholin-4-yl-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl )phenyl]-5-[2-(hydroxymethyl) morpholin-4-yl]-3-phenyl-1,6-naphthyridine;
2-[4-(aminomethyl)phenyl]-N-ethyl-3-phenyl-1,6-naphthyridin-5-amine;
{4-[3-phenyl-5-(4H-1,2,4-triazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine;
[4-(3-phenyl-5-piperazin-1-yl-1,6-naphthyridin-2-yl)phenyl]methanamine;
4-[5-(ethylthio)-3-phenyl-1,6-naphthyridin-2-yl]benzylamine;
[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
1-{4-[3-phenyl-5-(2-piperidin-1-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine;
2-[4-(ammoniomethyl) phenyl]-5-phenoxy-3-phenyl-1,6-naphthyridine;
(4-{5-[4-(aminocarbonyl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
{4-[5-(4-nitrophenoxy)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
(4-{5-[4-(1H-imidazol-1-yl)phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
(4-{3-phenyl-5-[4-(1H-1,2,4-triazol-1-yl)phenoxy]-1,6-naphthyridin-2-yl}phenyl) methanamine;
(4-{5-[4-(methoxycarbonyl) phenoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)acetamide;

1-(4-{5-[(1-methylpiperidin-3-yl)methoxy]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
tert-butyl 2-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethylcarbamate;
tert-butyl 4-({2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)butylcarbamate;
2-[3-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)propyl]pyridine;
2-[2-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy)ethyl]pyridine;
2-[({2-[4-(ammoniomethyl )phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) methyl]morpholine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethoxy)-1,6-naphthyridine;
1-{4-[5-(2-morpholin-4-ylethoxy)-3-phenyl-1,6-naphthyridin-2-yl] phenyl}methanamine;
1-{4-[3-phenyl-5-(2-piperidin-4-ylethoxy)-1,6-naphthyridin-2-yl] phenyl}methanamine;
3-[2-({2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}oxy) ethyl]piperidine;
1-(4-{3-phenyl-5-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]-1,6-naphthyridin-2-yl}phenyl) methanamine;
4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl) benzylamine;
2-[4-(ammoniomethyl) phenyl]-3,5-diphenyl-1,6-naphthyridine;
{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
[(3,3'-diphenyl-5,5'-bi-1,6-naphthyridine-2,2'-diyl)di-4,1-phenylene] dimethanamine;
4-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}benzyl)morpholine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(1H-pyrazol-1-ium-3-yl)-1,6-naphthyridine;
1-{4-[3-phenyl-5-(1H-pyrrol-2-yl)-1,6-naphthyridin-2-yl]phenyl} methanamine;
3-{2-[4-(aminomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}aniline;
[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene] dimethanamine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-pyrimidin-5-yl-1,6-naphthyridine;
3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}pyridine;
4-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} pyridine;
1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl }methanamine;
5-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}isoquinoline;
{4-[3-phenyl-5-(3-thienyl)-1,6-naphthyridin-2-yl]phenyl} methanamine;
1-{4-[5-(3,5-dimethylisoxazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[5-(3,5-dimethyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
1-(4-{5-[3-(benzyloxy) phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
1-(4-{5-[3-(benzyloxy)phenyl] -3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
{4-[5-(2-naphthyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
5-(4-aminophenyl)-2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[(E)-2-phenylvinyl]-1,6-naphthyridine;
(4-{5-[4-(benzyloxy)phenyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
{4-[5-(4-{[(2-hydroxyethyl) amino] carbonyl}phenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;

