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(71) Applicant(s)
Viamet Pharmaceuticals (NC), Inc.

(72) Inventor(s)
Hoekstra, William J.;Yates, Christopher M.;Rafferty, Stephen W.

(74) Agent / Attorney
Griffith Hack, GPO Box 1285, Melbourne, VIC, 3001, AU

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(71) Applicant: **VIAMET PHARMACEUTICALS, INC.** [US/US]; 4505 Emperor Blvd., Suite 300, Durham, NC 27703 (US).

(72) Inventors: **HOEKSTRA, William, J.**; 7 Treviso Place, Durham, NC 27707 (US). **YATES, Christopher, M.**; 6201 Therfield Drive, Raleigh, NC 27614 (US). **RAFFERTY, Stephen, W.**; 525 Okeechobee Blvd., Suite 1600, West Palm Beach, FL 33401 (US).

(74) Agents: **HSI, Jeffrey D.** et al.; Edwards Wildman Palmer LLP, P.O. Box 55874, Boston, MA 02205 (US).

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(54) Title: METALLOENZYME INHIBITOR COMPOUNDS

(57) Abstract: The instant invention describes compounds having metalloenzyme modulating activity, and methods of treating diseases, disorders or symptoms thereof mediated by such metalloenzymes.

Metalloenzyme Inhibitor Compounds

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/757,594 filed January 28, 2013, the contents of which is incorporated herein by reference in its entirety.

BACKGROUND

Living organisms have developed tightly regulated processes that specifically imports metals, transport them to intracellular storage sites and ultimately transport them to sites of use. One of the most important functions of metals such as zinc and iron in biological systems is to enable the activity of metalloenzymes. Metalloenzymes are enzymes that incorporate metal ions into the enzyme active site and utilize the metal as a part of the catalytic process. More than one-third of all characterized enzymes are metalloenzymes.

The function of metalloenzymes is highly dependent on the presence of the metal ion in the active site of the enzyme. It is well recognized that agents which bind to and inactivate the active site metal ion dramatically decrease the activity of the enzyme. Nature employs this same strategy to decrease the activity of certain metalloenzymes during periods in which the enzymatic activity is undesirable. For example, the protein TIMP (tissue inhibitor of metalloproteases) binds to the zinc ion in the active site of various matrix metalloprotease enzymes and thereby arrests the enzymatic activity. The pharmaceutical industry has used the same strategy in the design of therapeutic agents. For example, the matrix metalloproteinase (MMP) inhibitor marimastat contains a hydroxamic acid group that binds to the zinc present in the active site of the target isoforms of the enzyme MMP and thereby inactivates the enzyme. Another example includes hydroxamic acid group that has been incorporated into most published inhibitors of histone deacetylases. A third example is the zinc-binding carboxylic acid group that has been incorporated into most published angiotensin-converting enzyme inhibitors.

In the design of clinically safe and effective metalloenzyme inhibitors, use of the most appropriate metal-binding group for the particular target and clinical indication is critical. If a weakly binding metal-binding group is utilized, potency may be suboptimal. On the other hand, if a very tightly binding metal-binding group is utilized, selectivity for the target enzyme

versus related metalloenzymes may be suboptimal. The lack of optimal selectivity can be a cause for clinical toxicity due to unintended inhibition of these off-target metalloenzymes. It is believed that off-target inhibition is caused primarily by the indiscriminate binding of the currently utilized hydroxamic acid to zinc in the active site of MMP enzyme isoforms. An example of this is the joint pain that has been observed in many clinical trials of matrix metalloproteinase inhibitors. This toxicity is considered to be related to inhibition of off-target metalloenzymes due to indiscriminate binding of the hydroxamic acid group to zinc in the off-target active sites.

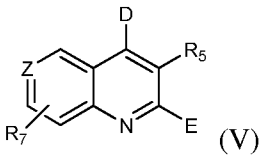
Therefore, the search for metal-binding groups that can achieve a better balance of potency and selectivity remains an important goal and would be significant in the realization of therapeutic agents and methods to address currently unmet needs in treating and preventing diseases, disorders and symptoms thereof.

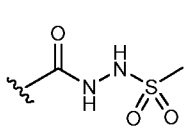
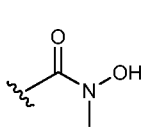
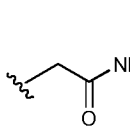
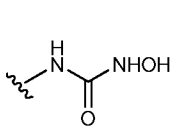
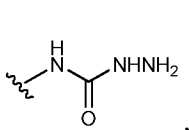
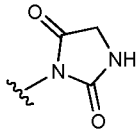
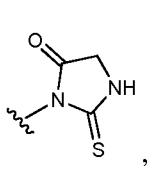
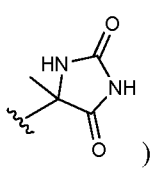
BRIEF SUMMARY OF THE INVENTION

The invention is directed towards compounds (e.g., any of those delineated herein), methods of modulating activity of metalloenzymes, and methods of treating diseases, disorders or symptoms thereof. The methods can comprise the compounds herein.

It is understood that the embodiments of the invention discussed below with respect to the preferred variable selections can be taken alone or in combination with one or more embodiments, or preferred variable selections, of the invention, as if each combination were explicitly listed herein.

A compound of formula (V), or salt, solvate, hydrate or prodrug thereof, wherein:


(V)

D is  ,  , or  (preferably  ,  ,  ,  ,  ,  ,  ,  ,  ,  , );

E is optionally substituted aryl or optionally substituted heteroaryl (preferably pyridyl, pyrazinyl, furanyl, or thienyl);

X is O; S; NR_4; or H and R_4;

R_3 is $CH(R_4)NHR_4$, $CH(R_4)NHSO_2R_4$, $CH(R_4)SH$, $CH(R_4)OH$, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $N(R_4)OH$, $N(OH)C(=O)R_4$, NHR_4, $NHNHR_4$, $NHC(=O)R_4$, $N(R_4)NHC(=O)R_4$, $NHC(=O)NHR_4$, $NHC(=S)NHR_4$, $NHSO_2R_4$, $NHSO_2NHR_4$; $NHNHSO_2R_4$, NO_2, SO_2NHR_4 (only in the case of formula I), SO_2NHOH (only in the case of formula I), SO_3H (only in the case of formula I), OR_4, OSO_2R_4, OSO_2NHR_4, SR_4, $B(OR_4)_2$, $CH_2B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$, a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a 5-membered heterocycle that is connected through a CH_2;

Y is O or null;

Z is CR_{16} or N;

each R_4 is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) optionally substituted aryl; e) optionally substituted heteroaryl; or f) optionally substituted heterocycloalkyl;

each R_5 is independently H, alkyl, fluoroalkyl, halogen, alkoxy, fluoroalkoxy, substituted amino, aryl, or heteroaryl;

A is O, S, CH_2 or $N(R_4)$;

A may also be the following when R_6 is null: an optionally substituted heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, $B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$;

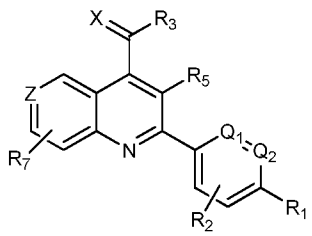
R_6 is null, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NR_4OH$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NR_4OH$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, SO_2NHNR_4 (with the proviso that A cannot be S), SO_2NHR_4 (with the proviso that A cannot be S), SO_2NHOH (with the proviso that A cannot be S); a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a (preferably 5-membered) heterocycle that is connected through a CH_2; and

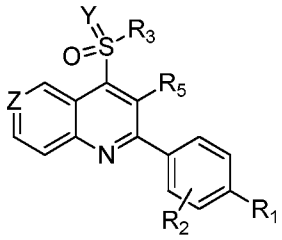
each R_7 is independently H, alkyl, alkoxy, hydroxy, NHR_4, $C(=O)R_4$, $NHC(=O)R_4$, $N(alkyl)C(=O)R_4$, $NHSO_2R_4$, $N(alkyl)SO_2R_4$, $C(=O)NR_{27}R_4$, $SO_2NR_{27}R_4$, $C(=O)NR_{27}NHR_4$, $C(=O)NR_{27}OR_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycloalkyl, or optionally substituted heterocycloalkylcarbonyl;

each R_{16} is independently hydrogen, alkyl, alkoxy, hydroxy, NHR_4, $NHC(=O)R_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycloalkyl; and

each R_{27} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl.

A compound of formula (I), (II), (III), or salt, solvate, hydrate or prodrug thereof, wherein:


(I)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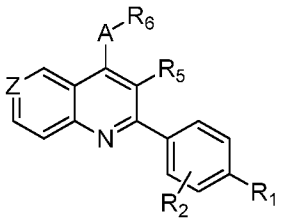
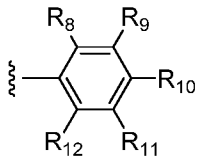

(III)

X is O; S; NR_4; or H and R_4;

each R_1 is independently selected from:


a) ; b) optionally substituted heteroaryl; c) $C\equiv C\text{-}R_{13}$; d) $C(=O)NR_4R_7$; e) $N(R_7)C(=O)R_4$; f) $SO_2NR_4R_7$; g) $N(R_7)SO_2R_4$; h) hydrogen; i) hydroxy; j) optionally substituted alkoxy; k) SO_2NHR_4; l) optionally substituted alkenyl; or m) optionally substituted arylalkyl;

each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) H; b) hydroxyalkylamino; c) optionally substituted alkoxy; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) optionally substituted heterocycloalkyl; j) optionally substituted heteroaryl; k) cyano; l) hydroxy; m) SO_2R_4; n) optionally substituted heterocycloalkylcarbonyl; o) optionally substituted heterocycloalkylsulfonyl; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; t) optionally substituted alkyl; or u) dialkylamino;

R_2 is H, alkyl, fluoroalkyl, alkoxy, fluoroalkoxy, halogen, aryl, or heteroaryl;

each R_3 is independently $CH(R_4)NHR_4$, $CH(R_4)NHSO_2R_4$, $CH(R_4)SH$, $CH(R_4)OH$, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$,

$NHC(=NH)NH_2$, $N(R_4)OH$, $N(OH)C(=O)R_4$, NHR_4, $NHNHR_4$, $NHC(=O)R_4$, $N(R_4)NHC(=O)R_4$, $NHC(=O)NHR_4$, $NHC(=S)NHR_4$, $NHSO_2R_4$, $NHSO_2NHR_4$; $NHNHSO_2R_4$, NO_2, SO_2NHR_4 (only in the case of formula I), SO_2NHOH (only in the case of formula I), SO_3H (only in the case of formula I), OR_4, OSO_2R_4, OSO_2NHR_4, SR_4, $B(OR_4)_2$, $CH_2B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$, a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a 5-membered heterocycle that is connected through a CH_2;

Y is O or null;

each Z is independently CR_{16} or N;

each R_4 is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl;

each R_5 is independently H, alkyl, fluoroalkyl, halogen, alkoxy, fluoroalkoxy, substituted amino, aryl, or heteroaryl;

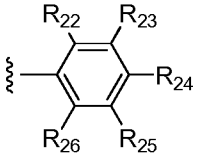
A is O, S, CH_2 or $N(R_4)$;

A may also be the following when R_6 is null: an optionally substituted heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, $B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$;

R_6 is null, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NR_4OH$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NR_4OH$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, SO_2NHNR_4 (with the proviso that A cannot be S), SO_2NHR_4 (with the proviso that A cannot be S), SO_2NHOH (with the proviso that A cannot be S); a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a (preferably 5-membered) heterocycle that is connected through a CH_2; and

each R_7 is independently H, alkyl, alkoxy, hydroxy, NHR_4, $NHC(=O)R_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycloalkyl;

each R_{13} is independently selected from:

a) 

; b) optionally substituted heterocycloalkyl; or c) optionally substituted heteroaryl;

each R_{14} is independently selected from heterocycloalkylcarbonyl, heterocycloalkylsulfonyl, or heterocycloalkyl, each optionally substituted;

each R_{15} is independently H; alkyl; fluoroalkyl; aryl; or heteroaryl;

each R_{16} is independently hydrogen, alkyl, alkoxy, hydroxy, NHR_4, $NHC(=O)R_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocycloalkyl;

each R_{17} is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{18} is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{19} is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{20} is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{21} is independently a) H; b) optionally substituted alkyl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

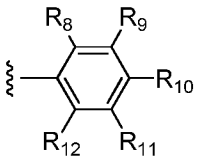
each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from:

i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) optionally substituted heterocycloalkylcarbonyl; v) optionally substituted heterocycloalkylsulfonyl; vi) halogen; vii) optionally substituted alkyl; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) SO_2NHR_{21}; or xv) optionally substituted heterocycloalkyl;

each n is independently 0, 1, 2, 3, or 4; and

Q_1 and Q_2 are each independently CH or N.

Another aspect is a compound of any of the formulae herein, wherein R_1 is

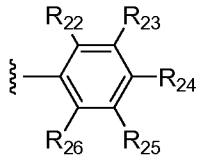


, and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) H; b) hydroxyalkylamino; c) optionally substituted alkoxy; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) optionally substituted heterocycloalkyl; j) optionally substituted heteroaryl; k) cyano; l) hydroxy; m) SO_2R_4; n) optionally substituted heterocycloalkylcarbonyl; o) optionally substituted heterocycloalkylsulfonyl; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; or t) dialkylamino.

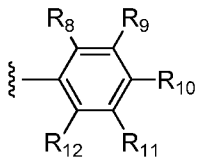
Another aspect is a compound of any of the formulae herein, wherein R_1 is heteroaryl optionally substituted with alkoxy wherein alkoxy is optionally substituted with 1, 2, or 3 hydroxy.

Another aspect is a compound of any of the formulae herein, wherein R_1 is C≡C-C≡C-



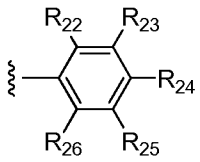
R_{13}, and R_{13} is selected from a) ; b) optionally substituted heterocycloalkyl; c) optionally substituted heteroaryl; or d) optionally substituted cycloalkyl; and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) optionally substituted heterocycloalkylcarbonyl; v) optionally substituted heterocycloalkylsulfonyl; vi) halogen; vii) optionally substituted alkyl; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) optionally substituted alkoxy; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) $SO_2NR_4R_{21}$; or xv) optionally substituted heterocycloalkyl.

Another aspect is a compound of any of the formulae herein, wherein R_1 is selected



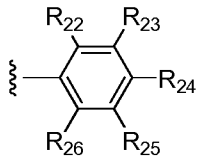
from a) ; b) heteroaryl optionally substituted with alkoxy wherein alkoxy is optionally substituted with 1, 2, or 3 hydroxy; c) $C≡C-R_{13}$; d) $C(=O)NR_4R_7$; e) $N(R_7)C(=O)R_4$; f) $SO_2NR_4R_7$; g) $N(R_7)SO_2R_4$; h) hydrogen; i) hydroxy; j) optionally substituted alkoxy; k) SO_2NHR_4; l) optionally substituted alkenyl; or m) optionally substituted arylalkyl; and the remaining variables are as defined above.

Another aspect is a compound of any of the formulae herein, wherein R_1 is $C≡C-R_{13}$,



and R_{13} is independently selected from a) ; b) optionally substituted heterocycloalkyl; or c) optionally substituted heteroaryl; and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) optionally substituted heterocycloalkylcarbonyl; v) optionally substituted heterocycloalkylsulfonyl; vi) halogen; vii) optionally substituted alkyl; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) SO_2NHR_{21}; or xv) optionally substituted heterocycloalkyl.

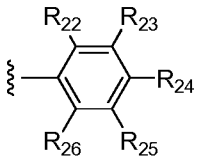
Another aspect is a compound of any of the formulae herein, wherein R_1 is C≡C-R_{13},

R_{13} is independently selected from a)  ; b) optionally substituted heterocycloalkyl; c) optionally substituted heteroaryl; or d) optionally substituted cycloalkyl; and

each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from

i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent alkyl, $CH_2C(=O)OR_{19}$, $CH_2C(=O)NR_4R_7$, OR_4, $CH_2SO_2NR_4R_7$, $C(=O)OR_{19}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; v) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or alkyl; vi) halogen; vii) alkyl optionally substituted with heterocycloalkyl wherein heterocycloalkyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) $SO_2NR_4R_{21}$; or xv) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or $CH_2C(=O)OR_4$.

Another aspect is a compound of any of the formulae herein, wherein R_{13} is independently selected from:

a)  ;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

iii) $C(=O)OR_4$;

iv) $C(=O)NHR_4$; or

c) heteroaryl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl or alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

Another aspect is a compound of any of the formulae herein, wherein R_{13} is independently selected from 1) heteroaryl optionally substituted with 1, 2, or 3 independent a) $NR_{27}SO_2R_4$ or b) $NR_{27}C(=O)R_4$; or 2) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) H; b) hydroxyalkylamino; c) optionally substituted alkoxy; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) optionally substituted heterocycloalkyl; j) optionally substituted heteroaryl; k) cyano; l) hydroxy; m) SO_2R_4; n) optionally substituted heterocycloalkylcarbonyl; o) optionally substituted heterocycloalkylsulfonyl; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; or t) dialkylamino.

Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

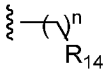
a) H; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent heterocycloalkoxy, heterocycloalkylcarbonyl, hydroxy, amino, $NHSO_2R_4$, $NHC(=O)R_4$, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; j) heteroaryl containing 5 to 6 ring atoms optionally substituted with 1, 2, or 3 independent:

(1) $C(=O)OR_{17}$;

(2) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

(3) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$; or

(4) $C(=O)NHR_4$;

k) cyano; l) hydroxy; m) SO_2R_4; n) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; o) heterocycloalkylsulfonyl optionally substituted with 1, 2, or, 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; t) alkyl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl, heterocycloalkyl, or heterocycloalkylsulfonyl, each

optionally substituted with independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; u) dialkylamino; or v) $-O-(CH_2)_n-C(=O)$-heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

Another aspect is a compound of any of the formulae herein, wherein each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from:

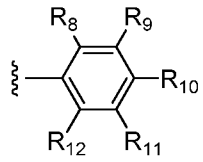
i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent alkyl, $CH_2C(=O)OR_{19}$, $CH_2C(=O)NR_4R_7$, $CH_2SO_2NR_4R_7$, $C(=O)OR_{19}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; v) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or alkyl; vi) halogen; vii) alkyl optionally substituted with heterocycloalkyl wherein heterocycloalkyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) SO_2NHR_{21}; or xv) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or $CH_2C(=O)OR_4$.

Another aspect is a compound of any of the formulae herein, wherein each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl.