3-[(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl} benzoyl)amino]-N,N-dimethylpropan-1-amine;
[4-(5-{4-[(cyclopropylamino) carbonyl]phenyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
1-{4-[5-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
(1*R*)-1-{4-[3-phenyl-5-(1*H*-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine;
{4-[5-(2-methoxyphenyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
(1R)-1-{4-[3-phenyl-5-(thiophen-3-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine;
(1R)-1-{4-[3-phenyl-5-(thiophen-2-yl)-1,6-naphthyridin-2-yl]phenyl}ethanamine;
(1R)-1-{4-[5-(5-chlorothiophen-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}ethanamine;
1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclopropanamine;
1-{4-[3-phenyl-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine;
1,1'-[(3-phenyl-1,6-naphthyridine-2,5-diyl)di-4,1-phenylene]dicyclobutanamine;
1-{4-[5-(3-methyl-1H-pyrazol-4-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[5-(4-methyl-1,3-thiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[3-phenyl-5-(1,3-thiazol-2-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanamine;
2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro[3.4]octan-2amine;
2-{4-[3-phenyl-5-(pyridin-3-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2 amine;
2-{4-[3-phenyl-5-(pyridin-4-yl)-1,6-naphthyridin-2-yl]phenyl}-5,8-dioxaspiro[3.4]octan-2-amine;
2-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-5,8-dioxaspiro [3.4]octan-2-amine;
trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-4-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol;
trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-(1H-pyrazol-3-yl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol;
2-[4-(1-ammoniocyclobutyl)phenyl]-5-methyl-3-phenyl-1,6-naphthyridine;
1-[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
1-[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanamine;
1-[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]propan-1-amine;
[4-(5-methyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-isobutyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-ethyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(3-phenyl-5-propyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-benzyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-isopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
[4-(5-cyclohexyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
[4-(5-cyclopropyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
[4-(5-butyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;

{4-[5-(3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
trans-3-amino-1-cyclopropyl-3-{4-[3-phenyl-5-methyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol;
trans-3-amino-1-cyclopropyl-3-{4-[3-(2-fluorophenyl)-5-methyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol;
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-[( pyridine-4-ylmethoxy)methyl]-1,6-naphthyridine;

{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol;
{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methanol;
trans-3-amino-1-cyclopropyl-3-{4-[5-(fluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol;
trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanol;
1-{4-[5-(difluoromethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} cyclobutanamine;
trans-3-amino-1-cyclopropyl-3-{4-[5-(difluoromethyl)-3-(2-fluorophenyl)-1,6-naphthyridin-2-yl]phenyl}cyclobutanol;
1-[4-(5-{[(2-fluoropyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutanamine;
1-[4-(5-{[(2-methoxypyridin-4-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] cyclobutanamine;
4-[({2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methoxy)methyl]pyridin-2(1H)-one;
1-[4-(5-{[(3-hydroxy[1,2,4]triazolo[4,3-a]pyridin-7-yl)methoxy]methyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
1-[4-(5-ethenyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
2-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}ethanol;
{4-[5-(3-hydroxypropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-(4-hydroxybutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-(4-morpholin-4-ylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-(3-morpholin-4-ylpropyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(2-pyridin-4-ylethyl)-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-[2-(1-methyl-1H-imidazol-5-yl)ethyl]-3-phenyl-1,6-naphthyridine;
(4-{5-[2-(3-aminophenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl )methanamine;
(4-{5-[2-(3-hydroxyphenyl) ethyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
N-(3-{2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}propyl)-4-oxo-5-phenyl-4,5-dihydro-1,3-oxazol-2-amine;
2-[4-(ammoniomethyl) phenyl]-5-(3-hydroxy-3-phenylpropyl)-3-phenyl-1,6-naphthyridine;
5-[2-(4-aminophenyl)ethyl]-2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridine;