Another aspect is a compound of any of the formulae herein, wherein:

X is O; S; NR_4; or H and R_4;

R_1 is selected from:

a)  ; b) heteroaryl optionally substituted with alkoxy wherein alkoxy is optionally substituted with 1, 2, or 3 OR_4; c) $C\equiv C-R_{13}$; d) $C(=O)NR_4R_7$; e) $N(R_7)C(=O)R_4$; f) $SO_2NR_4R_7$; g) $N(R_7)SO_2R_4$; h) hydrogen; i) hydroxy; j) optionally substituted alkoxy; k) SO_2NHR_4; l) optionally substituted alkenyl; or m) optionally substituted arylalkyl;

each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) H; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent heterocycloalkoxy, heterocycloalkylcarbonyl, hydroxy, amino, $NHSO_2R_4$, $NHC(=O)R_4$, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)R_4OH$; d) halogen; e) SO_2NHR_{18}; f)

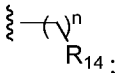
$NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; j) heteroaryl containing 5 to 6 ring atoms optionally substituted with 1, 2, or 3 independent:

(1) $C(=O)OR_{17}$ or $SO_2NR_4R_7$;

(2) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 $C(=O)OR_{17}$;

(3) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$; or

(4) $C(=O)NHR_4$;

k) cyano; l) hydroxy; m) SO_2R_4; n) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; o) heterocycloalkylsulfonyl optionally substituted with 1, 2, or, 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; t) alkyl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl, heterocycloalkyl, or heterocycloalkylsulfonyl, each optionally substituted with independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; u) dialkylamino; or v) $-O-(CH_2)_n-C(=O)$-heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

R_2 is H, alkyl, fluoroalkyl, alkoxy, fluoroalkoxy, halogen, aryl, or heteroaryl;

R_3 is $CH(R_4)NHR_4$, $CH(R_4)NHSO_2R_4$, $CH(R_4)SH$, $CH(R_4)OH$, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $N(R_4)OH$, $N(OH)C(=O)R_4$, NHR_4, $NHNHR_4$, $NHC(=O)R_4$, $N(R_4)NHC(=O)R_4$, $NHC(=O)NHR_4$, $NHC(=S)NHR_4$, $NHSO_2R_4$, $NHSO_2NHR_4$; $NHNHSO_2R_4$, NO_2, SO_2NHR_4 (only in the case of formula I), SO_2NHOH (only in the case of formula I), SO_3H (only in the case of formula I), OR_4, OSO_2R_4, OSO_2NHR_4, SR_4, $B(OR_4)_2$, $CH_2B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$, a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a 5-membered heterocycle that is connected through a CH_2;

Y is O or null;

Z is CR_{16} or N;

each R_4 is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_{27}$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl;

each R_5 is independently H, alkyl, fluoroalkyl, halogen, alkoxy, fluoroalkoxy, substituted amino, aryl, or heteroaryl;

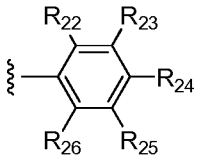
A is O, S, CH_2 or $N(R_4)$;

A may also be the following when R_6 is null: an optionally substituted heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms, $B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$;

R_6 is null, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NR_4OH$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NR_4OH$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, SO_2NHNR_4 (with the proviso that A cannot be S), SO_2NHR_4 (with the proviso that A cannot be S), SO_2NHOH (with the proviso that A cannot be S); a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a (preferably 5-membered) heterocycle that is connected through a CH_2; and

each R_7 is independently H, alkyl, alkoxy, hydroxy, NHR_4, $NHC(=O)R_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, or $NHSO_2R_4$;

each R_{13} is independently selected from:

a) 

;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$; or

c) heteroaryl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl or alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_{14} is independently selected from heterocycloalkylcarbonyl, heterocycloalkylsulfonyl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_{15} is independently H; alkyl; fluoroalkyl; aryl; or heteroaryl;

each R_{16} is independently hydrogen, alkyl, alkoxy, hydroxy, NHR_4, $NHC(=O)R_4$, halogen, optionally substituted aryl, optionally substituted heteroaryl, heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or $NHSO_2R_4$;

each R_{17} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{18} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{19} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{20} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{21} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from

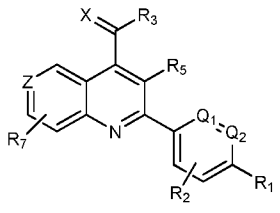
i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent alkyl, $CH_2C(=O)OR_{19}$, $CH_2C(=O)NR_4R_7$, $CH_2SO_2NR_4R_7$, $C(=O)OR_{19}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; v) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, or alkyl; vi) halogen; vii) alkyl optionally substituted with heterocycloalkyl wherein heterocycloalkyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy; xi) haloalkoxy; xii) haloalkyl; xiii) hydroxy; xiv) SO_2NHR_{21}; or xv) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$ or $CH_2C(=O)OR_4$;

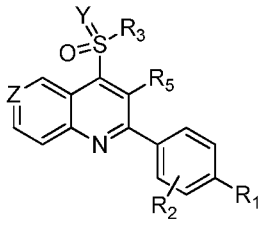
each R_{27} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl;

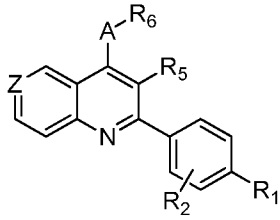
each n is independently 0, 1, 2, 3, or 4; and

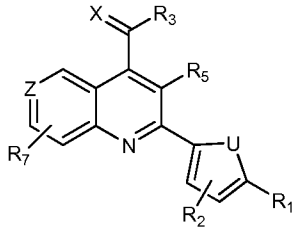
Q_1 and Q_2 are each independently CH or N.

A compound of formula (I), (II), (III), (IV), or salt thereof, wherein:


(I)


(II)

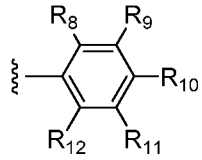

(III)


(IV)

U is O or S;

each X is independently O; S; NR_4; or H and R_4;

each R_1 is independently selected from:


a) ; b) heteroaryl optionally substituted with alkoxy wherein alkoxy is optionally substituted with 1, 2, or 3 OR_4; c) C≡C-R_{13}; d) C(=O)NR_4R_7; e) N(R_7)C(=O)R_4; f) $SO_2NR_4R_7$; g) N(R_7)SO_2R_4; h) hydrogen; i) hydroxy; j) optionally substituted alkoxy; k) SO_2NHR_4; l) optionally substituted alkenyl; m) optionally substituted arylalkyl; or n) C≡C-C≡C-R_{13};

each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

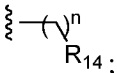
a) H; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent heterocycloalkoxy, heterocycloalkylcarbonyl, hydroxy, amino, $NHSO_2R_4$, NHC(=O)R_4, C(=O)OR_4, C(=O)NHNHR_4, or C(=O)NR_4OH; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) NHC(=O)R_4; h) C(=O)NHR_4; i) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent C(=O)OR_4, C(=O)NR_4R_7, or $SO_2NR_4R_7$; j) heteroaryl containing 5 to 6 ring atoms optionally substituted with 1, 2, or 3 independent:

(1) C(=O)OR_{17};

(2) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent C(=O)OR_{17}, C(=O)NR_4R_7, or $SO_2NR_4R_7$;

(3) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$; or

(4) $C(=O)NHR_4$;

k) cyano; l) hydroxy; m) SO_2R_4; n) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; o) heterocycloalkylsulfonyl optionally substituted with 1, 2, or, 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; t) alkyl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl, heterocycloalkyl, or heterocycloalkylsulfonyl, each optionally substituted with independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; u) dialkylamino; or v) $–O-(CH_2)_n-C(=O)$-heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_2 is independently H, alkyl, fluoroalkyl, alkoxy, fluoroalkoxy, halogen, aryl, or heteroaryl;

each R_3 is independently $CH(R_4)NHR_4$, $CH(R_4)NHSO_2R_4$, $CH(R_4)SH$, $CH(R_4)OH$, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $N(R_4)OH$, $N(OH)C(=O)R_4$, NHR_4, $NHNHR_4$, $NHC(=O)R_4$, $N(R_4)NHC(=O)R_4$, $NHC(=O)NHR_4$, $NHC(=S)NHR_4$, $NHSO_2R_4$, $NHSO_2NHR_4$; $NHNHSO_2R_4$, NO_2, SO_2NHR_4 (only in the case of formula I), SO_2NHOH (only in the case of formula I), SO_3H (only in the case of formula I), OR_4, OSO_2R_4, OSO_2NHR_4, SR_4, $B(OR_4)_2$, $CH_2B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$, a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a 5-membered heterocycle that is connected through a CH_2;

Y is O or null;

Z is CR_{16} or N;

each R_4 is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_{27}$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; e) optionally substituted heteroaryl; or f) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{27}$, $C(=O)NR_{27}R_{27}$, or $SO_2NR_{27}R_{27}$;

each R_5 is independently H, alkyl, fluoroalkyl, halogen, alkoxy, fluoroalkoxy, substituted amino, aryl, or heteroaryl;

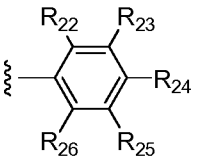
A is O, S, CH_2 or $N(R_4)$;

A may also be the following when R_6 is null: an optionally substituted heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms, $B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$;

R_6 is null, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NR_4OH$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NR_4OH$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, SO_2NHNR_4 (with the proviso that A cannot be S), SO_2NHR_4 (with the proviso that A cannot be S), SO_2NHOH (with the proviso that A cannot be S); a heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms, or a (preferably 5-membered) heterocycle that is connected through a CH_2; and

each R_7 is independently H; alkyl; alkoxy; hydroxy; $C(=O)OR_4$; $NHSO_2R_4$; $N(alkyl)SO_2R_4$; NHR_4; $NHC(=O)R_4$; $N(alkyl)C(=O)R_4$; $C(=O)NR_{27}R_4$, $SO_2NR_{27}R_4$, $C(=O)NR_{27}NHR_4$; $C(=O)NR_{27}OR_4$; halogen; optionally substituted aryl; optionally substituted heteroaryl; heterocycloalkyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$; or heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$;

each R_{13} is independently selected from:

a) 

;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$;

c) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) $NR_{27}SO_2R_4$, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, 4) (heterocycloalkyl)alkyl, or 5) $NR_{27}C(=O)R_4$; or

d) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_{14} is independently selected from heterocycloalkylcarbonyl, heterocycloalkylsulfonyl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_{15} is independently H; alkyl; fluoroalkyl; aryl; arylalkyl; or heteroaryl;

each R_{16} is independently hydrogen; alkyl; alkoxy; hydroxy; NHR_4; $NHC(=O)R_4$; halogen; optionally substituted aryl; optionally substituted heteroaryl; heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or $NHSO_2R_4$;

each R_{17} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{18} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{19} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{20} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, optionally substituted heteroaryl, or optionally substituted aryl; c) fluoroalkyl; d) aryl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$ or OR_4; or e) heteroaryl;

each R_{21} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from

i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent alkyl, $CH_2C(=O)OR_{19}$, $CH_2C(=O)NR_4R_7$, OR_4, $CH_2SO_2NR_4R_7$, $C(=O)OR_{19}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; v) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or alkyl; vi) halogen; vii) alkyl optionally substituted with heterocycloalkyl wherein heterocycloalkyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; xi) haloalkoxy; xii) haloalkyl; xiii)

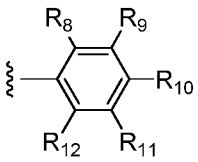
hydroxy; xiv) $SO_2NR_4R_{21}$; or xv) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or $CH_2C(=O)OR_4$;

each R_{27} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl;

each n is independently 0, 1, 2, 3, or 4; and

Q_1 and Q_2 are each independently CH or N.

Another aspect is a compound of any of the formulae herein, wherein R_1 is



and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

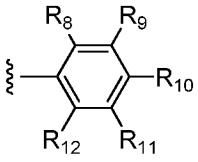
a) hydrogen; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; f) heteroaryl optionally substituted with 1, 2, or 3 independent:

i) $C(=O)OR_{17}$; or

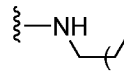
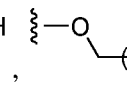
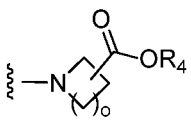
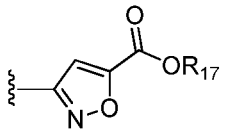
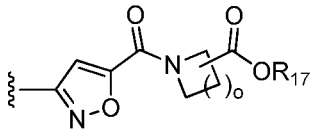
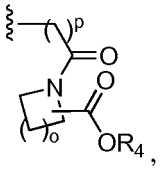
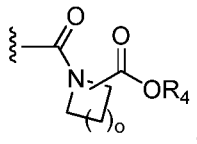
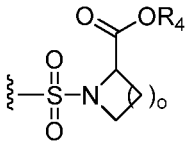
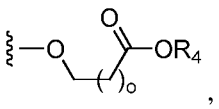
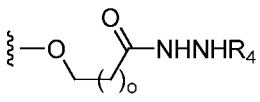
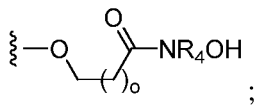
ii) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

g) alkyl optionally substituted with 1, 2, or 3 heterocycloalkylcarbonyl substituted with independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; h) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or i) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

Another aspect is a compound of any of the formulae herein, wherein R_1 is

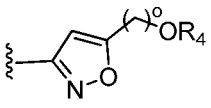


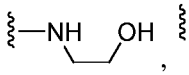
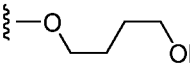
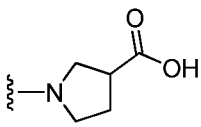
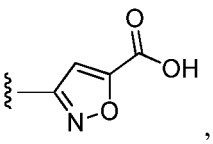
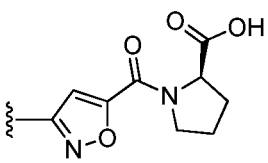
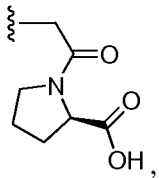
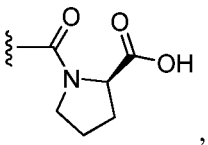
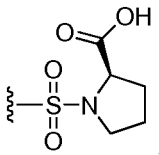
and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from heteroaryl optionally substituted with 1, 2, or 3 independent alkyl wherein said alkyl is optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$.

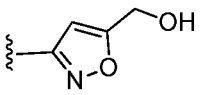
Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from halogen, hydrogen,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ;

each o is independently 1, 2, 3, or 4; and

each p is independently 1, 2, 3, or 4.

Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from  ; and each o is independently 1, 2, 3, or 4.

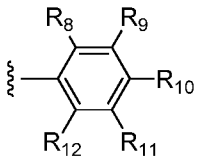
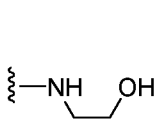
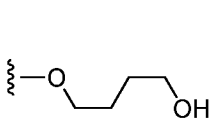
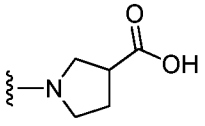
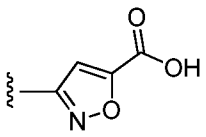
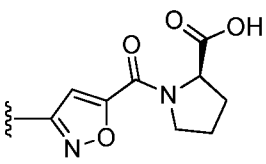
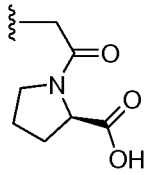
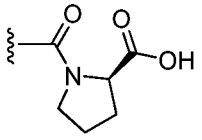
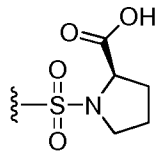
Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from hydrogen,  ,  , F,  ,  ,  ,  ,  , or  .

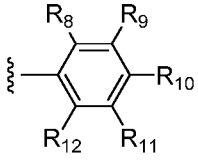
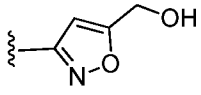
Another aspect is a compound of any of the formulae herein, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from  .

Another aspect is a compound of any of the formulae herein, wherein X is O.

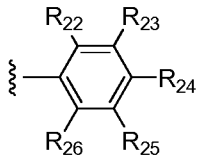
Another aspect is a compound of any of the formulae herein, wherein R_3 is selected from $NHNHR_4$, $NHNHSO_2R_4$, $C(=O)NR_4OH$, or $C(=O)OR_4$.

Another aspect is a compound of any of the formulae herein, wherein R_3 is $NHNH_2$.

Another aspect is a compound of any of the formulae herein, wherein R_3 is $NHNH_2$, R_1 is  , R_{10} is selected from  ,  , F,  ,  ,  ,  ,  , or  , and R_8, R_9, R_{11}, and R_{12} are each H.

Another aspect is a compound of any of the formulae herein, wherein R_3 is $NHNH_2$, R_1 is  , R_{10} is selected from  , and R_8, R_9, R_{11}, and R_{12} are each H.

Another aspect is a compound of any of the formulae herein, wherein R_1 is $C{\equiv}C\text{-}R_{13}$ and R_{13} is selected from:

a)  ;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

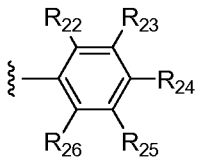
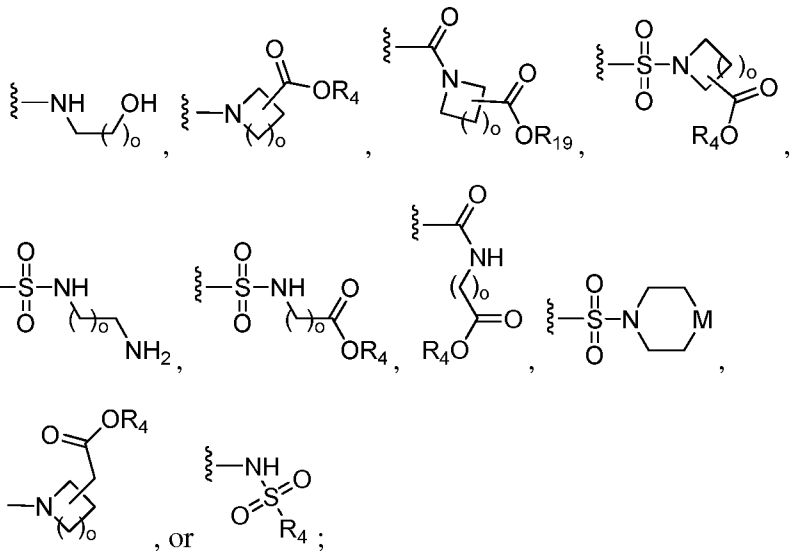
iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$; or

c) heteroaryl optionally substituted with 1, 2, or 3 heterocycloalkylcarbonyl wherein heterocycloalkylcarbonyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

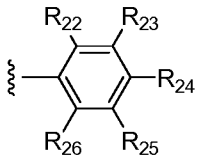
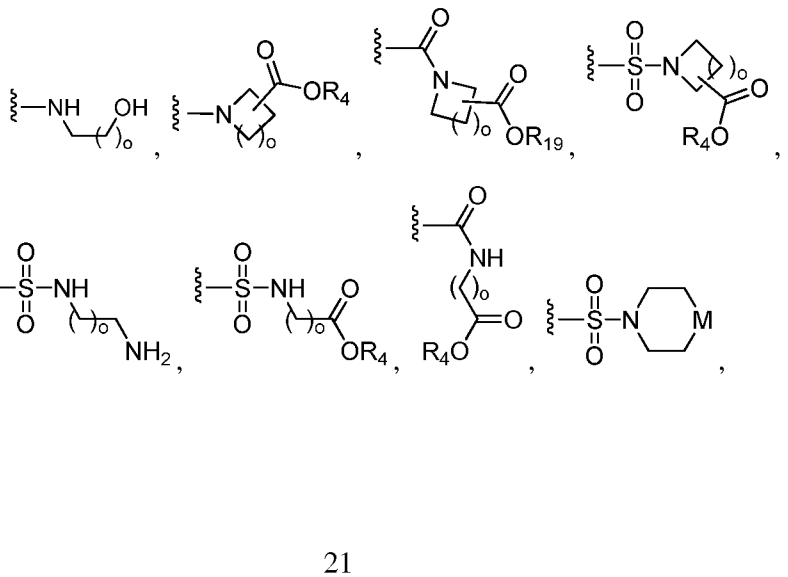
Another aspect is a compound of any of the formulae herein, wherein R_1 is $C{\equiv}C\text{-}R_{13}$ and R_{13} is selected from: a) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) $NR_{27}SO_2R_4$, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, 4)

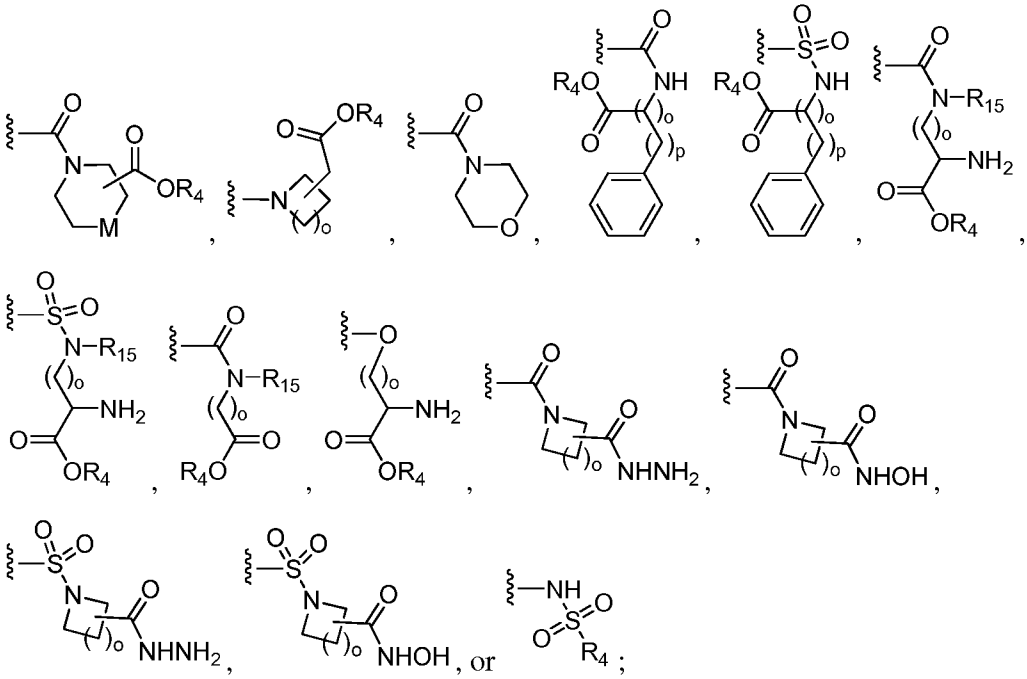
(heterocycloalkyl)alkyl, or 5) $NR_{27}COR_4$; or b) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

Another aspect is a compound of any of the formulae herein, wherein R_1 is $C\equiv C\text{-}R_{13}$, R_{13} is  , and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from halogen, hydrogen,  , , , or ;

each M is independently O, CH_2, or S; and

each o is independently 1, 2, 3, or 4.