[4-(5-{3-[2-(hydroxymethyl) phenoxy]propyl}-3-phenyl-1,6-naphthyridin-2-yl)phenyl] methanamine;
benzyl 4-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2,2-dimethylbut-3-ynoate;
{4-[5-(3-carboxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-(3-carboxy-3-methylbut-1-yn-1-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
{4-[5-(3-hydroxy-3-methylbutyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-methylbut-3-yn-2-ol;
4-{2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-3-chloro-2-methylbut-3-en-2-ol;
(4-{5-[5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
(4-{5-[5-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
{4-[5-(2-ethoxy-2-oxo-1-pyridin-4-ylethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
2-{2-[4-(aminomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-2-pyridin-4-ylacetohydrazide;
[4-(5-cyano-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
{4-[5-(1-hydroxyethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
[4-(5-acetyl-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methanamine;
2-[4-(1-aminocyclobutyl)phenyl]-3-(2-fluorophenyl)-1,6-naphthyridine-5-carbonitrile;
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile;
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile;
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile;
2-[4-(trans-1-amino-3-fluoro-3-methylcyclobutyl)phenyl]-3-phenyl-1,6-naphthyridine-5-carbonitrile;
1-[4-(5-carboxy-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclobutanamine;
{4-[5-(3-methyl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[3-phenyl-5-(3-phenyl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine;
{4-[3-phenyl-5-(1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl}methanamine;
(4-{5-[3-(1H-indol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
(4-{5-[3-(2,3-dihydro-1H-inden-2-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
{4-[3-phenyl-5-(3-pyrimidin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridin-2-yl]phenyl} methanamine;

{4-[5-(3-biphenyl-4-yl-1H-1,2,4-triazol-5-yl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl} methanamine;
2-(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl) pyrrolidinium;
(4-{5-[3-(4-methylmorpholin-3-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
(4-{5-[3-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,4-triazol-5-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
4-[(5-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)methyl]morpholin-4-ium;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-4-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-3-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine;
(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) methanamine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-[3-(1H-pyrazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyrazin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-(3-pyridin-2-yl-1H-1,2,4-triazol-5-yl)-1,6-naphthyridine;
{4-[5-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenyl-1,6-naphthyridin-2-yl] phenyl} methanamine;
1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine;
1-(4-{3-phenyl-5-[3-(1,3-thiazol-5-yl)-1H-1,2,4-triazol-5-yl]-1,6-naphthyridin-2-yl}phenyl) cyclobutanamine;
3-(5-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1H-1,2,4-triazol-3-yl)-4-methylmorpholine;
1-(4-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
(4-{5-[(E)-amino(hydroxyimino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
2-(3-{2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}-1,2,4-oxadiazol-5-yl)ethanamine;
(4-{5-[(benzoylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl) methanamine;
{4-[5-(ammoniomethyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
(4-{5-[(benzoylamino) methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;
[4-(3-phenyl-5-{[(phenylacetyl )amino]methyl}-1,6-naphthyridin-2-yl)phenyl]methanamine;
(4-{5-[(glycoloylamino)methyl]-3-phenyl-1,6-naphthyridin-2-yl}phenyl)methanamine;

2-[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)amino]-2-oxoethanamine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(pyrazin-2-ylcarbonyl)amino]methyl}-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-({[(5-phenyl-4H-1,2,4-triazol-3-yl)acetyl]amino} methyl)-1,6-naphthyridine;
7-{[({2-[4-(ammoniomethyl) phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) amino]carbonyl}-1,2,3,4-tetrahydro-1,8-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-3-phenyl-5-{[(quinoxalin-6-ylcarbonyl)amino]methyl}-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-1-ylacetyl)amino]methyl}-3-phenyl-1,6-naphthyridine;
2-[4-(ammoniomethyl) phenyl]-5-{[(1H-imidazol-2-ylcarbonyl)amino]methyl}-3-phenyl-1,6-naphthyridine;
{4-[5-({[4-(ammoniomethyl) benzoyl]amino}methyl)-3-phenyl-1,6-naphthyridin-2-yl]phenyl}methanamine;
2-[4-(ammoniomethyl) phenyl]-5-[(isonicotinoylamino)methyl]-3-phenyl-1,6-naphthyridine;
4-{[({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl) ammonio]methyl} pyridine;
N-({2-[4-(ammoniomethyl)phenyl]-3-phenyl-1,6-naphthyridin-5-yl}methyl)-2-hydroxy-N-(2-hydroxyethyl)ethanamine;
2-[4-(ammoniomethyl)phenyl]-3-phenyl-5-{[( pyridine-4-ylcarbonyl)( pyridine-4-ylmethyl)amino]methyl}-1,6-naphthyridine;
2-[4-(1-ammoniocyclobutyl)phenyl]-5-{[isonicotinoyl(pyridin-4-ylmethyl) amino]methyl}-3-phenyl-1,6-naphthyridine;
2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenyl-6-pyridin-3-yl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(6-methoxypyridin-3-yl)-3-phenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-imidazol-4-yl)-3-phenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1-propyl-1H-pyrazol-4-yl)-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(1H-pyrazol-4-yl)-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-pyrimidin-5-yl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-3,6-diphenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-methyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-3-phenyl-6-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl) phenyl]-6-(1-benzyl-1H-pyrazol-4-yl)-3-phenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,7-naphthyridine;
2-[4-(1-ammoniocyclobutyl)phenyl]-6-chloro-3-phenyl-1,5-naphthyridine;