Another aspect is a compound of any of the formulae herein, wherein R_1 is $C\equiv C\text{-}R_{13}$, R_{13} is  , and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from halogen, hydrogen,  , ,

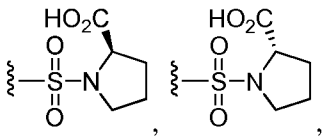


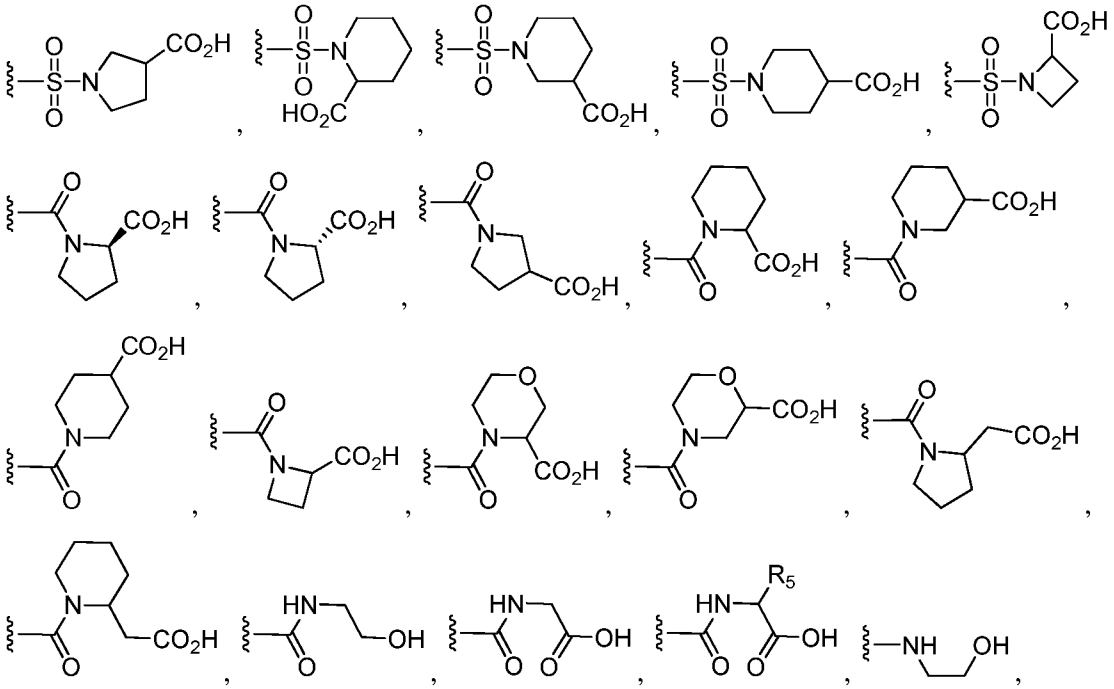
each M is independently O, CH_2, or S;

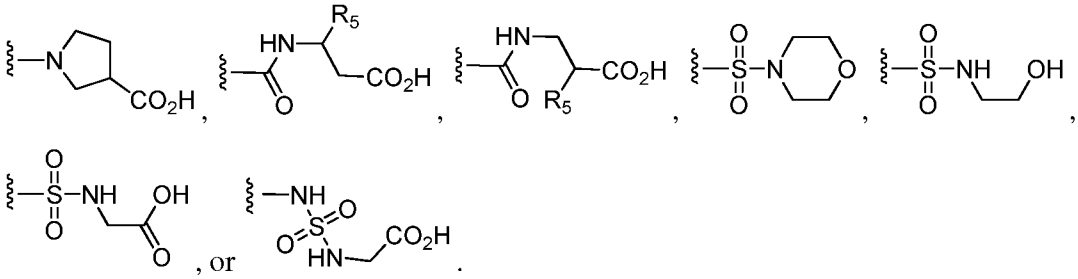
each o is independently 1, 2, 3, or 4; and

each p is 1, 2, 3, or 4.

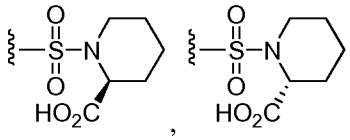
Another aspect is a compound of any of the formulae herein, wherein each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from hydrogen,

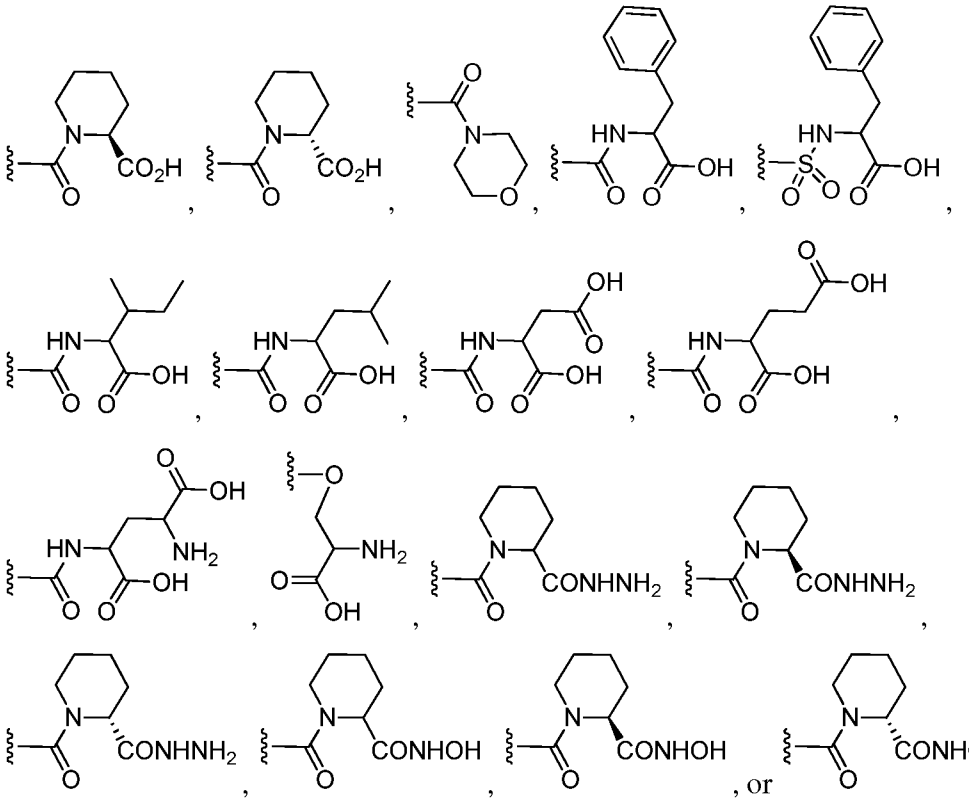




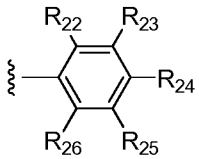


Another aspect is a compound of any of the formulae herein, wherein each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from halogen,

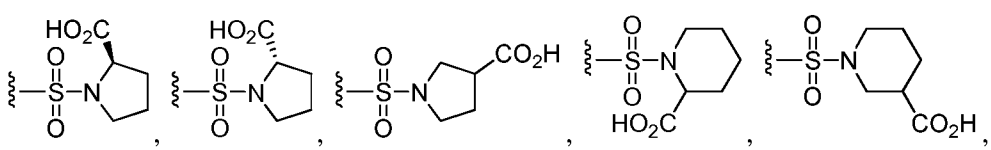


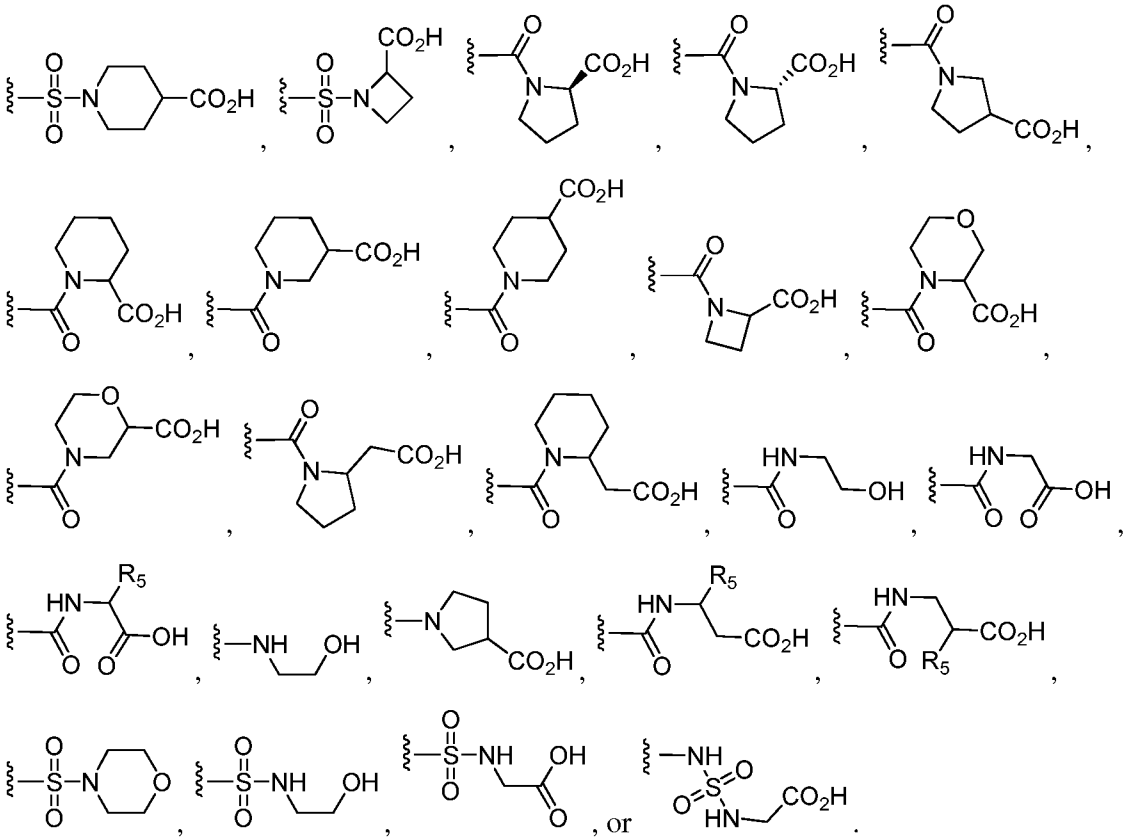


Another aspect is a compound of any of the formulae herein, wherein R_1 is C≡C-R_{13},

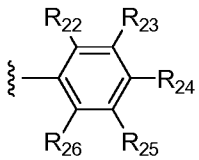


R_{13} is , and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from hydrogen,

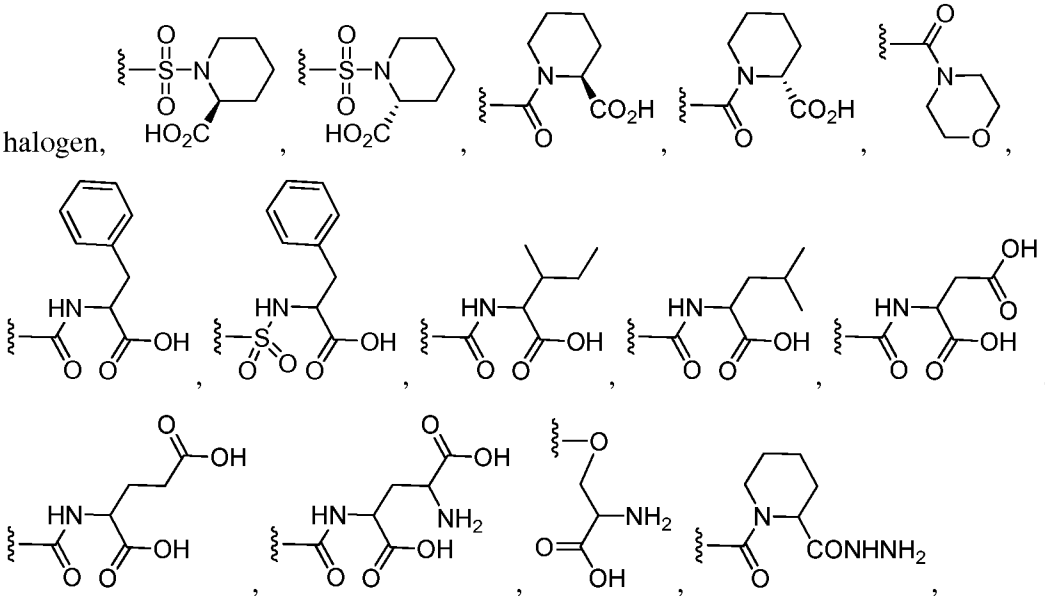


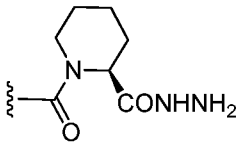
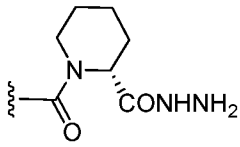
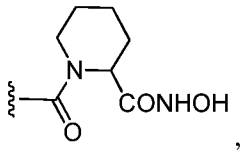
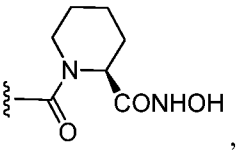


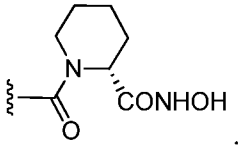
Another aspect is a compound of any of the formulae herein, wherein R_1 is C≡C-R_{13},

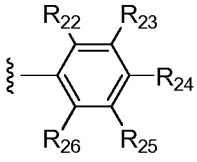


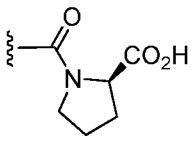
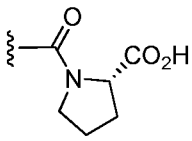
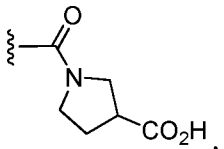
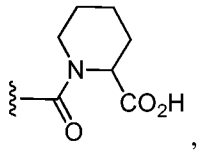
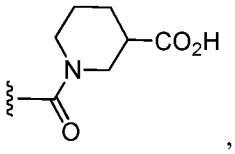
R_{13} is , and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from halogen,







, or


.

Another aspect is a compound of any of the formulae herein, wherein R_3 is $NHNH_2$, R_1 is $C\equiv C\text{-}R_{13}$, R_{13} is  , R_{24} is independently selected from hydrogen,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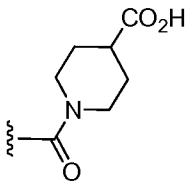
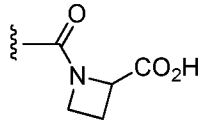
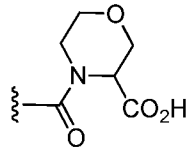
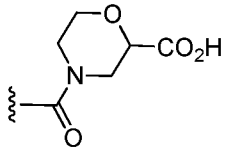
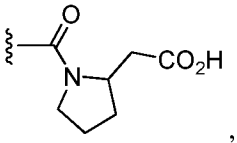
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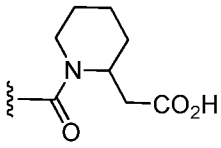
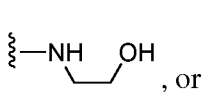
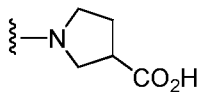
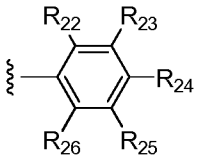
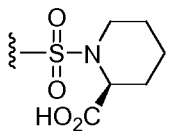
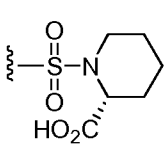
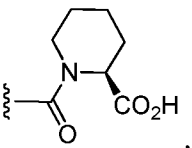
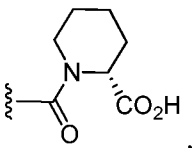
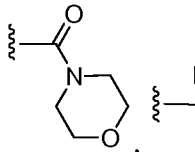
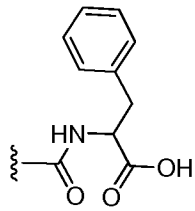
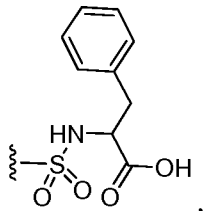


, or  ; and

R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

Another aspect is a compound of any of the formulae herein, wherein R_3 is $NHNH_2$, R_1 is $C\equiv C\text{-}R_{13}$, R_{13} is  , R_{24} is independently selected from  ,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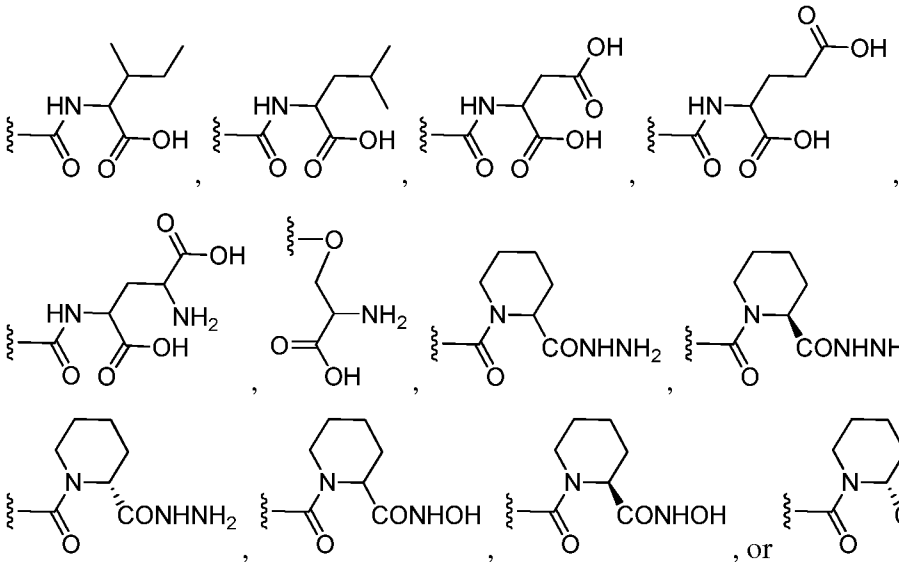


; and

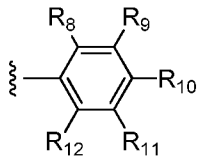
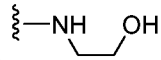
R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

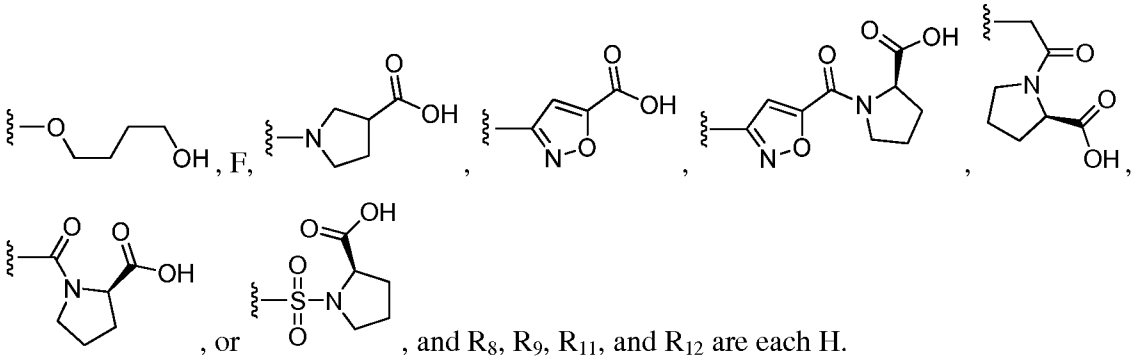
Another aspect is a compound of any of the formulae herein, wherein A is NR_4 and R_6 is $C(=O)NR_4OH$.