2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-1,7-naphthyridine-8-carbonitrile;
2-[4-(1-aminocyclobutyl)phenyl]-3-phenyl-N-(2-phenylethyl)-1,7-naphthyridin-8-amine;
1-[4-(3-phenyl-1,5-naphthyridin-2-yl)phenyl]methanamine;
1-{4-[3-phenyl-6-(1*H*-pyrazol-4-yl)-1,5-naphthyridin-2-yl]phenyl} cyclobutanamine;
6-[4-(1-aminocyclobutyl)phenyl]-7-phenyl-1,5-naphthyridin-2(1H)-one;
6-[4-(1-aminocyclobutyl)phenyl]-1-methyl-7-phenyl-1,5-naphthyridin-2(1H)-one;
6-trans-3-cyclopropyl-3-hydroxy-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanamine;
trans-3-hydroxy-3-methyl-1-[4-(5-methyl-6-oxo-3-phenyl-5,6-dihydro-1,5-naphthyridin-2-yl)phenyl]cyclobutanamine;
trans-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy-3-methyl cyclobutanamine;
trans-3-cyclopropyl-1-{4-[3-(2-fluorophenyl)-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-2-yl]phenyl}-3-hydroxy cyclobutanamine;
1-[4-(6-morpholin-4-yl-3-phenyl-1,5-naphthyridin-2-yl)phenyl] cyclobutanamine;
1-{4-[6-(diethylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanamine;
1-{4-[6-(butylamino)-3-phenyl-1,5-naphthyridin-2-yl]phenyl}cyclobutanamine;
[4-(6,7-dichloro-3-phenylquinoxalin-2-yl)phenyl]methanamine;
2-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-3-phenylquinoxalin-5-ol;
3-[4-(aminomethyl)phenyl]-6-(6-methoxypyridin-3-yl)-2-phenylquinoxalin-5-ol;
(4-{3-phenyl-5-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanamine;
(4-{3-phenyl-8-[3-(pyridin-4-yl)propoxy]quinoxalin-2-yl}phenyl)methanamine;
1-{4-[3-phenyl-6-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine;
1-{4-[3-phenyl-7-(2*H*-tetrazol-5-yl)quinoxalin-2-yl]phenyl}methanamine;
1-[4-(5-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanamine;
1-[4-(8-hydroxy-3-phenylquinoxalin-2-yl)phenyl]cyclobutanamine;
1-(4-{3-phenyl-5-[2-(pyridin-4-yl)ethoxy]quinoxalin-2-yl}phenyl) cyclobutanamine;
1-{4-[3-phenyl-8-(2-pyridin-4-ylethoxy)quinoxalin-2-yl]phenyl} cyclobutanamine;
1-{4-[3-phenyl-5-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl}cyclobutanamine;
1-{4-[3-phenyl-8-(2-(N-oxo-pyridin-4-yl)ethoxy)quinoxalin-2-yl]phenyl}cyclobutanamine;
(4-{6-[(2-hydroxyethyl)amino]-3-phenylpyrido[2,3-b]pyrazin-2-yl}phenyl) methanamine;
(4-{6-[(2-hydroxyethyl)amino]-2-phenylpyrido[2,3-b]pyrazin-3-yl}phenyl) methanamine;
[4-(6-hydroxy-3-phenylpyrido[2,3-b] pyrazin-2-yl)phenyl] methanamine;
[4-(6-hydroxy-2-phenylpyrido[2,3-b] pyrazin-3-yl)phenyl] methanamine;
4-{2-[4-(ammonio methyl) phenyl]-3-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazine;
4-{3-[4-(ammoniomethyl) phenyl]-2-phenylpyrido [2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino) ethyl]piperazine;
1-{4-[3-phenyl-6-(2-pyridin-4-ylethoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine;