Another aspect is a compound of any of the formulae herein, wherein A is an optionally substituted heterocycle that is preferably a 5-membered ring with up to 1-4 heteroatoms and R_6 is null.

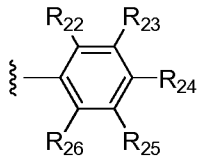
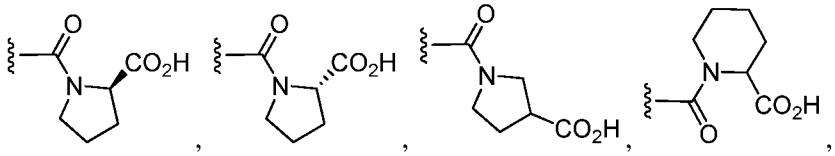
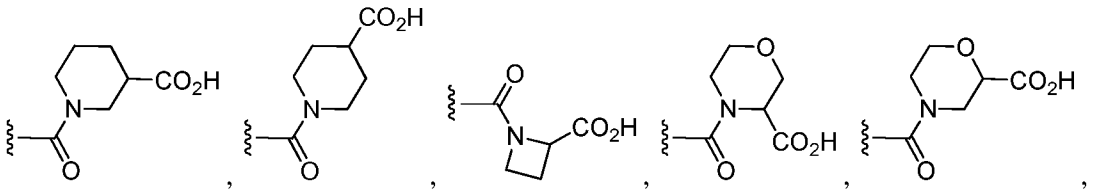
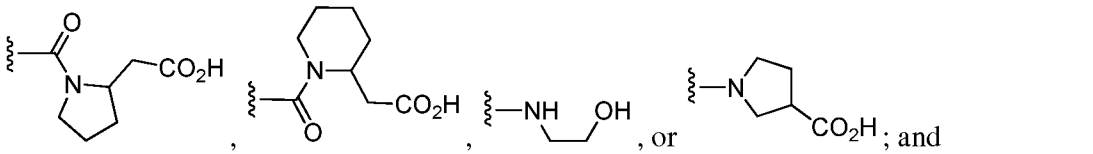
Another aspect is a compound of any of the formulae herein, wherein A is 5-methylimidazolidinyl-2,4-dione, 2-thioxoimidazolidin-4-one, or imidazolidine-2,4-dione.

Another aspect is a compound of any of the formulae herein, wherein A is 2-thioxoimidazolidin-4-one.

Another aspect is a compound of any of the formulae herein, wherein A is 2-thioxoimidazolidin-4-one, R_1 is  , R_{10} is selected from  ,

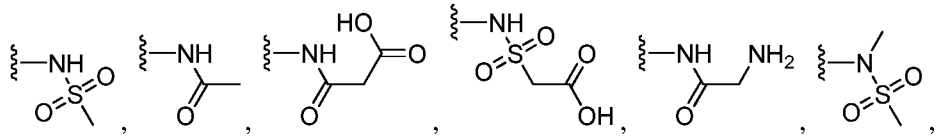
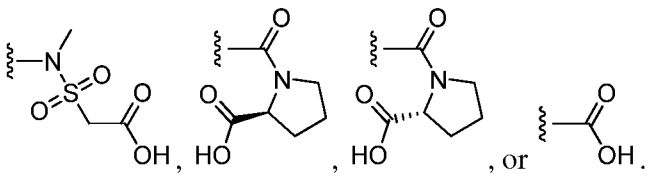


, and R_8, R_9, R_{11}, and R_{12} are each H.

Another aspect is a compound of any of the formulae herein, wherein A is 2-thioxoimidazolidin-4-one, R_1 is C≡C-R_{13}, R_{13} is  , R_{24} is independently selected from hydrogen,  ,  ,  , and ; and

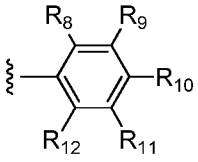
R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

Another aspect is a compound of any of the formulae herein, wherein each R_7 is independently C(=O)OR_4; $NHSO_2R_4$; N(alkyl)SO_2R_4; NHC(=O)R_4; N(alkyl)C(=O)R_4; C(=O)$NR_{27}R_4$; $SO_2NR_{27}R_4$; C(=O)$NR_{27}NHR_4$; C(=O)$NR_{27}OR_4$; or heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent OR_4, C(=O)OR_4, or $NHSO_2R_4$.

Another aspect is a compound of any of the formulae herein, wherein each R_7 is independently  ,  , and .

Another aspect is a compound of any of the formulae herein, wherein each R_7 is independently C(=O)OR_4, $NHSO_2R_4$, N(alkyl)SO_2R_4, NHC(=O)R_4, N(alkyl)C(=O)R_4, C(=O)$NR_{27}R_4$, $SO_2NR_{27}R_4$, C(=O)$NR_{27}NHR_4$, C(=O)$NR_{27}OR_4$, or heterocycloalkylcarbonyl

optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$; R_1 is



; and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) hydrogen; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; f) heteroaryl optionally substituted with 1, 2, or 3 independent:

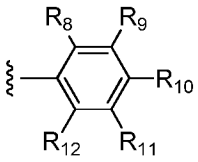
i) $C(=O)OR_{17}$; or

ii) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or

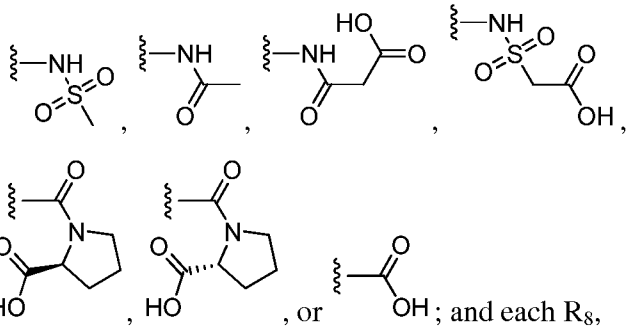
iii) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$;

g) alkyl optionally substituted with 1, 2, or 3 heterocycloalkylcarbonyl substituted with $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; h) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or i) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

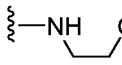
Another aspect is a compound of any of the formulae herein, wherein R_1 is

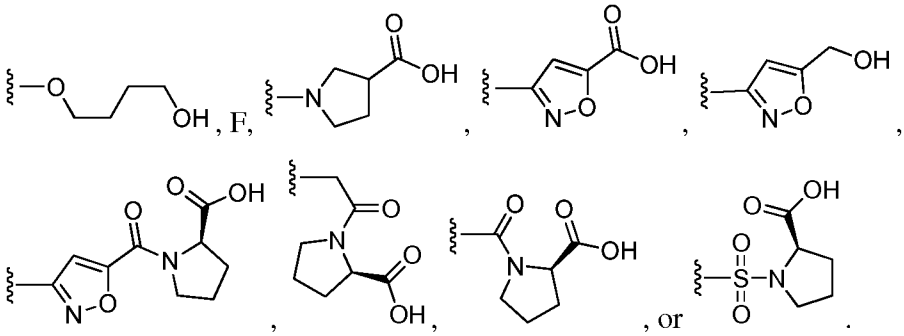


; each R_7 is independently

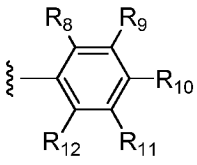


; and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from hydrogen,

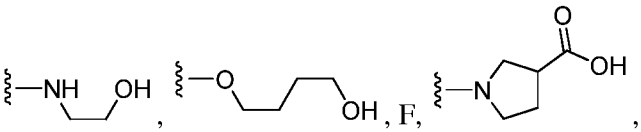


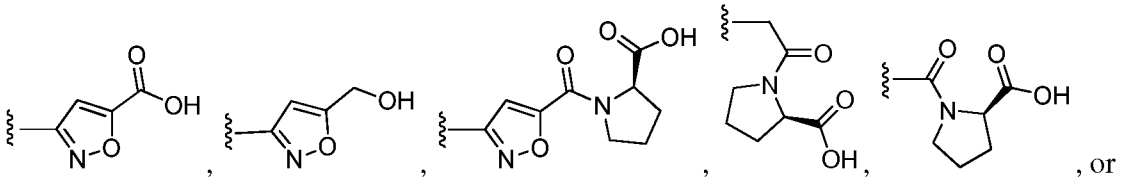


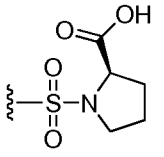
Another aspect is a compound of any of the formulae herein, wherein R_1 is



; R_{10} is selected from







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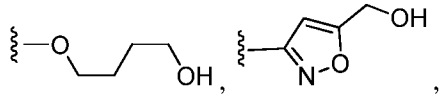
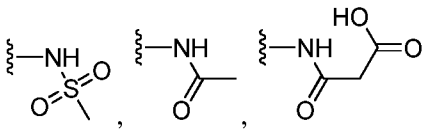
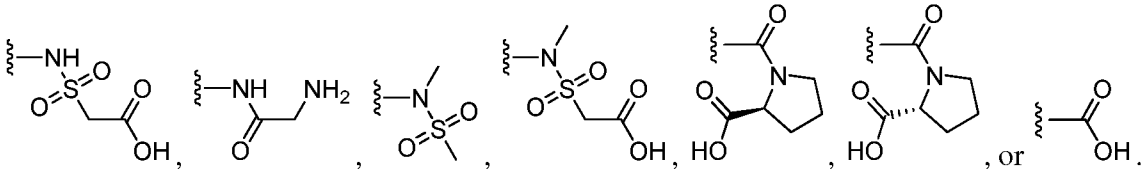


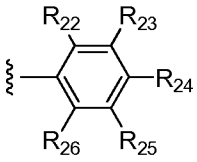
); R_8, R_9, R_{11}, and R_{12} are each H; and each R_7 is independently





Another aspect is a compound of any of the formulae herein, wherein each R_7 is independently $C(=O)OR_4$, $NHSO_2R_4$, $N(alkyl)SO_2R_4$, $NHC(=O)R_4$, $N(alkyl)C(=O)R_4$, $C(=O)NR_{27}R_4$, $SO_2NR_{27}R_4$, $C(=O)NR_{27}NHR_4$, $C(=O)NR_{27}OR_4$, or heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$; R_1 is C≡C-R_{13}; and

R_{13} is independently selected from:

a)  ;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

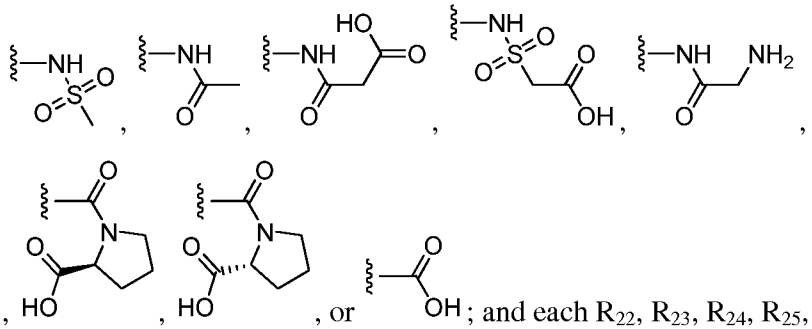
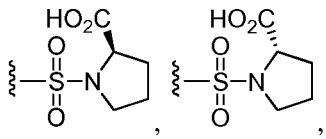
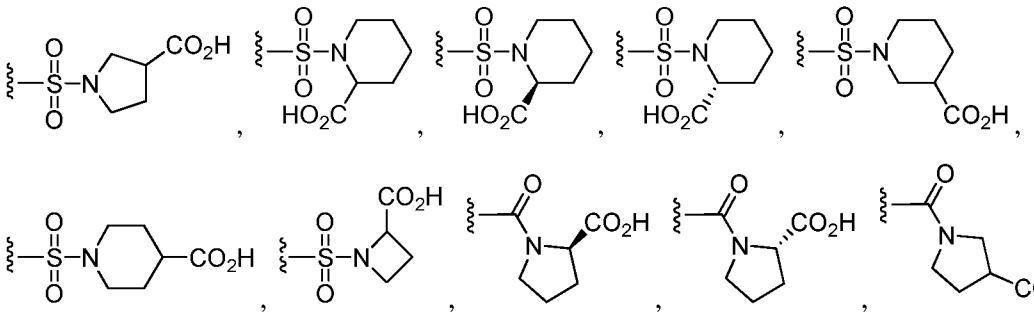
ii) $NHC(=O)R_4$;

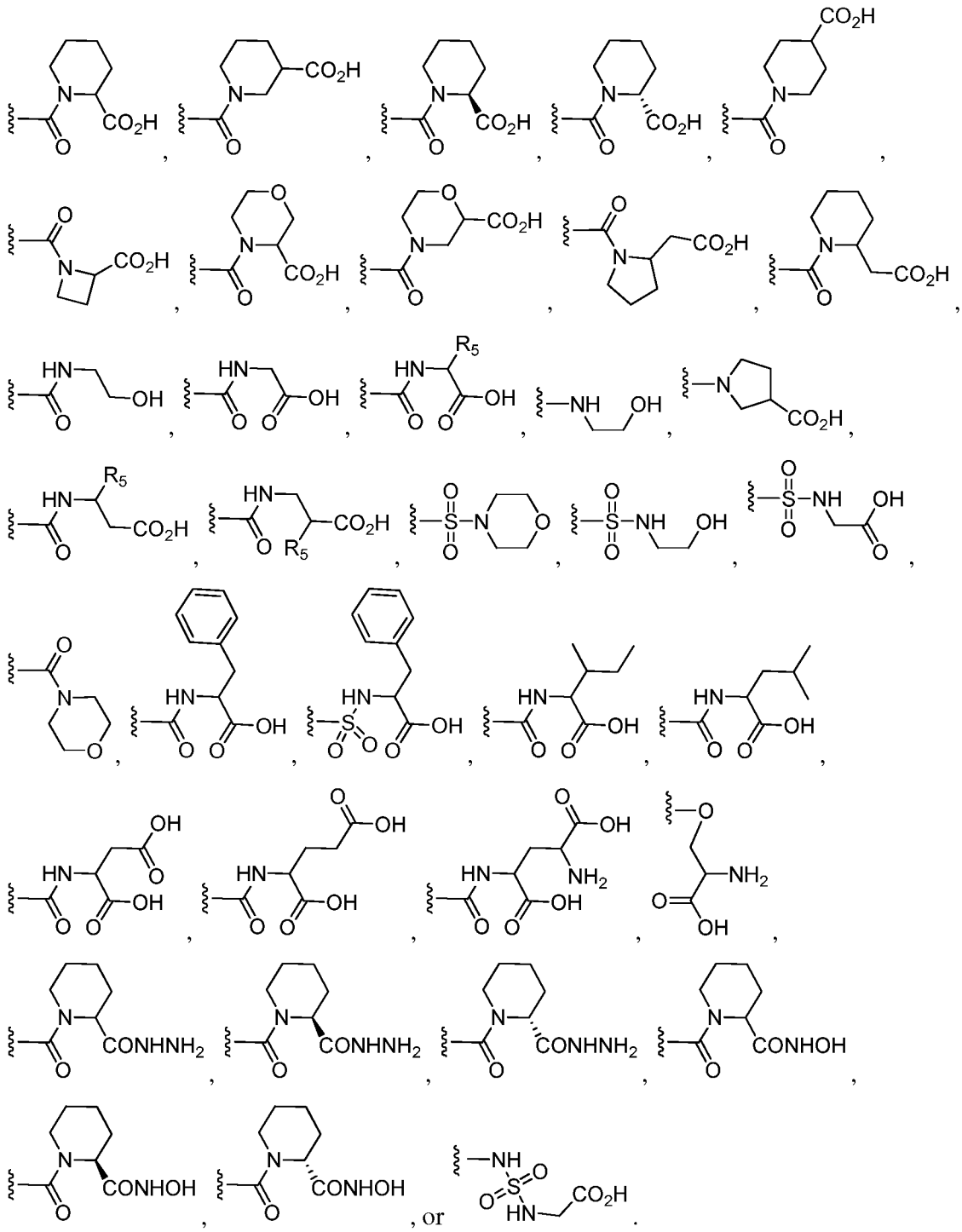
iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$;

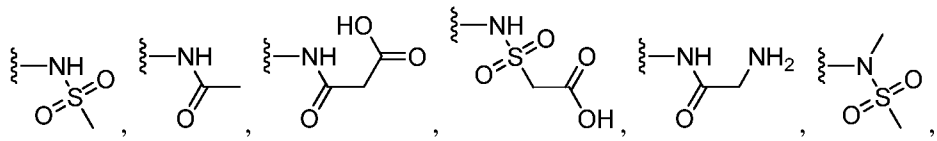
c) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) $NR_{27}SO_2R_4$, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, 4) (heterocycloalkyl)alkyl, or 5) $NR_{27}C(=O)R_4$; or

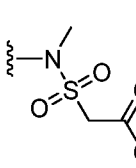
d) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

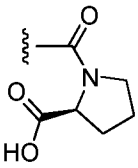
Another aspect is a compound of any of the formulae herein, wherein R_1 is $C\equiv C\text{-}R_{13}$; each R_7 is independently  ; and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from hydrogen,  ,  .

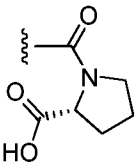


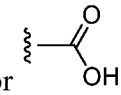
Another aspect is a compound of any of the formulae herein, wherein each R_7 is independently

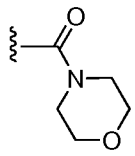


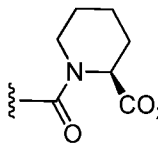


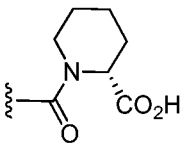


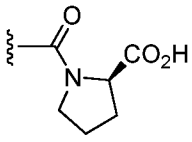


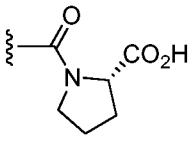


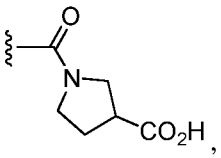


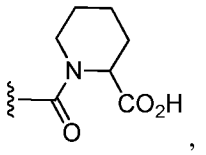


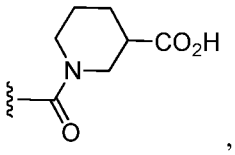


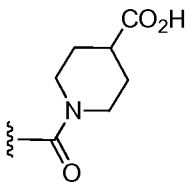


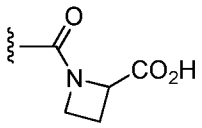


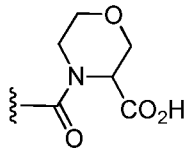


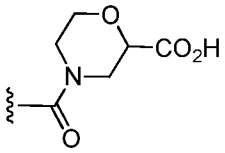


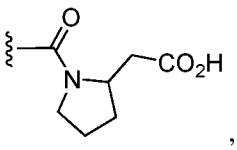


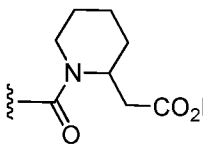


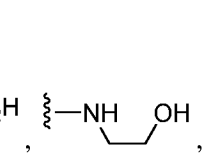


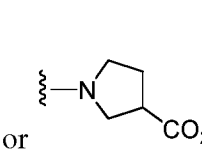


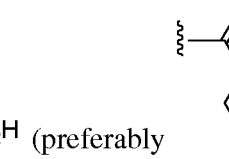


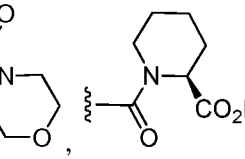


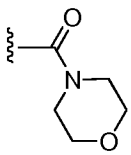


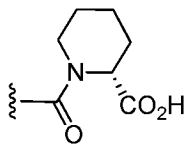












, , , or ; R_3 is $NHNH_2$, R_1 is C≡C-R_{13}; R_{24} is independently selected from hydrogen, , , ,

, , , , ,

, , , , ,

, , or (preferably , ,

or); and R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

Another aspect is a compound of any of the formulae herein, wherein:

each R_1 is independently 4-(hydroxyethylamino)phenyl, 4-(2-(isopropylcarbonylamino)ethoxy)phenyl, 4-(2-(methanesulfonylamino)ethoxy)phenyl, 4-(5-(hydroxymethyl)isoxazol-3-yl)phenyl, 4-(4-(2-tetrahydropyranyl)oxy)butyloxy)phenyl, 4-(4-hydroxybutyloxy)phenyl, 4-(3-aminopropyloxy)phenyl, 4-(3-(methanesulfonylamino)propyloxy)phenyl, 4-(3-(acetamido)propyloxy)phenyl, 4-fluorophenyl, 4-(methylaminosulfonyl)phenyl, 4-(acetylamino)phenyl, 4-(methylaminocarbonyl)phenyl, 4-(1-(3-carboxypyrrolidinyl))phenyl, 4-(1-(morpholino)ethanonyl)phenyl, 4-(morpholinocarbonyl)methoxyphenyl, 4-(morpholinosulfonyl)methylphenyl, 4-(5-carboxyisoxazol-3-yl)phenyl, 4-(5-(2-carboxy-1-pyrrolidinylcarbonyl)isoxazol-3-yl)phenyl, 4-(5-((methylaminocarbonyl)oxymethyl)isoxazol-

3-yl)phenyl, 4-(5-((methylaminocarbonyl)aminomethyl)isoxazol-3-yl)phenyl, 4-(5-(acetyl)aminomethyl)isoxazol-3-yl)phenyl, 4-(5-((acetyl)aminomethyl)isoxazol-3-yl)phenyl, 4-(5-((methylsulfonyl)aminomethyl)isoxazol-3-yl)phenyl, 4-cyanophenyl, 3-pyridyl, 4-pyridyl, 3-pyrazolyl, 4-pyrazolyl, 2-oxazolyl, 5-oxazolyl, phenyl, 4-(morpholinomethyl)phenyl, 2-hydroxyphenyl, 2-thiazolyl, 4-(methylsulfonyl)phenyl, 4-(2-hydroxyethylaminosulfonyl)phenyl, 4-(3-hydroxypropylaminosulfonyl)phenyl, 4-(3-carboxypropyloxy)phenyl, 4-(3-(hydrazinocarbonyl)propyloxy)phenyl, 4-(3-(hydroxylaminocarbonyl)propyloxy)phenyl, 4-(3-(ethyloxycarbonyl)propyloxy)phenyl, 4-(aminoethyloxy)phenyl, 4-(acetylaminoethyloxy)phenyl, 4-(1-(2-carboxypyrrolidinyl))phenyl, 4-(1-(3-carboxypiperidinyl))phenyl, 4-(1-(4-carboxypiperidinyl))phenyl, 4-(propionylaminopropyloxy)phenyl, 4-(isobutyrylaminopropyloxy)phenyl, 4-(trifluoromethylcarbonylaminopropyloxy)phenyl, 4-(ethylsulfonylaminopropyloxy)phenyl, 4-(isopropylsulfonylaminopropyloxy)phenyl, 4-(trifluoromethylsulfonylaminopropyloxy)phenyl, 4-(propionylaminoethyloxy)phenyl, 4-(trifluoromethylcarbonylaminoethyloxy)phenyl, 4-(ethylsulfonylaminoethyloxy)phenyl, 4-(isopropylsulfonylaminoethyloxy)phenyl, 4-(trifluoromethylsulfonylaminoethyloxy)phenyl, 3,4-dihydroxyphenyl, 4-(1-(2-carboxypyrrolidinylcarbonyl)methyl)phenyl, 4-(1-(2-carboxypyrrolidinylcarbonyl)methyloxy)phenyl, 4-(1-(2-carboxypyrrolidinylsulfonyl)methyl)phenyl, 4-(morpholinocarbonyl)phenyl, 4-(1-(2-carboxypyrrolidinylcarbonyl))phenyl, 4-(1-(3-carboxypiperidinylcarbonyl))phenyl, 4-(5-(morpholinocarbonyl)isoxazol-3-yl)phenyl, 4-(morpholinosulfonyl)phenyl, 4-(1-(2-carboxypyrrolidinylsulfonyl))phenyl, 4-(1-(3-carboxypiperidinylsulfonyl))phenyl, 4-(5-(methylaminocarbonyl)isoxazol-3-yl)phenyl, 4-(5-(3-carboxypiperidinyl)isoxazol-3-yl)phenyl, 4-(5-(2-carboxypiperidinyl)isoxazol-3-yl)phenyl, 4-(acetylamino)phenylethynyl, 4-(methylsulfonylamino)phenylethynyl, 4-(morpholinocarbonyl)phenylethynyl, 4-(2-carboxypyrrolidinylsulfonyl)phenylethynyl, (1-(hydroxyethyl)pyridon-4-yl)ethynyl, (1-(acetylaminoethyl)pyridon-4-yl)ethynyl, (2-fluoro-4-(2-carboxypiperidinyl)carbonylphenyl)ethynyl, (3-fluoro-4-(2-carboxypiperidinyl)carbonylphenyl)ethynyl, 4-(morpholinomethyl)phenylethynyl, 4-(hydroxyethylamino)phenylethynyl, 3-(pyridyl)ethynyl, 4-(methylaminocarbonyl)phenylethynyl, 4-(methylaminosulfonyl)phenylethynyl, 4-(2-carboxypyrrolidinylcarbonyl)phenylethynyl, 4-(3-carboxypiperidinylcarbonyl)phenylethynyl, 4-(3-carboxypyrrolidinylcarbonyl)phenylethynyl, 4-(4-carboxypiperidinylcarbonyl)phenylethynyl, 4-(N-methylpiperazinocarbonyl)phenylethynyl, 4-

(hydroxyethylaminocarbonyl)phenylethynyl, 4-((carboxymethyl)aminocarbonyl)phenylethynyl, 4-(2-carboxypyrrolidinylsulfonyl)phenylethynyl, 4-(3-carboxypiperidinylsulfonyl)phenylethynyl, 4-(3-carboxypyrrolidinylsulfonyl)phenylethynyl, 4-(4-carboxypiperidinylsulfonyl)phenylethynyl, 4-(morpholinosulfonyl)phenylethynyl, 4-(N-methylpiperazinylsulfonyl)phenylethynyl, 4-(hydroxyethylaminosulfonyl)phenylethynyl, 4-(hydroxypropylaminosulfonyl)phenylethynyl, 4-((carboxymethyl)aminosulfonyl)phenylethynyl, 4-(aminoethylaminocarbonyl)phenylethynyl, 4-((aminoethyl)aminocarbonyl)phenylethynyl, 4-((aminoethyl)aminosulfonyl)phenylethynyl, 4-(2-carboxyazetidinylcarbonyl)phenylethynyl, 4-(2-carboxypiperidinylcarbonyl)phenylethynyl, 4-(2-carboxyazetidinylsulfonyl)phenylethynyl, 4-(2-carboxypiperidinylsulfonyl)phenylethynyl, 4-(3-carboxy-morpholinocarbonyl)phenylethynyl,

4-(2-carboxy-morpholinocarbonyl)phenylethynyl, (1-(carboxymethyl)pyridon-4-yl)ethynyl, (1-((methylaminocarbonyl)methyl)pyridon-4-yl)ethynyl, 5-(3-carboxypiperidinylcarbonyl)thienylethynyl, 5-(2-carboxypiperidinylcarbonyl)thienylethynyl, 5-(3-carboxypiperidinylcarbonyl)furanylethynyl, 5-(2-carboxypiperidinylcarbonyl)furanylethynyl, 2-(2-carboxypiperidinylcarbonyl)pyridin-5-ylethynyl, 4-((1-carboxyethyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-methyl)propyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-methyl)butyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-3-methyl)butyl)aminocarbonyl)phenylethynyl, 4-(((1,3-di-carboxy)propyl)aminocarbonyl)phenylethynyl, 4-(((1,2-di-carboxy)ethyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-hydroxy)ethyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-hydroxy)propyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-3-methylthio)propyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-phenyl)ethyl)aminocarbonyl)phenylethynyl, 4-(((1-carboxy-2-(4-hydroxyphenyl))ethyl)aminocarbonyl)phenylethynyl, 4-(3-carboxy-thiomorpholino)phenylethynyl, 4-((((1-carboxy-1,1-dimethyl)methyl))aminocarbonyl)phenylethynyl, 4-(ethylsulfonylamino)phenylethynyl, 4-(isopropylsulfonylamino)phenylethynyl, 4-(trifluoromethylsulfonylamino)phenylethynyl, 4-(carboxymethylsulfonylamino)phenylethynyl, 4-(carboxymethylsulfonylamino)phenylethynyl, 4-(2-(2-carboxymethyl)pyrrolidinylcarbonyl)phenylethynyl, 4-((2-carboxymethyl)pyrrolidin-

1-ylcarbonyl)phenylethynyl, 4-((2-carboxymethyl)piperidin-1-ylcarbonyl)phenylethynyl, 4-((N-methyl-N-carboxymethylamino)carbonyl)phenylethynyl, 4-((N-methyl-N-(1-carboxyethyl))aminocarbonyl)phenylethynyl, 4-((N-(2-carboxyethyl))aminocarbonyl)phenylethynyl, 4-((N-methyl-N-(2-carboxyethyl))aminocarbonyl)phenylethynyl, 4-((N-(2-carboxypropyl))aminocarbonyl)phenylethynyl, 4-((N-(2-carboxy-1-methyl-ethyl))aminocarbonyl)phenylethynyl, 4-((N-methyl-N-(2-carboxypropyl))aminocarbonyl)phenylethynyl, 4-((N-methyl-N-(2-carboxy-1-methyl-ethyl))aminocarbonyl)phenylethynyl, 4-(((2-carboxy-2-phenyl)ethyl)aminocarbonyl)phenylethynyl, 4-(((2-carboxy-1-phenyl)ethyl)aminocarbonyl)phenylethynyl, 4-(N-(3-carboxy-4-hydroxyphenyl)aminocarbonyl)phenylethynyl, 4-(N-(3-carboxyphenyl)aminocarbonyl)phenylethynyl, 4-(N-((1,1-dicarboxy)methyl)aminocarbonyl)phenylethynyl, 2-chloro-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 4-(2-carboxyanilinocarbonyl)phenylethynyl, 2-methoxy-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 2-hydroxy-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 2-(trifluoromethyl)-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 4-((3-carboxy-4-hydroxypiperidin-1-yl)carbonyl)phenylethynyl, 2-fluoro-4-(((R)-2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 2-fluoro-4-(((S)-2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 2,5-difluoro-4-((-2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 4-(5-oxazolidin-2-onyl)phenylethynyl, 2-chloro-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 4-(N-(N-methyl-phenylalanine)carbonyl)phenylethynyl, 2-fluoro-4-(N-(N-methyl-phenylalanine)carbonyl)phenylethynyl, 4-(((3-hydroxy-4-carboxy)phenyl)aminocarbonyl)phenylethynyl, 4-(((N-methyl-1-carboxy-2-methyl)butylamino)carbonyl)phenylethynyl, 2,3-difluoro-4-((-2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 4-(((N-methyl-1-carboxy-3-methyl)butylamino)carbonyl)phenylethynyl, 2-fluoro-4-(((1-carboxy-2-methyl)butylamino)carbonyl)phenylethynyl, 4-(((N-methyl-1-carboxy-2-methyl)propylamino)carbonyl)phenylethynyl, 4-(((N-methyl-1,3-dicarboxy)propylamino)carbonyl)phenylethynyl, 2-fluoro-4-(((N-methyl-1-carboxy-2-methyl)butylamino)carbonyl)phenylethynyl, 4-(((N-methyl-1,2-dicarboxy)ethylamino)carbonyl)phenylethynyl, 3-methoxy-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 3-chloro-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 3-

(trifluoromethyl)-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 3-hydroxy-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 5-((2-carboxypiperidin-1-yl)carbonyl)pyrid-2-ylethynyl, 2-chloro-4-(N-(N-methyl-phenylalanine)carbonyl)phenylethynyl, 4-(N-(phenylalanine)sulfonyl)phenylethynyl, 4-(N-(N-methyl-phenylalanine)sulfonyl)phenylethynyl, 2,6-difluoro-4-((2-carboxypiperidin-1-yl)carbonyl)phenylethynyl, 2-chloro-4-(((1-carboxy-2-methyl)butylamino)carbonyl)phenylethynyl, 4-(N-(N-ethyl-1-carboxymethylamine)carbonyl)phenylethynyl, 4-(N-(N-propyl-1-carboxymethylamine)carbonyl)phenylethynyl, 4-(((N-methyl-1-carboxy-2-methyl)butylamino)sulfonyl)phenylethynyl, 4-(((1-carboxy-2-methyl)butylamino)sulfonyl)phenylethynyl, 4-((carboxymethyl)benylaminocarbonyl)phenylethynyl, 2-(trifluoromethylsulfonylamino)pyrid-5-ylethynyl, 4-(N-(N-isopropyl-1-carboxymethylamine)carbonyl)phenylethynyl, 4-(N-(N-isobutyl-1-carboxymethylamine)carbonyl)phenylethynyl, 2-fluoro-4-(((1-carboxy-2-methyl)butylamino)sulfonyl)phenylethynyl, 4-(N-(N-benzyl-phenylalanine)carbonyl)phenylethynyl, 2-fluoro-4-(((N-methyl-1-carboxy-2-methyl)butylamino)sulfonyl)phenylethynyl, (R)-2-fluoro-4-((2-carboxypiperidin-1-yl)sulfonyl)phenylethynyl, (S)-2-fluoro-4-((2-carboxypiperidin-1-yl)sulfonyl)phenylethynyl, 2-fluoro-4-(N-(phenylalanine)sulfonyl)phenylethynyl, 2-fluoro-4-(N-(N-methyl-phenylalanine)sulfonyl)phenylethynyl, 4-(N-(N-ethyl-phenylalanine)carbonyl)phenylethynyl, 4-(N-(N-isopropyl-phenylalanine)carbonyl)phenylethynyl, (R)- 2-(2-(carboxypyrrolidinyl)methyl)pyrid-5-ylethynyl, 4-(N-(N-isobutyl-phenylalanine)carbonyl)phenylethynyl, (R)-2-chloro-4-((2-carboxypiperidin-1-yl)sulfonyl)phenylethynyl, (S)-2-chloro-4-((2-carboxypiperidin-1-yl)sulfonyl)phenylethynyl, 2-chloro-4-(((2-amino-2-carboxy)ethylamino)carbonyl)phenylethynyl, 4-(N-(N-propyl-phenylalanine)carbonyl)phenylethynyl, 2-fluoro-4-((3-carboxy-piperidinyl)carbonyl)phenylethynyl, (R)-2-fluoro-4-((2-carboxy-pyrrolidinyl)carbonyl)phenylethynyl, 2-chloro-4-((3-carboxy-piperidinyl)carbonyl)phenylethynyl, (R)-2-chloro-4-((2-carboxy-pyrrolidinyl)carbonyl)phenylethynyl, 2-fluoro-4-((3-carboxy-piperidinyl)sulfonyl)phenylethynyl, (R)-2-fluoro-4-((2-carboxy-pyrrolidinyl)sulfonyl)phenylethynyl, 2-chloro-4-((N-isobutyl-N-(carboxymethyl)amino)carbonyl)phenylethynyl, 2-fluoro-4-((N-isobutyl-N-(carboxymethyl)amino)carbonyl)phenylethynyl, 2-chloro-4-((N-isobutyl-N-

(carboxymethyl)amino)sulfonyl)phenylethynyl, 2-fluoro-4-((N-isobutyl-N-(carboxymethyl)amino)sulfonyl)phenylethynyl, 2-chloro-4-((3-carboxy-piperidinyl)sulfonyl)phenylethynyl, (R)-2-chloro-4-((2-carboxy-pyrrolidinyl)sulfonyl)phenylethynyl, 4-(2-amino-2-carboxyethyloxy)phenylethynyl, 4-((N-isobutyl-N-(1-methyl-carboxymethyl)amino)carbonyl)phenylethynyl. 2-fluoro-4-((N-isobutyl-N-(1-methyl-carboxymethyl)amino)carbonyl)phenylethynyl, 2-chloro-4-((N-methyl-N-(2-amino-2-carboxyethyl)amino)carbonyl)phenylethynyl, 2-chloro-4-((N-isobutyl-N-(1-methyl-carboxymethyl)amino)carbonyl)phenylethynyl, 4-((N-isobutyl-N-(1-hydroxymethyl-carboxymethyl)amino)carbonyl)phenylethynyl, (S)-2-chloro-4-((2-(hydrazinocarbonyl)piperidin-1-yl)carbonyl)phenylethynyl, (S)-2-chloro-4-((2-(N-hydroxylaminocarbonyl)piperidin-1-yl)carbonyl)phenylethynyl, 4-((1-carboxy-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 4-((N-isobutyl-N-(1-(4-hydroxybenzyl)-carboxymethyl)amino)carbonyl)phenylethynyl, 4-((1-methoxycarbonyl-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 2-fluoro-4-((N-isobutyl-N-(1-hydroxymethyl-carboxymethyl)amino)carbonyl)phenylethynyl, 2-chloro-4-((1-carboxy-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 2-fluoro-4-((1-carboxy-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 2-chloro-4-((1-methoxycarbonyl-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 2-fluoro-4-((1-methoxycarbonyl-1-(imidazol-4-ylmethyl))methylaminocarbonyl)phenylethynyl, 4-((1-aminomethyl-1-carboxy)methylaminocarbonyl)phenylethynyl, 2-chloro-4-((1-aminomethyl-1-carboxy)methylaminocarbonyl)phenylethynyl, 2-fluoro-4-((1-aminomethyl-1-carboxy)methylaminocarbonyl)phenylethynyl, 4-((N-isobutyl-1-aminomethyl-1-carboxy)methylaminocarbonyl)phenylethynyl, 4-(((1-aminomethyl-1-carboxy)methyl)isobutylaminocarbonyl)phenylethynyl, 2-chloro-4-(((1-aminomethyl-1-carboxy)methyl)isobutylaminocarbonyl)phenylethynyl, 2-fluoro-4-(((1-aminomethyl-1-carboxy)methyl)isobutylaminocarbonyl)phenylethynyl, 4-(2-tetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dionyl)phenylethynyl, 4-((N-methyl-1-aminomethyl-1-carboxy)methylaminocarbonyl)phenylethynyl, 4-(((1-aminomethyl-1-carboxy)methyl)(methylamino)carbonyl)phenylethynyl, 2-fluoro-4-(((1-aminomethyl-1-carboxy)methyl)(methylamino)carbonyl)phenylethynyl, 1-(2-carboxycyclopropyl)-buta-1,3-diynyl, 1-(2-((2-carboxypiperidinyl)carbonyl)cyclopropyl)-buta-1,3-diynyl, or 4-((2-carboxypiperidinylcarbonyl)amino)phenylethynyl.Another aspect is a compound of any of the formulae herein, wherein:

each R_{10} is independently hydroxyethylamino, 2-((isopropylcarbonyl)amino)ethyloxy, 2-((methanesulfonyl)amino)ethyloxy, 5-(hydroxymethyl)isoxazol-3-yl, (2-(tetrahydropyranyl)oxy)butyloxy, 4-hydroxybutyloxy, 3-aminopropyloxy, 3-((methanesulfonyl)amino)propyloxy, 3-((acetyl)amino)propyloxy, fluoro, N-methylaminosulfonyl, (methanesulfonyl)amino, (acetyl)amino, (methylamino)carbonyl, 3-carboxypyrrolidinyl, (morpholinocarbonyl)methyl, (morpholinocarbonyl)methyloxy, (morpholinosulfonyl)methyl, 5-carboxyisoxazol-3-yl, 5-((2-carboxypyrrolidinyl)carbonyl)isoxazol-3-yl, 5-(((N-methylaminocarbonyl)oxy)methyl)isoxazol-3-yl, 5-(((N-methylaminocarbonyl)amino)methyl)isoxazol-3-yl, 5-(((acetyl)amino)methyl)isoxazol-3-yl, 5-(((methanesulfonyl)amino)methyl)isoxazol-3-yl, cyano, hydrogen, morpholinomethyl, methanesulfonyl, (2-hydroxyethylamino)sulfonyl, (3-hydroxypropylamino)sulfonyl, 3-(carboxy)propyloxy, 3-(hydrazinocarbonyl)propyloxy, 3-(hydroxylaminocarbonyl)propyloxy, 3-(ethyloxycarbonyl)propyloxy, 2-aminoethyloxy, 2-((acetyl)amino)ethyloxy, 2-carboxypyrrolidinyl, 3-carboxypiperidinyl, 4-carboxypiperidinyl, 3-(propionylamino)propyloxy, 3-(isobutyrylamino)propyloxy, 3-(((trifluoromethyl)carbonyl)amino)propyloxy, 3-(ethylsulfonylamino)propyloxy, 3-(isopropylsulfonylamino)propyloxy, 3-(((trifluoromethyl)sulfonyl)amino)propyloxy, 2-(propionylamino)ethyloxy, 2-(((trifluoromethyl)carbonyl)amino)ethyloxy, 2-(ethylsulfonylamino)ethyloxy, 2-(isopropylsulfonylamino)ethyloxy, 2-(((trifluoromethyl)sulfonyl)amino)ethyloxy, hydroxy, ((2-carboxypyrrolidinyl)carbonyl)methyl, ((2-carboxypyrrolidinyl)carbonyl)methyloxy, ((2-carboxypyrrolidinyl)sulfonyl)methyl, morpholinocarbonyl, (2-carboxypyrrolidinyl)carbonyl, (3-carboxypiperidinyl)carbonyl, 5-(morpholinocarbonyl)isoxazol-3-yl, morpholinosulfonyl, (2-carboxypyrrolidinyl)sulfonyl, (3-carboxypiperidinyl)sulfonyl, 5-(methylaminocarbonyl)isoxazol-3-yl, 5-((3-carboxypiperidinyl)carbonyl) isoxazol-3-yl, 5-((2-carboxypiperidinyl)carbonyl) isoxazol-3-yl, 5-(morpholinocarbonyl)isoxazol-3-yl, 5-(methanesulfonylaminomethyl)isoxazol-3-yl.