1-(4-{2-phenyl-6-[2-(pyridin-4-yl)ethoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine;
1-{4-[3-phenyl-6-(3-pyridin-4-ylpropoxy) pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine;
1-(4-{2-phenyl-6-[3-(pyridin-4-yl)propoxy] pyrido[2,3-b]pyrazin-3-yl}phenyl)methanamine;
{4-[3-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine;
{4-[2-phenyl-6-(1H-pyrazol-5-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanamine;
1-{4-[3-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl}methanamine;
1-{4-[2-phenyl-6-(1H-pyrazol-4-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl}methanamine;
{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine;
{4-[6-(5-amino-1,3,4-thiadiazol-2-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine;
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-3-phenylpyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine;
{4-[6-(5-methyl-4H-1,2,4-triazol-3-yl)-2-phenylpyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine;
{4-[3-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-2-yl]phenyl} methanamine;
{4-[2-phenyl-6-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)pyrido[2,3-b]pyrazin-3-yl]phenyl} methanamine;
2-[4-(trans-1-amino-3-cyclopropyl-3-hydroxycyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one;
2-[4-(trans-1-amino-3-hydroxy-3-methylcyclobutyl)phenyl]-5-methyl-3-phenylpyrido[2,3-b]pyrazin-6(5H)-one;
2-[4-(aminomethyl)phenyl]-3-phenylpyrido[3,4-*b*]pyrazin-5-ol;
3-[4-(aminomethyl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-5-ol;
1-[4-(3-phenylpyrido[3,4-b]pyrazin-2-yl)phenyl]methanamine;
1-[4-(2-phenylpyrido[3,4-b]pyrazin-3-yl)phenyl]methanamine;
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazine;
4-{2-[4-(1-ammoniocyclopropyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-3-yl}-1-[2-(dimethylamino)ethyl]piperazine;
4-{2-[4-(1-ammoniocyclobutyl)phenyl]-3-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(methylamino)ethyl]piperazine;
4-{3-[4-(1-ammoniocyclobutyl)phenyl]-2-phenylpyrido[2,3-b]pyrazin-6-yl}-1-[2-(dimethylamino)ethyl]piperazine;
7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine;
7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-*d*]pyrimidin-4-amine;
[4-(3-phenyl-1,8-naphthyridin-2-yl)phenyl]methanamine;
1-[4-(4-hydroxy-6-phenylpteridin-7-yl)phenyl]cyclobutanamine;
1-[4-(4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanamine;
1-[4-(3-phenylquinoxalin-2-yl)phenyl] cyclobutanamine;

1-[4-(2-amino-4-hydroxy-7-phenylpteridin-6-yl)phenyl]cyclobutanamine;
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(4-methylpiperazin-4-ium-1-yl)-6-phenylpyrido[2,3-d]pyrimidine;
7-[4-(1-ammonio cyclobutyl)phenyl]-2-[(2-hydroxyethyl)amino]-6-phenylpyrido[2,3-d] pyrimidine;
2-[4-(aminocarbonyl) piperidin-1-yl]-7-[4-(1-ammoniocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidine;
2-(4-acetylpiperazin-1-yl)-7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidine;
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-piperazin-4-ium-1-ylpyrido[2,3-d]pyrimidine;
7-[4-(1-ammonio cyclobutyl)phenyl]-6-phenyl-2-(4-pyrazin-2-ylpiperazin-1-yl) pyrido [2,3-d]pyrimidine;
7-[4-(1-ammonio cyclobutyl)phenyl]-2-(4-benzoylpiperazin-1-yl)-6-phenylpyrido[2,3-d] pyrimidine;
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(methylamino)-6-phenylpyrido[2,3-d]pyrimide;
7-[4-(1-ammoniocyclobutyl)phenyl]-2-(dimethylamino)-6-phenylpyrido[2,3-d]pyrimide;
1-{4-[2-(4-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanamine;
1-{4-[2-(3-hydroxypiperidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanamine;
(2R)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol;
(2S)-1-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)propan-2-ol;
4-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)butan-1-ol;
5-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)pentan-1-ol;
3-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)-2,2-dimethylpropan-1-ol;
6-({7-[4-(1-aminocyclobutyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}amino)hexan-1-ol;
1-{4-[2-(3-hydroxypyrrolidin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl} cyclobutanamine;
1-(4-{2-[(2-ammonioethyl)(2-methoxy-2-oxoethyl)amino]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) cyclobutanamine;
1-[4-(2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanamine;
1-[4-(2-{[2-(acetylamino) ethyl]amino}-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl] cyclobutanamine;
[4-(6-phenyl-2-piperidin-1-ylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine;
7-[4-(ammoniomethyl) phenyl]-2-(ethylthio)-6-phenylpyrido[2,3-d]pyrimidine;

{4-[2-(4-acetylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine;
(4-{2-[4-(2-hydroxy ethyl) piperazin-1-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl} phenyl) methanamine;
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperazin-1-yl)-N,N-dimethylethanamine;
4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-1-methylpiperazin-1-ium;
[4-(2-hydroxy-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine;
[4-(2-amino-6-phenylpyrido[2,3-d]pyrimidin-7-yl)phenyl]methanamine;
{4-[2-(methylamino)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine;
2-(4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}piperazin-1-yl)-N,N-diethylethanamine;
(4-{2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-phenylpyrido[2,3-d]pyrimidin-7-yl}phenyl) methanamine;
{4-[2-(1H-imidazol-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine;
1-(1-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl} piperidin-4-yl) pyrrolidinium;
{4-[2-(2,5-dimethylpiperazin-1-yl)-6-phenylpyrido[2,3-d]pyrimidin-7-yl]phenyl}methanamine;
(2S)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium; and
(2R)-4-{7-[4-(ammoniomethyl)phenyl]-6-phenylpyrido[2,3-d]pyrimidin-2-yl}-2-methylpiperazin-1-ium;

or a pharmaceutically acceptable salt or stereoisomer thereof.

6. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

7. The use of the compound according to Claim 1 for the preparation of a medicament useful in the treatment or prevention of cancer in a mammal in need of such treatment.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/21945

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 471/02 (2010.01)
USPC - 546/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 546/122

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/253.04, 544/362, 514/300 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents: biphenyl, naphthyridine, akt, alkylamino, cancer, AKT inhibitor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>------<br>Y | US 7,034,026 B2 (Barnett et al.) 25 April 2006 (25.04.2006) col 3, ln 9-16, 52-53; col 4, ln 6-22; col 5, ln 64 to col 6, ln 8 | 1-2, 6-7<br>----------<br>3-5 |
| Y | 2008/0287457 A1 (Arruda et al.) 20 November 2008 (20.11.2008) para [0015]-[0016] | 3-5 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 26 February 2010 (26.02.2010) | 08 MAR 2010 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)