Another aspect is a compound of any of the formulae herein, wherein:

each R_{24} is independently acetylamino, methanesulfonylamino, morpholinocarbonyl, (2-carboxypyrrolidinyl)sulfonyl, (2-carboxypiperidinyl)carbonyl, morpholinomethyl, hydroxyethylamino, methylaminocarbonyl, methylaminosulfonyl, (2-carboxypyrrolidinyl)carbonyl, (3-carboxypiperidinyl)carbonyl, (3-carboxypyrrolidinyl)carbonyl, (4-carboxypiperidinyl)carbonyl, (N-

methylpiperazinyl)carbonyl, (hydroxyethylamino)carbonyl, (carboxymethylamino)carbonyl, (3-carboxypiperidinyl)sulfonyl, (3-carboxypyrrolidinyl)sulfonyl, (4-carboxypiperidinyl)sulfonyl, morpholinosulfonyl, (N-methylpiperazinyl)sulfonyl, (hydroxyethylamino)sulfonyl, (3-hydroxypropylamino)sulfonyl, (carboxymethylamino)sulfonyl, (aminoethylamino)carbonyl, (aminoethylamino)sulfonyl, (2-carboxyazetidinyl)carbonyl, (2-carboxypiperidinyl)sulfonyl, (2-carboxyazetidinyl)sulfonyl, (2-carboxymorpholinyl)carbonyl, (3-carboxymorpholinyl)carbonyl, (1-carboxyethyl)aminocarbonyl, (1-carboxy-2-methylpropyl)aminocarbonyl, (1-carboxy-2-methylbutyl)aminocarbonyl, (1-carboxy-3-methylbutyl)aminocarbonyl, (1,2-dicarboxyethyl)aminocarbonyl, (1,3-dicarboxypropyl)aminocarbonyl, (1-carboxy-2-hydroxy-ethyl)aminocarbonyl, (1-carboxy-2-hydroxy-propyl)aminocarbonyl, (1-carboxy-3-(methylthio)propyl)aminocarbonyl, (1-carboxy-2-phenyl-ethyl)aminocarbonyl, (1-carboxy-2-(4-hydroxyphenyl)-ethyl)aminocarbonyl, (3-carboxy-thiomorpholino)carbonyl, (1-carboxy-1,1-dimethyl)methylaminocarbonyl, ethanesulfonylamino, isopropylsulfonylamino, trifluoromethylsulfonylamino, (carboxymethyl)sulfonylamino, 2-(carboxymethyl)pyrrolidinylcarbonyl, 2-(carboxymethyl)piperidinylcarbonyl, (N-methyl-N-(carboxymethyl)amino)carbonyl, (N-methyl-N-(1-carboxyethyl)amino)carbonyl, (N-(2-carboxyethyl)amino)carbonyl, (N-methyl-N-(2-carboxyethyl)amino)carbonyl, (N-(2-carboxypropyl)amino)carbonyl, (N-(2-carboxy-1-methylethyl)amino)carbonyl, (N-methyl-N-(2-carboxypropyl)amino)carbonyl, (N-methyl-N-(2-carboxy-1-methylethyl)amino)carbonyl, (2-carboxy-2-phenyl-ethyl)aminocarbonyl, (2-carboxy-1-phenyl-ethyl)aminocarbonyl, (3-carboxy-4-hydroxyphenyl)aminocarbonyl, (3-carboxyphenyl)aminocarbonyl, (((1,1-dicarboxy)methyl)amino)carbonyl, (2-carboxyanilino)carbonyl, 3-carboxy-4-hydroxy-piperidinylcarbonyl, (1-carboxy-1-benzyl)methylaminocarbonyl, (1-carboxy-1-benzyl)methyl(methylamino)carbonyl, 3-hydroxy-4-carboxy-anilinocarbonyl, (1-carboxy-2-methyl)butyl(methylamino)carbonyl, (1-carboxy-2-methyl)butylaminocarbonyl, (1-carboxy-3-methyl)butyl(methylamino)carbonyl, (1-carboxy-2-methyl)propyl(methylamino)carbonyl, (1,3-dicarboxy)propyl(methylamino)carbonyl, (1,2-dicarboxy)ethyl(methylamino)carbonyl, (1-carboxy-1-benzyl)methylaminosulfonyl, (1-carboxy-1-benzyl)methyl(methylamino)sulfonyl, carboxymethyl(ethylamino)carbonyl, carboxymethyl(propylamino)carbonyl, (1-carboxy-2-methyl)butyl(methylamino)sulfonyl, (1-carboxy-2-methyl)butylaminosulfonyl, carboxymethyl(benzylamino)carbonyl, carboxymethyl(isopropylamino)carbonyl, carboxymethyl(isobutylamino)carbonyl, (1-carboxy-1-benzyl)methyl(benzylamino)carbonyl, (1-carboxy-1-

benzyl)methyl(ethylamino)carbonyl, (1-carboxy-1-benzyl)methyl(isopropylamino)carbonyl, (1-carboxy-1-benzyl)methyl(isobutylamino)carbonyl, (1-carboxy-1-benzyl)methyl(propylamino)carbonyl, carboxymethyl(isobutylamino)sulfonyl, 2-amino-2-carboxy-ethyloxy, 1-carboxyethyl(isobutylamino)carbonyl, 2-carboxy-2-aminoethyl(methylamino)carbonyl, 2-carboxy-2-aminoethyl(isobutylamino)carbonyl, (1-carboxy-1-hydroxymethyl)methyl(isobutylamino)carbonyl, 2-(hydrazinocarbonyl)piperidinylcarbonyl, 2-(hydroxylaminocarbonyl)piperidinylcarbonyl, 1-carboxy-1-(imidazol-4-ylmethyl)methylaminocarbonyl, 1-carboxy-1-(4-hydroxyphenylmethyl)methyl(isobutylamino)carbonyl, 1-methoxycarbonyl-1-(imidazol-4-ylmethyl)methylaminocarbonyl, 1-carboxy-1-(aminomethyl)methylaminocarbonyl, 1-carboxy-1-(aminomethyl)methyl(isobutylamino)carbonyl, 2-tetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dionyl, 1-carboxy-1-(aminomethyl)methyl(methylamino)carbonyl, 2-carboxypiperidinylcarbonylamino.

Another aspect is a compound of any of the formulae herein, wherein:
each heteroaryl may be optionally substituted with hydroxybutyloxy, hydroxyalkyl, carboxy, carboxyheterocycloalkylcarbonyl, (alkylaminocarbonyl)oxyalkyl, (alkylaminocarbonyl)aminoalkyl, (alkylcarbonyl)aminoalkyl, (alkylsulfonyl)aminoalkyl, heterocycloalkylcarbonyl, alkylaminocarbonyl, or 2-carboxypiperidinylcarbonyl, trifluoromethylsulfonylamino.

Another aspect is a compound of any of the formulae herein, wherein:
each alkoxy may be optionally substituted with alkylcarbonylamino, alkylsulfonylamino, heterocycloalkyloxy, hydroxy, amino, heterocycloalkylcarbonyl, carboxy, hydrazinocarbonyl, hydroxylaminocarbonyl, alkoxycarbonyl, haloalkylcarbonylamino, haloalkylsulfonylamino, or carboxyheterocycloalkylcarbonyl.

Another aspect is a compound of any of the formulae herein, wherein:
each heterocycloalkyl may be optionally substituted with carboxy, (alkylaminocarbonyl)alkyl, carboxyalkyl, ((alkylaminocarbonyl)amino)alkyl, hydroxyalkyl, hydroxy, hydrazinocarbonyl, hydroxylaminocarbonyl.

Another aspect is a compound of any of the formulae herein, wherein:
each alkyl may be optionally substituted with hydroxy, halo, heterocycloalkylcarbonyl, heterocycloalkylsulfonyl, heterocycloalkyl, carboxyheterocycloalkylcarbonyl, carboxyheterocycloalkylsulfonyl, alkylcarbonylamino, carboxy, alkylaminocarbonyl, alkylthio, aryl, hydroxyaryl, alkylsulfonylamino, carboxyheterocycloalkyl, amino, heteroaryl, alkoxycarbonyl.

In one aspect, the compound of any of the formulae herein (e.g., formulae I-V) is that wherein the compound inhibits (or is identified to inhibit) UDP-3-O-[R-3-hydroxymyristoyl]-GlcNAc deacetylase (LpxC).

In one aspect, the compound of any of the formulae herein (e.g., formulae I-V) is that wherein the compound is identified as having an activity range against a target enzyme and an activity range against an off-target enzyme (e.g., LpxC IC50<1.0 μM and IC50>3.0 μM for CYP3A4; LpxC IC50<0.5 μM and IC50>1.0 μM for CYP3A4; LpxC IC50<0.24 μM and IC50>3.5 μM for CYP3A4; LpxC IC50<XX μM and IC50>YY μM for CYP3A4, in each instance XX is an independent number; in each instance YY is an independent number; in certain aspects XX is a number less than YY). In certain aspects, for example, XX is 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, or 1000-fold less than YY.

The compounds herein include those wherein the compound is identified as attaining affinity, at least in part, for a metalloenzyme by formation of one or more of the following types of chemical interactions or bonds to a metal: sigma bonds, covalent bonds, coordinate-covalent bonds, ionic bonds, pi bonds, delta bonds, or back-bonding interactions. The compounds can also attain affinity through weaker interactions with the metal such as van der Waals interactions, pi cation interactions, pi-anion interactions, dipole-dipole interactions, ion-dipole interactions. In one aspect, the compound is identified as having a bonding interaction with the metal.

Methods for assessing metal-ligand binding interactions are known in the art as exemplified in references including, for example, "Principles of Bioinorganic Chemistry" by Lippard and Berg, University Science Books, (1994); "Mechanisms of Inorganic Reactions" by Basolo and Pearson John Wiley & Sons Inc; 2nd edition (September 1967); "Biological Inorganic Chemistry" by Ivano Bertini, Harry Gray, Ed Stiefel, Joan Valentine, University Science Books (2007); Xue et al. "Nature Chemical Biology", vol. 4, no. 2, 107-109 (2008).

In certain instances, the compounds of the invention are selected from the following of Formulae (I-V) (and pharmaceutically acceptable salts, solvates, or hydrates thereof):

5-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-5-methylimidazolidine-2,4-dione (**1**);

1-hydroxy-3-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)urea (**2**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carboxylic acid (**3**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**4**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)isobutyramide (**5**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)methanesulfonamide (**6**);

2-(4'-(5-(hydroxymethyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**7**);

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**8**);

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**9**);

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**10**);

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**11**);

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)imidazolidine-2,4-dione (**12**);

2-(4'-(3-aminopropoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**13**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)methanesulfonamide (**14**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)acetamide (**15**);

N-(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-7-yl)methanesulfonamide (**16**);

N'-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbonyl)methanesulfonohydrazide (**17**);

N-hydroxy-2-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)acetamide (**18**);

1-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidin-2-one (**19**);

1-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**20**);

5-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-1,3,4-oxadiazol-2-amine (**21**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-methyl-[1,1'-biphenyl]-4-sulfonamide (**22**);

N-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)methanesulfonamide (**23**);

N-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)acetamide (**24**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-methyl-[1,1'-biphenyl]-4-carboxamide (**25**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-3-carboxylic acid (**26**);

2-(4'-(2-morpholino-2-oxoethyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**27**);

2-(4'-(2-morpholino-2-oxoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**28**);

2-(4'-((morpholinosulfonyl)methyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**29**);

3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carboxylic acid (**30**);

(R)-1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)pyrrolidine-2-carboxylic acid (**31**);

(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl methylcarbamate (**32**);

1-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)-3-methylurea (**33**);

N-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)acetamide (**34**);

N-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)methanesulfonamide (**35**);

(R)-1-(3-(4'-(4-(hydroxy(methyl)carbamoyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)pyrrolidine-2-carboxylic acid (**36**);

N-(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-6-yl)methanesulfonamide (**37**);

2-(4'-cyano-[1,1'-biphenyl]-4-yl)quinoline-4-carbohydrazide (**38**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methyl-1,6-naphthyridine-4-carbohydrazide (**39**);

N'-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methyl-1,6-naphthyridine-4-carbonyl)methanesulfonohydrazide (**40**);

N-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)hydrazinecarboxamide (**41**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinoline-4-carboxylic acid (**42**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinoline-4-carbohydrazide (**43**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methoxy-1,6-naphthyridine-4-carbohydrazide (**44**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methoxy-1,6-naphthyridine-4-carboxylic acid (**45**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methyl-1,6-naphthyridine-4-carboxylic acid (**46**);

2-(4'-cyano-[1,1'-biphenyl]-4-yl)quinoline-4-carboxylic acid (**47**);

2-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)acetohydrazide (**48**);

N-hydroxy-2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-N-methyl-1,6-naphthyridine-4-carboxamide (**49**);

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-4-(hydrazinecarbonyl)-1,6-naphthyridine 6-oxide (**50**);

4-(hydrazinecarbonyl)-2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine 6-oxide (**51**);

3-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)imidazolidine-2,4-dione (**52**);

2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**53**);

2-(4'-cyano-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**54**);

2-(5-(4-((2-hydroxyethyl)amino)phenyl)pyridin-2-yl)-1,6-naphthyridine-4-carbohydrazide (**55**);

2-(6-(4-((2-hydroxyethyl)amino)phenyl)pyridin-3-yl)-1,6-naphthyridine-4-carbohydrazide (**56**);

2-(4-(pyridin-3-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**57**);

2-(4-(pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**58**);

2-(4-(pyridin-4-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**59**);

2-(4-(1H-pyrazol-3-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**60**);

2-(4-(1H-pyrazol-4-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**61**);

2-(4-(oxazol-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**62**);

2-(4-(oxazol-5-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**63**);

2-([1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**64**);

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**65**);

2-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**66**);

2-(4-(5-(4-hydroxybutoxy)pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**67**);

2-(2'-hydroxy-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**68**);

2-(4-(thiazol-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**69**);

3-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**70**);

3-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**71**);

2-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**72**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-(2-hydroxyethyl)-[1,1'-biphenyl]-4-sulfonamide (**73**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-(3-hydroxypropyl)-[1,1'-biphenyl]-4-sulfonamide (**74**);

3-(2-(4-(5-(4-hydroxybutoxy)pyridin-2-yl)phenyl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**75**);

4-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**76**);

2-(4'-(4-hydrazinyl-4-oxobutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**77**);

4-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)-N-hydroxybutanamide (**78**);

4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)-N-hydroxybutanamide (**79**);

4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**80**);

ethyl 4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoate (**81**);

N-hydroxy-4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanamide (**82**);

4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**83**);

ethyl 4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoate (**84**);

2-(4'-(2-aminoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**85**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)acetamide (**86**);

(R)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-2-carboxylic acid (**87**);

(S)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-2-carboxylic acid (**88**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)piperidine-3-carboxylic acid (**89**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)piperidine-4-carboxylic acid (**90**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)propionamide (**91**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)isobutyramide (**92**);

2,2,2-trifluoro-N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)acetamide (**93**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)ethanesulfonamide (**94**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)propane-2-sulfonamide (**95**);

1,1,1-trifluoro-N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)methanesulfonamide (**96**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)propionamide (**97**);

2,2,2-trifluoro-N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)acetamide (**98**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)ethanesulfonamide (**99**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)propane-2-sulfonamide (**100**);

1,1,1-trifluoro-N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)methanesulfonamide (**101**);

2-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**102**);

(R)-1-(2-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)acetyl)pyrrolidine-2-carboxylic acid (**103**);

(R)-1-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)acetyl)pyrrolidine-2-carboxylic acid (**104**);

(R)-1-(((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)sulfonyl)pyrrolidine-2-carboxylic acid (**105**);

2-(4'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**106**);

(R)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid (**107**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-carbonyl)piperidine-3-carboxylic acid (**108**);

2-(4'-(5-(morpholine-4-carbonyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**109**);

2-(4'-(morpholinosulfonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**110**);

(R)-1-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)sulfonyl)pyrrolidine-2-carboxylic acid (**111**);

1-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)sulfonyl)piperidine-3-carboxylic acid (**112**);

3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)-N-methylisoxazole-5-carboxamide (**113**);

1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)piperidine-3-carboxylic acid (**114**);

1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)piperidine-2-carboxylic acid (**115**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)acetamide (**116**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)methanesulfonamide (**117**);

2-(4-((4-(morpholine-4-carbonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**118**);

(R)-1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**119**);

2-(4-((1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**120**);

N-(2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)ethyl)acetamide (**121**);

1-(3-fluoro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**122**);

1-(4-((2-fluoro-4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**123**);

2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**124**);

2-(4-((4-((2-hydroxyethyl)amino)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**125**);

2-(4-(pyridin-3-ylethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**126**);

3-(2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**127**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamide (**128**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzenesulfonamide (**129**);

(S)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid (**130**);

(R)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid (**131**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**132**);

(-)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**133**);

(+)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**134**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-3-carboxylic acid (**135**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-4-carboxylic acid (**136**);

2-(4-((4-(4-methylpiperazine-1-carbonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**137**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(2-hydroxyethyl)benzamide (**138**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(3-hydroxypropyl)benzamide (**139**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)acetic acid (**140**);

(S)-1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**141**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-3-carboxylic acid (**142**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-3-carboxylic acid (**143**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-4-carboxylic acid (**144**);

2-(4-((4-(morpholinosulfonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**145**);

2-(4-((4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**146**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(2-hydroxyethyl)benzenesulfonamide (**147**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(3-hydroxypropyl)benzenesulfonamide (**148**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenylsulfonamido)acetic acid (**149**);

N-(2-aminoethyl)-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamide (**150**);

N-(2-aminoethyl)-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzenesulfonamide (**151**);

(R)-1-((4-((4-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**152**);

(R)-1-((4-((4-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**153**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)azetidine-2-carboxylic acid (**154**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**155**);

(-)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**156**);

(+)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**157**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)azetidine-2-carboxylic acid (**158**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-2-carboxylic acid (**159**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)morpholine-3-carboxylic acid (**160**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)morpholine-2-carboxylic acid (**161**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)acetic acid (**162**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)-N-methylacetamide (**163**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)thiophene-2-carbonyl)piperidine-3-carboxylic acid (**164**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)thiophene-2-carbonyl)piperidine-2-carboxylic acid (**165**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)furan-2-carbonyl)piperidine-2-carboxylic acid (**166**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)furan-2-carbonyl)piperidine-3-carboxylic acid (**167**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)picolinoyl)piperidine-2-carboxylic acid (**168**);

1-(2-fluoro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**169**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)propanoic acid (**170**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-methylbutanoic acid (**171**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-methylpentanoic acid (**172**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-4-methylpentanoic acid (**173**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)succinic acid (**174**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)pentanedioic acid (**175**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-hydroxypropanoic acid (**176**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-hydroxybutanoic acid (**177**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-4-(methylthio)butanoic acid (**178**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-phenylpropanoic acid (**179**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-(4-hydroxyphenyl)propanoic acid (**180**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)thiomorpholine-3-carboxylic acid (**181**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-methylpropanoic acid (**182**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)ethanesulfonamide (**183**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)propane-2-sulfonamide (**184**);

1,1,1-trifluoro-N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)methanesulfonamide (**185**);

2-(N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfamoyl)acetic acid (**186**);

2-(1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidin-2-yl)acetic acid (**187**);

2-(1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidin-2-yl)acetic acid (**188**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)acetic acid (**189**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)propanoic acid (**190**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)propanoic acid (**191**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)propanoic acid (**192**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-methylpropanoic acid (**193**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)butanoic acid (**194**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)-2-methylpropanoic acid (**195**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)butanoic acid (**196**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-phenylpropanoic acid (**197**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-phenylpropanoic acid (**198**);

5-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-hydroxybenzoic acid (**199**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)benzoic acid (**200**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)malonic acid (**201**); or

(S)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**202**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzamido]benzoic acid (**203**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-methoxybenzoyl]piperidine-2-carboxylic acid (**204**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-hydroxybenzoyl]piperidine-2-carboxylic acid (**205**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-(trifluoromethyl)benzoyl]piperidine-2-carboxylic acid (**206**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]-4-hydroxypiperidine-3-carboxylic acid (**207**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**208**);

(2S)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**209**);

1-[2,5-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**210**);

2-(4-{2-[4-(2-oxo-1,3-oxazolidin-5-yl)phenyl]ethynyl}phenyl)-1,6-naphthyridine-4-carbohydrazide (**211**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**212**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-phenylpropanoic acid (**213**);

2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**214**);

4-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzamido]-2-hydroxybenzoic acid (**215**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-phenylpropanoic acid (**216**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylpentanoic acid (**217**);

1-[2,3-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**218**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-4-methylpentanoic acid (**219**);

2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-methylpentanoic acid (**220**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylbutanoic acid (**221**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}pentanedioic acid (**222**);

N-hydroxy-N-methyl-2-(4-{4-[5-(morpholine-4-carbonyl)-1,2-oxazol-3-yl]phenyl}phenyl)-1,6-naphthyridine-4-carboxamide (**223**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylpentanoic acid (**224**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}butanedioic acid (**225**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-methoxybenzoyl]piperidine-2-carboxylic acid (**226**);

1-[2-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**227**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-(trifluoromethyl)benzoyl]piperidine-2-carboxylic acid (**228**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-hydroxybenzoyl]piperidine-2-carboxylic acid (**229**);

1-[6-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)pyridine-3-carbonyl]piperidine-2-carboxylic acid (**230**);

N-hydroxy-2-(4-{4-[5-(methanesulfonamidomethyl)-1,2-oxazol-3-yl]phenyl}phenyl)-N-methyl-1,6-naphthyridine-4-carboxamide (**231**);

2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**232**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**233**);

2-[N-methyl4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**234**);

1-[3,5-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**235**);

2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-methylpentanoic acid (**236**);

2-{N-ethyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}acetic acid (**237**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-propylformamido}acetic acid (**238**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-methylpentanoic acid (**239**);

3-methyl-2-[N-methyl4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]pentanoic acid (**240**);

2-{N-benzyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}acetic acid (**241**);

N-hydroxy-N-methyl-2-{4-[2-(6-trifluoromethanesulfonamidopyridin-3-yl)ethynyl]phenyl}-1,6-naphthyridine-4-carboxamide (**242**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(propan-2-yl)formamido}acetic acid (**243**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**244**);

N-hydroxy-N-methyl-2-{4-[2-(4-trifluoromethanesulfonamidophenyl)ethynyl]phenyl}-1,6-naphthyridine-4-carboxamide (**245**);

2-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-methylpentanoic acid (**246**);

2-{N-benzyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**247**);

3-methyl-2-[N-methyl3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]pentanoic acid (**248**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**249**);

(2S)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**250**);

2-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**251**);

2-[N-methyl3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**252**);

1-[4-(2-{5-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]pyridin-2-yl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**253**);

1-[3-fluoro-4-(2-{2-fluoro-4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**254**);

2-{N-ethyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**255**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(propan-2-yl)formamido}-3-phenylpropanoic acid (**256**);

1-{3-fluoro-4-[2-(4-{4-[hydroxy(methyl)carbamoyl]-1,6-naphthyridin-2-yl}phenyl)ethynyl]benzoyl}piperidine-2-carboxylic acid (**257**);

(2R)-1-{[5-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)pyridin-2-yl]methyl}pyrrolidine-2-carboxylic acid (**258**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-phenylpropanoic acid (**259**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**260**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**261**);

2-amino-3-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**262**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-propylformamido}-3-phenylpropanoic acid (**263**);

1-[4-(2-{2-chloro-4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**264**);

1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-3-carboxylic acid (**265**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]pyrrolidine-2-carboxylic acid (**266**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-3-carboxylic acid (**267**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]pyrrolidine-2-carboxylic acid (**268**);

1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-3-carboxylic acid (**269**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]pyrrolidine-2-carboxylic acid (**270**);

2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**271**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**272**);

2-[N-(2-methylpropyl)3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]acetic acid (**273**);

2-[N-(2-methylpropyl)3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]acetic acid (**274**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-3-carboxylic acid (**275**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]pyrrolidine-2-carboxylic acid (**276**);

2-amino-3-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenoxy]propanoic acid (**277**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]-2-methoxyphenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**278**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**279**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]-2-hydroxyphenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**280**);

2-[4-(2-{4-[(2S)-2-carboxypiperidine-1-carbonyl]-2-chlorophenyl}ethynyl)phenyl]-1,6-naphthyridine-4-carboxylic acid (**281**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**282**);

2-amino-3-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**283**);

2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**284**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**285**);

2-[4-(2-{2-chloro-4-[(2S)-2-(hydrazinecarbonyl)piperidine-1-carbonyl]phenyl}ethynyl)phenyl]-1,6-naphthyridine-4-carbohydrazide (**286**);

2-[4-(2-{2-chloro-4-[(2S)-2-(hydrazinecarbonyl)piperidine-1-carbonyl]phenyl}ethynyl)phenyl]-1,6-naphthyridine-4-carboxylic acid (**287**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]-N-hydroxypiperidine-2-carboxamide (**288**);

2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoic acid (**289**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-(4-hydroxyphenyl)propanoic acid (**290**);

methyl 2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**291**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**292**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**293**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**294**);

methyl 2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**295**);

methyl 2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**296**);

3-amino-2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**297**);

3-amino-2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**298**);

3-amino-2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**299**);

(2S)-1-[3-chloro-4-(2-{4-[7-chloro-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**300**);

3-amino-2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**301**);

3-amino-2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**302**);

3-amino-2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**303**);

2-{4-[2-(4-{1,3-dioxo-octahydroimidazolidino[1,5-a]pyridin-2-yl}phenyl)ethynyl]phenyl}-1,6-naphthyridine-4-carbohydrazide (**304**);

3-amino-2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**305**);

(2S)-1-[4-(2-{4-[7-amino-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**306**);

3-amino-2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**307**);

1-[4-(2-{5-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]thiophen-2-yl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**308**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-methanesulfonamido-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**309**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-methoxy-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**310**);

2-(4-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}buta-1,3-diyn-1-yl)cyclopropane-1-carboxylic acid (**311**);

(2S)-1-[3-chloro-4-(2-{4-[7-acetamido-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**312**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-(morpholin-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**313**);

1-[2-(4-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}buta-1,3-diyn-1-yl)cyclopropanecarbonyl]piperidine-2-carboxylic acid (**314**);

(2S)-1-[4-(2-{4-[7-(2-carboxyacetamido)-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**315**);

(2S)-1-[4-(2-{4-[7-carboxymethanesulfonamido-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**316**);

1-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]carbamoyl}piperidine-2-carboxylic acid (**317**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-(3-methoxypyrrolidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**318**);

4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carboxylic acid (**319**);

N-[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]methanesulfonamide (**320**);

(2S)-1-[4-(2-{4-[7-(2-aminoacetamido)-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**321**);

2-{[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**322**);

(2R)-1-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carbonyl]pyrrolidine-2-carboxylic acid (**323**);

(2S)-1-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carbonyl]pyrrolidine-2-carboxylic acid (**324**);

N-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridin-7-yl]methanesulfonamide (**325**);

2-{[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**326**);

N-[4-(hydrazinecarbonyl)-2-(4-{4-[5-(hydroxymethyl)-1,2-oxazol-3-yl]phenyl}phenyl)-1,6-naphthyridin-7-yl]methanesulfonamide (**327**);

2-{[4-(hydrazinecarbonyl)-2-(4-{4-[5-(hydroxymethyl)-1,2-oxazol-3-yl]phenyl}phenyl)-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**328**);

N-[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]-N-methylmethanesulfonamide (**329**); or

2-{[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl](methyl)sulfamoyl}acetic acid (**330**).

In another aspect, the invention provides a pharmaceutical composition comprising a compound of any of the formulae herein (e.g., formulae I-V) and a pharmaceutically acceptable carrier.

In other aspects, the invention provides a method of modulating metalloenzyme activity in a subject, comprising contacting the subject with a compound of any of the formulae herein (e.g., formulae I-V), in an amount and under conditions sufficient to modulate metalloenzyme activity.

In one aspect, the invention provides a method of treating a subject suffering from or susceptible to a metalloenzyme-related disorder or disease, comprising administering to the subject an effective amount of a compound or pharmaceutical composition of any of the formulae herein (e.g., formulae I-V).

In another aspect, the invention provides a method of treating a subject suffering from or susceptible to a metalloenzyme-related disorder or disease, wherein the subject has been identified as in need of treatment for a metalloenzyme-related disorder or disease, comprising administering to said subject in need thereof, an effective amount of a compound or pharmaceutical composition of any of the formulae herein (e.g., formulae I-V), such that said subject is treated for said disorder.

In another aspect, the invention provides a method of treating a subject suffering from or susceptible to a metalloenzyme-mediated disorder or disease, wherein the subject has been identified as in need of treatment for a metalloenzyme-mediated disorder or disease, comprising administering to said subject in need thereof, an effective amount of a compound or pharmaceutical composition of any of the formulae herein (e.g., formulae I-V), such that metalloenzyme activity in said subject is modulated (e.g., down regulated, inhibited).

The methods herein include those wherein the disease or disorder is mediated by any of 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR), 17-alpha hydroxylase (CYP17), aldosterone synthase (CYP11B2), aminopeptidase p, anthrax lethal factor, arginase, beta-lactamase, cytochrome P450 2A6, d-ala d-ala ligase, dopamine beta-hydroxylase, endothelin converting enzyme-1, glutamate carboxypeptidase II, glutaminyl cyclase, glyoxalase, heme oxygenase, HPV/HSV E1 helicase, indoleamine 2,3-dioxygenase, leukotriene A4 hydrolase, methionine aminopeptidase 2, peptide deformylase, phosphodiesterase VII, relaxase, retinoic acid hydroxylase (CYP26), TNF-alpha converting enzyme (TACE), UDP-(3-O-(R-3-hydroxymyristoyl))-N-acetylglucosamine deacetylase (LpxC), vascular adhesion protein-1 (VAP-1), or vitamin D hydroxylase (CYP24).

The methods herein include those wherein the disease or disorder is mediated by any of 4-hydroxyphenyl pyruvate dioxygenase, 5-lipoxygenase, adenosine deaminase, alcohol dehydrogenase, aminopeptidase n, angiotensin converting enzyme, aromatase (CYP19), calcineurin, carbamoyl phosphate synthetase, carbonic anhydrase family, catechol o-methyl transferase, cyclooxygenase family, dihydropyrimidine dehydrogenase-1, DNA polymerase, farnesyl diphosphate synthase, farnesyl transferase, fumarate reductase, GABA aminotransferase, HIF-prolyl hydroxylase, histone deacetylase family, HIV integrase, HIV-1 reverse transcriptase, isoleucine tRNA ligase, lanosterol demethylase (CYP51), matrix

metalloprotease family, methionine aminopeptidase, neutral endopeptidase, nitric oxide synthase family, phosphodiesterase III, phosphodiesterase IV, phosphodiesterase V, pyruvate ferredoxin oxidoreductase, renal peptidase, ribonucleoside diphosphate reductase, thromboxane synthase (CYP5a), thyroid peroxidase, tyrosinase, urease, or xanthine oxidase.

The methods herein include those wherein the disease or disorder is cancer, cardiovascular disease, inflammatory disease, infectious disease, metabolic disease, ophthalmologic disease, central nervous system (CNS) disease, urologic disease, or gastrointestinal disease.

The methods herein include those wherein the disease or disorder is prostate cancer, breast cancer, inflammatory bowel disease, psoriasis, systemic bacterial infection, skin structure bacterial infection, and specifically gram-negative bacterial infection.

Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Another aspect of the invention is a composition comprising a compound of a formulae herein (e.g., formulae (I-V)) and an agriculturally acceptable carrier.

Another aspect of the invention is a method of treating or preventing a metalloenzyme-mediated disease or disorder in or on a plant comprising contacting a compound herein with the plant.

Another aspect of the invention is a method of inhibiting metalloenzyme activity in or on a plant comprising contacting a compound herein with the plant.

DETAILED DESCRIPTION

Definitions

In order that the invention may be more readily understood, certain terms are first defined here for convenience.

As used herein, the term "treating" a disorder encompasses preventing, ameliorating, mitigating and/or managing the disorder and/or conditions that may cause the disorder. The terms "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms. In accordance with the present invention "treating" includes preventing, blocking, inhibiting, attenuating, protecting against, modulating, reversing the effects of and reducing the occurrence of e.g., the harmful effects of a disorder.

As used herein, "inhibiting" encompasses preventing, reducing and halting progression. Note that “enzyme inhibition” (e.g., metalloenzyme inhibition) is distinguished and described below.

The term "modulate" refers to increases or decreases in the activity of an enzyme in response to exposure to a compound of the invention.

The terms "isolated," "purified," or "biologically pure" refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. Particularly, in embodiments the compound is at least 85% pure, more preferably at least 90% pure, more preferably at least 95% pure, and most preferably at least 99% pure.

The term "administration" or “administering” includes routes of introducing the compound(s) to a subject to perform their intended function. Examples of routes of administration which can be used include injection (subcutaneous, intravenous, parenterally, intraperitoneally, intrathecal), topical, oral, inhalation, rectal and transdermal.

The term “effective amount” includes an amount effective, at dosages and for periods of time necessary, to achieve the desired result. An effective amount of compound may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (*e.g.,* side effects) of the inhibitor compound are outweighed by the therapeutically beneficial effects.

The phrases "systemic administration," "administered systemically", "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound(s), drug or other material, such that it enters the patient's system and, thus, is subject to metabolism and other like processes.

The term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

A therapeutically effective amount of compound (*i.e.*, an effective dosage) may range from about 0.005 μg/kg to about 200 mg/kg, preferably about 0.01 mg/kg to about 200 mg/kg, more preferably about 0.015 mg/kg to about 30 mg/kg of body weight. In other embodiments,

the therapeutically effect amount may range from about 1.0 pM to about 10 μM. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound can include a single treatment or, preferably, can include a series of treatments. In one example, a subject is treated with a compound in the range of between about 0.005 μg/kg to about 200 mg/kg of body weight, one time per day for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. In another example, a subject may be treated daily for several years in the setting of a chronic condition or illness. It will also be appreciated that the effective dosage of a compound used for treatment may increase or decrease over the course of a particular treatment.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "diastereomers" refers to stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another.

The term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another. An equimolar mixture of two enantiomers is called a "racemic mixture" or a "racemate."

The term "isomers" or "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

The term “prodrug” includes compounds with moieties which can be metabolized *in vivo*. Generally, the prodrugs are metabolized *in vivo* by esterases or by other mechanisms to active drugs. Examples of prodrugs and their uses are well known in the art (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxyl with a suitable esterifying agent. Hydroxyl groups can be converted into esters *via* treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branched or unbranched lower alkyl ester moieties, (*e.g.*, propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-

alkyl esters (*e.g.*, dimethylaminoethyl ester), acylamino lower alkyl esters (*e.g.*, acetyloxymethyl ester), acyloxy lower alkyl esters (*e.g.*, pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (*e.g.*, benzyl ester), substituted (*e.g.*, with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters. Prodrugs which are converted to active forms through other mechanisms *in vivo* are also included. In aspects, the compounds of the invention are prodrugs of any of the formulae herein.

The term "subject" refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In certain embodiments, the subject is a human.

The terms “a,” “an,” and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a sample” includes a plurality of samples, unless the context clearly is to the contrary (e.g., a plurality of samples), and so forth.

Throughout this specification and the claims, the words “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country. As used herein, the term “about,” when referring to a value is meant to encompass variations of, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ± 1%, in some embodiments ± 0.5%, and in some embodiments ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Use of the word “inhibitor” herein is meant to mean a molecule that exhibits activity for inhibiting a metalloenzyme. By “inhibit” herein is meant to decrease the activity of metalloenzyme , as compared to the activity of metalloenzyme in the absence of the inhibitor. In some embodiments, the term “inhibit” means a decrease in metalloenzyme activity of at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%. In other embodiments, inhibit means a decrease in metalloenzyme activity of about 5% to about 25%, about 25% to about 50%, about 50% to about 75%, or about 75% to 100%. In some embodiments, inhibit means a decrease in metalloenzyme activity of about 95% to

100%, e.g., a decrease in activity of 95%, 96%, 97%, 98%, 99%, or 100%. Such decreases can be measured using a variety of techniques that would be recognizable by one of skill in the art. Particular assays for measuring individual activity are described below.

Furthermore the compounds of the invention include olefins having either geometry: "Z" refers to what is referred to as a "cis" (same side) configuration whereas "E" refers to what is referred to as a "trans" (opposite side) configuration. With respect to the nomenclature of a chiral center, the terms "d" and "l" configuration are as defined by the IUPAC Recommendations. As to the use of the terms, diastereomer, racemate, epimer and enantiomer, these will be used in their normal context to describe the stereochemistry of preparations.

As used herein, the term "alkyl" refers to a straight-chained or branched hydrocarbon group containing 1 to 12 carbon atoms. The term "lower alkyl" refers to a C1-C6 alkyl chain. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, *tert*-butyl, and n-pentyl. Alkyl groups may be optionally substituted with one or more substituents.

The term "alkenyl" refers to an unsaturated hydrocarbon chain that may be a straight chain or branched chain, containing 2 to 12 carbon atoms and at least one carbon-carbon double bond. Alkenyl groups may be optionally substituted with one or more substituents.

The term "alkynyl" refers to an unsaturated hydrocarbon chain that may be a straight chain or branched chain, containing the 2 to 12 carbon atoms and at least one carbon-carbon triple bond. Alkynyl groups may be optionally substituted with one or more substituents.

The sp^2 or sp carbons of an alkenyl group and an alkynyl group, respectively, may optionally be the point of attachment of the alkenyl or alkynyl groups.

The term "alkoxy" refers to an -O-alkyl group.

As used herein, the term "halogen", "hal" or "halo" means -F, -Cl, -Br or -I.

The term "haloalkyl" refers to an -alkyl group that is substituted by one or more halo substituents. Examples of haloalkyl groups include trifluoromethyl, and 2,2,2-trifluoroethyl.

The term "haloalkoxy" refers to an -O-alkyl radical that is substituted by one or more halo substituents. Examples of haloalkoxy groups include trifluoromethoxy, and 2,2,2-trifluoroethoxy.

The term "cycloalkyl" refers to a hydrocarbon 3-8 membered monocyclic or 7-14 membered bicyclic ring system having at least one saturated ring or having at least one non-aromatic ring, wherein the non-aromatic ring may have some degree of unsaturation. Cycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a cycloalkyl group may be substituted by a substituent. Representative examples of cycloalkyl group include cyclopropyl, cyclopentyl, cyclohexyl, cyclobutyl, cycloheptyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, and the like.

The term "alkylthio" refers to an -S-alkyl substituent.

The term "alkoxyalkyl" refers to an -alkyl-O-alkyl substituent.

The term "haloalkoxy" refers to an -O-alkyl that is substituted by one or more halo substituents. Examples of haloalkoxy groups include trifluoromethoxy, and 2,2,2-trifluoroethoxy.

The term "haloalkoxyalkyl" refers to an –alkyl-O-alkyl' where the alkyl' is substituted by one or more halo substituents.

The term "haloalkylaminocarbonyl" refers to a –C(O)-amino-alkyl where the alkyl is substituted by one or more halo substituents.

The term "haloalkylthio" refers to an -S-alkyl that is substituted by one or more halo substituents. Examples of haloalkylthio groups include trifluoromethylthio, and 2,2,2-trifluoroethylthio.

The term "haloalkylcarbonyl" refers to an –C(O)-alkyl that is substituted by one or more halo substituents. An example of a haloalkylcarbonyl group includes trifluoroacetyl.

The term "cycloalkoxy" refers to an -O-cycloalkyl substituent.

The term "cycloalkoxyalkyl" refers to an -alkyl-O-cycloalkyl substituent.

The term "cycloalkylalkoxy" refers to an -O-alkyl-cycloalkyl substituent.

The term "cycloalkylaminocarbonyl" refers to an –C(O)-NH-cycloalkyl substituent.

The term "aryl" refers to a hydrocarbon monocyclic, bicyclic or tricyclic aromatic ring system. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, 4, 5 or 6 atoms of each ring of an aryl group may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl, azulenyl, and the like.

The term "aryloxy" refers to an -O-aryl substituent.

The term "arylalkoxy" refers to an -O-alkyl-aryl substituent.

The term "arylalkylthio" refers to an -S-alkyl-aryl substituent.

The term "arylthioalkyl" refers to an –alkyl-S -aryl substituent.

The term "arylalkylaminocarbonyl" refers to a –C(O)-amino-alkyl-aryl substituent.

The term "arylalkylsulfonyl" refers to an –S(O)2-alkyl-aryl substituent.

The term "arylalkylsulfinyl" refers to an –S(O)-alkyl-aryl substituent.

The term "aryloxyalkyl" refers to an –alkyl-O-aryl substituent.

The term "alkylaryl" refers to an –aryl-alkyl substituent.

The term "arylalkyl" refers to an –alkyl-aryl substituent.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-4 ring heteroatoms if

monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and the remainder ring atoms being carbon (with appropriate hydrogen atoms unless otherwise indicated). Heteroaryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furanyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl, thiazolyl, isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoquinolinyl, indazolyl, and the like.

The term "heteroaryloxy" refers to an -O-heteroaryl substituent.

The term "heteroarylalkoxy" refers to an -O-alkyl-heteroaryl substituent.

The term "heteroaryloxyalkyl" refers to an –alkyl-O-heteroaryl substituent.

The term "nitrogen-containing heteroaryl" refers to a heteroaryl group having 1-4 ring nitrogen heteroatoms if monocyclic, 1-6 ring nitrogen heteroatoms if bicyclic, or 1-9 ring nitrogen heteroatoms if tricyclic.

The term "heterocycloalkyl", "heterocyclyl", or "heterocycle" refers to a nonaromatic 3-8 membered monocyclic, 7-12 membered bicyclic, or 10-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, S, B, P or Si, wherein the nonaromatic ring system is completely saturated. Heterocycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heterocycloalkyl group may be substituted by a substituent. Representative heterocycloalkyl groups include piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,3-dioxolane, tetrahydrofuranyl, tetrahydrothienyl, thiirenyl, and the like.

The term "heterocycloalkylcarbonyl" refers to a -C(=O)-heterocycloalkyl substituent.

The term "carboxyheterocycloalkylcarbonyl" refers to a -C(=O)-heterocycloalkyl-CO_2H substituent.

The term "heterocycloalkylsulfonyl" refers to a $–SO_2$-heterocycloalkyl substituent.

The term "carboxyheterocycloalkylsulfonyl" refers to a $–SO_2$-heterocycloalkyl-CO_2H substituent.

The term "heterocycloalkoxy" refers to an -O-heterocycloalkyl group, which heterocycloalkyl moiety may be optionally substituted with 1-3 substituents.

The term "alkylamino" refers to an amino substituent which is further substituted with one or two alkyl groups. The term "aminoalkyl" refers to an alkyl substituent which is further substituted with one or more amino groups. The term "hydroxyalkyl" or "hydroxylalkyl"

refers to an alkyl substituent which is further substituted with one or more hydroxyl groups. The alkyl or aryl portion of alkylamino, aminoalkyl, mercaptoalkyl, hydroxyalkyl, mercaptoalkoxy, sulfonylalkyl, sulfonylaryl, alkylcarbonyl, and alkylcarbonylalkyl may be optionally substituted with one or more substituents.

Acids and bases useful in the methods herein are known in the art. Acid catalysts are any acidic chemical, which can be inorganic (e.g., hydrochloric, sulfuric, nitric acids, aluminum trichloride) or organic (e.g., camphorsulfonic acid, p-toluenesulfonic acid, acetic acid, ytterbium triflate) in nature. Acids are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions. Bases are any basic chemical, which can be inorganic (e.g., sodium bicarbonate, potassium hydroxide) or organic (e.g., triethylamine, pyridine) in nature. Bases are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions.

Alkylating agents are any reagent that is capable of effecting the alkylation of the functional group at issue (e.g., oxygen atom of an alcohol, nitrogen atom of an amino group). Alkylating agents are known in the art, including in the references cited herein, and include alkyl halides (e.g., methyl iodide, benzyl bromide or chloride), alkyl sulfates (e.g., methyl sulfate), or other alkyl group-leaving group combinations known in the art. Leaving groups are any stable species that can detach from a molecule during a reaction (e.g., elimination reaction, substitution reaction) and are known in the art, including in the references cited herein, and include halides (e.g., I-, Cl-, Br-, F-), hydroxy, alkoxy (e.g., -OMe, -O-t-Bu), acyloxy anions (e.g., -OAc, $-OC(O)CF_3$), sulfonates (e.g., mesyl, tosyl), acetamides (e.g., -NHC(O)Me), carbamates (e.g., N(Me)C(O)Ot-Bu), phosphonates (e.g., $-OP(O)(OEt)_2$), water or alcohols (protic conditions), and the like.

In certain embodiments, substituents on any group (such as, for example, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, heterocycloalkyl) can be at any atom of that group, wherein any group that can be substituted (such as, for example, alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, heterocycloalkyl) can be optionally substituted with one or more substituents (which may be the same or different), each replacing a hydrogen atom. Examples of suitable substituents include, but are not limited to alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, halogen, haloalkyl, cyano, nitro, alkoxy, aryloxy, hydroxyl, hydroxylalkyl, oxo (i.e., carbonyl), carboxyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, heteroaryloxy, heteroaryloxycarbonyl, thio, mercapto, mercaptoalkyl, arylsulfonyl, amino, aminoalkyl, dialkylamino, hydroxyalkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino, arylamino,

diarylamino, alkylcarbonyl, or arylamino-substituted aryl; arylalkylamino, aralkylaminocarbonyl, amido, alkylaminosulfonyl, arylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, imino, carboxamido, carbamido, carbamyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, mercaptoalkoxy, N-hydroxyamidinyl, or N'-aryl, N''-hydroxyamidinyl.

Compounds of the invention can be made by means known in the art of organic synthesis. Methods for optimizing reaction conditions, if necessary minimizing competing by-products, are known in the art. Reaction optimization and scale-up may advantageously utilize high-speed parallel synthesis equipment and computer-controlled microreactors (e.g. *Design And Optimization in Organic Synthesis, 2nd Edition*, Carlson R, Ed, 2005; Elsevier Science Ltd.; Jähnisch, K et al, Angew. Chem. Int. Ed. Engl. 2004 43: 406; and references therein). Additional reaction schemes and protocols may be determined by the skilled artesian by use of commercially available structure-searchable database software, for instance, SciFinder® (CAS division of the American Chemical Society) and CrossFire Beilstein® (Elsevier MDL), or by appropriate keyword searching using an internet search engine such as Google® or keyword databases such as the US Patent and Trademark Office text database.

As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art, including in the schemes and examples herein. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and one of ordinary skill in the art will recognize that variation of the reaction conditions can produce the desired compounds of the present invention.

The compounds herein may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring or double bond. Accordingly, all *cis/trans* and *E/Z* isomers are expressly included in the present invention. The compounds herein may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented. All such isomeric forms of such compounds herein are expressly included in the present invention. All crystal forms and polymorphs of the compounds described herein are expressly included in the present invention. Also embodied are extracts and fractions comprising compounds of the invention. The term isomers is intended to include diastereoisomers, enantiomers, regioisomers, structural isomers, rotational isomers, tautomers,

and the like. For compounds which contain one or more stereogenic centers, e.g., chiral compounds, the methods of the invention may be carried out with an enantiomerically enriched compound, a racemate, or a mixture of diastereomers.

Preferred enantiomerically enriched compounds have an enantiomeric excess of 50% or more, more preferably the compound has an enantiomeric excess of 60%, 70%, 80%, 90%, 95%, 98%, or 99% or more. In preferred embodiments, only one enantiomer or diastereomer of a chiral compound of the invention is administered to cells or a subject.

LIST OF ABBREVIATIONS

In order that the invention may be more readily understood, certain abbreviations are first defined here for convenience.

TIMP:	Tissue Inhibitor of Metalloproteases
MMP:	Matrix Metalloproteinase
LpxC:	UDP-3-O-[R-3-hydroxymyristoyl]-GlcNAc deacetylase
CYP:	Cytochrome P450
DXR:	1-Deoxy-d-xylulose-5-phosphate reductoisomerase
CYP17:	17-Alpha hydroxylase
CYP11B2:	Aldosterone synthase
HPV/HSV E1 helicase:	Human papillomavirus/Herpes simplex virus E1 helicase
CYP2D6:	Retinoic acid hydroxylase
TNF-alpha:	Tumor necrosis factor alpha
TACE:	TNF-alpha converting enzyme
VAP-1:	Vascular adhesion protein-1
CYP24:	Vitamin D hydroxylase
CYP19:	Aromatase
CYP51:	Lanosterol demethylase
CYP5a:	Thromboxane synthase
CNS:	Central nervous system
DMSO:	Dimethylsulfoxide
MIC:	Minimum inhibitory concentration
MFC:	Minimum fungicidal concentration
TEA or NEt_3:	Triethylamine
RT:	Room temperature
TLC:	Thin-layer chromatography

PivCl:	Pivaloyl chloride
$(COOEt)_2$:	Diethyl oxalate
n-BuLi:	n-Butyllithium
DIPEA:	Diisopropylethylamine
EDCI:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt:	Hydroxybenzotriazole
DMF:	N,N-Dimethylformamide
MeLi:	Methyllithium
THF:	Tetrahydrofuran
TBS:	t-Butyldimethylsilyl
$Pd(PPh_3)_4$:	Tetrakistriphosphino palladium(0)
EtOH:	Ethanol or Ethyl alcohol
MeOH:	Methanol or Methyl alcohol
DCM:	Dichloromethane
EtOAc:	Ethyl acetate
NMR:	Nuclear magnetic resonance
MS:	Mass spectroscopy
ESI:	Electrospray injection
IPA:	Isopropanol or Isopropyl alcohol
HPLC:	High-performance liquid chromatography
KOAc:	Potassium acetate
$Pd(dppf)_2Cl_2$:	[1,1'-Bis(diphenylphosphino)ferrocene]dichloro palladium(II)
t-BuOH:	t-Butanol or t-Butyl alcohol
DPPA:	Diphenylphosphoryl azide
TFA:	Trifluoroacetic acid
NH_2-OTHP:	O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine
Et_2O:	Diethylether
(Boc)2O:	Di-tert-butyl dicarbonate
LC-MS:	Liquid chromatography-mass spectroscopy
MsCl:	Methanesulfonylchloride
HNNHBoc:	N-(tert-Butoxycarbonyl)hydrazine
NCS:	N-chlorosuccinimide
AcOH:	Acetic acid

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

CDI: N,N-Carbonyldiimidazole

Fmoc: Fluorenylmethoxycarbonyl

p-TSA: p-Toluenesulfonic acid

TCDI: Thiocarbonyldiimidazole

DMAP: 4-Dimethylaminopyridine

$Pd_2(dba)_3$: Tris(dibenzylideneacetone) dipalladium(0)

NMU: N-Methyl-N-nitrosourea

BINAP: (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

NaOt-Bu: Sodium tert-butoxide

TMS-Br: Bromotrimethylsilane

HMDS: Hexamethyldisilazane

Boc: t-Butyloxycarbonyl

mCPBA: m-Chloroperbenzoic acid

TMS: Trimethylsilyl

Ac_2O: Acetic anhydride

$NaB(OAc)_3H$: Sodium triacetoxyborohydride

PMB-Cl: p-Methoxybenzylchloride

R_t: Retention time

ACN: Acetonitrile

MW: Microwave

Tritylchloride: Chlorotriphenylmethane

DEAD: Diethylazodicarboxylate

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

$Pd_2(dba)_3CHCl_3$: Tris(dibenzylideneacetone) dipalladium(0) – chloroform adduct

TPP: Triphenylphosphine

$Pd(OAc)_2$: Palladium(II) acetate

HBTU: N,N,N',N'-Tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate

Methods of Treatment

In one aspect, the invention provides a method of modulating the metalloenzyme

activity of a cell in a subject, comprising contacting the subject with a compound of any of the formulae herein (e.g., formulae I-V), in an amount and under conditions sufficient to modulate metalloenzyme activity.

In one embodiment, the modulation is inhibition.

In another aspect, the invention provides a method of treating a subject suffering from or susceptible to a metalloenzyme-mediated disorder or disease, comprising administering to the subject an effective amount of a compound or pharmaceutical composition of any of the formulae herein (e.g., formulae I-V).

In other aspects, the invention provides a method of treating a subject suffering from or susceptible to a metalloenzyme-mediated disorder or disease, wherein the subject has been identified as in need of treatment for a metalloenzyme-mediated disorder or disease, comprising administering to said subject in need thereof, an effective amount of a compound or pharmaceutical composition of any of the formulae herein (e.g., formulae I-V), such that said subject is treated for said disorder.

In certain embodiments, the invention provides a method of treating a disease, disorder or symptom thereof, wherein the disorder is cancer, cardiovascular disease, inflammatory disease or infectious disease. In other embodiments the disease, disorder or symptom thereof is metabolic disease, ophthalmologic disease, central nervous system (CNS) disease, urologic disease, or gastrointestinal disease. In certain embodiments the disease is prostate cancer, breast cancer, inflammatory bowel disease, psoriasis, systemic fungal infection, skin structure fungal infection, mucosal fungal infection, and onychomycosis.

In certain embodiments, the subject is a mammal, preferably a primate or human.

In another embodiment, the invention provides a method as described above, wherein the effective amount of the compound of any of the formulae herein (e.g., formulae I-V) is as described above.

In another embodiment, the invention provides a method as described above, wherein the compound of any of the formulae herein (e.g., formulae I-V) is administered intravenously, intramuscularly, subcutaneously, intracerebroventricularly, orally or topically.

In another embodiment, the invention provides a method as described herein wherein the compound of any of the formulae herein (e.g., formulae I-V) demonstrates selectivity for an activity range against a target enzyme and an activity range against an off-target enzyme (e.g., LpxC IC50<1.0 μM and IC50>3.0 μM for CYP3A4; LpxC IC50<0.5 μM and IC50>1.0 μM for CYP3A4; LpxC IC50<0.24 μM and IC50>3.5 μM for CYP3A4; LpxC IC50<XX μM and IC50>YY μM for CYP3A4, in each instance XX is an independent number; in each

instance YY is an independent number; in certain aspects XX is a number less than YY). In certain aspects, for example, XX is 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, or 1000-fold less than YY.

In other embodiments, the invention provides a method as described above, wherein the compound of any of the formulae herein (e.g., formulae I-V) is administered alone or in combination with one or more other therapeutics. In a further embodiment, the additional therapeutic agent is an anti-cancer agent, antifungal agent, cardiovascular agent, anti-inflammatory agent, chemotherapeutic agent, an anti-angiogenesis agent, cytotoxic agent, an anti-proliferation agent, metabolic disease agent, ophthalmologic disease agent, central nervous system (CNS) disease agent, urologic disease agent, or gastrointestinal disease agent.

Another object of the present invention is the use of a compound as described herein (e.g., of any of the formulae herein) in the manufacture of a medicament for use in the treatment of a metalloenzyme-mediated disorder or disease. Another object of the present invention is the use of a compound as described herein (e.g., of any of the formulae herein) for use in the treatment of a metalloenzyme-mediated disorder or disease. Another object of the present invention is the use of a compound as described herein (e.g., of any of the formulae herein) in the manufacture of an agricultural composition for use in the treatment or prevention of a metalloenzyme-mediated disorder or disease in agricultural or agrarian settings.

Pharmaceutical Compositions

In one aspect, the invention provides a pharmaceutical composition comprising the compound of any of the formulae herein (e.g., formulae I-V) and a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is an anti-cancer agent, antifungal agent, cardiovascular agent, anti-inflammatory agent, chemotherapeutic agent, an anti-angiogenesis agent, cytotoxic agent, an anti-proliferation agent, metabolic disease agent, ophthalmologic disease agent, central nervous system (CNS) disease agent, urologic disease agent, or gastrointestinal disease agent.

In one aspect, the invention provides a kit comprising an effective amount of a compound of any of the formulae herein (e.g., formulae I-V), in unit dosage form, together with instructions for administering the compound to a subject suffering from or susceptible to a metalloenzyme-mediated disease or disorder, including cancer, solid tumor, cardiovascular

disease, inflammatory disease, infectious disease. In other embodiments the disease, disorder or symptom thereof is metabolic disease, ophthalmologic disease, central nervous system (CNS) disease, urologic disease, or gastrointestinal disease.

The term "pharmaceutically acceptable salts" or "pharmaceutically acceptable carrier" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydroiodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al., Journal of Pharmaceutical Science 66:1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the

present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

The invention also provides a pharmaceutical composition, comprising an effective amount a compound described herein and a pharmaceutically acceptable carrier. In an embodiment, compound is administered to the subject using a pharmaceutically-acceptable formulation, *e.g.,* a pharmaceutically-acceptable formulation that provides sustained delivery of the compound to a subject for at least 12 hours, 24 hours, 36 hours, 48 hours, one week, two weeks, three weeks, or four weeks after the pharmaceutically-acceptable formulation is administered to the subject.

Actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic (or unacceptably toxic) to the patient.

In use, at least one compound according to the present invention is administered in a pharmaceutically effective amount to a subject in need thereof in a pharmaceutical carrier by intravenous, intramuscular, subcutaneous, or intracerebroventricular injection or by oral administration or topical application. In accordance with the present invention, a compound of the invention may be administered alone or in conjunction with a second, different therapeutic. By "in conjunction with" is meant together, substantially simultaneously or sequentially. In one embodiment, a compound of the invention is administered acutely. The compound of the invention may therefore be administered for a short course of treatment, such as for about 1 day to about 1 week. In another embodiment, the compound of the invention may be administered over a longer period of time to ameliorate chronic disorders, such as, for example, for about one week to several months depending upon the condition to be treated.

By "pharmaceutically effective amount" as used herein is meant an amount of a

compound of the invention, high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A pharmaceutically effective amount of a compound of the invention will vary with the particular goal to be achieved, the age and physical condition of the patient being treated, the severity of the underlying disease, the duration of treatment, the nature of concurrent therapy and the specific compound employed. For example, a therapeutically effective amount of a compound of the invention administered to a child or a neonate will be reduced proportionately in accordance with sound medical judgment. The effective amount of a compound of the invention will thus be the minimum amount which will provide the desired effect.

A decided practical advantage of the present invention is that the compound may be administered in a convenient manner such as by intravenous, intramuscular, subcutaneous, oral or intra-cerebroventricular injection routes or by topical application, such as in creams or gels. Depending on the route of administration, the active ingredients which comprise a compound of the invention may be required to be coated in a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the compound. In order to administer a compound of the invention by other than parenteral administration, the compound can be coated by, or administered with, a material to prevent inactivation.

The compound may be administered parenterally or intraperitoneally. Dispersions can also be prepared, for example, in glycerol, liquid polyethylene glycols, and mixtures thereof, and in oils.

Some examples of substances which can serve as pharmaceutical carriers are sugars, such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethycellulose, ethylcellulose and cellulose acetates; powdered tragancanth; malt; gelatin; talc; stearic acids; magnesium stearate; calcium sulfate; vegetable oils, such as peanut oils, cotton seed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; alginic acids; pyrogen-free water; isotonic saline; and phosphate buffer solution; skim milk powder; as well as other non-toxic compatible substances used in pharmaceutical formulations such as Vitamin C, estrogen and echinacea, for example. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, lubricants, excipients, tableting agents, stabilizers, anti-oxidants and preservatives, can

also be present. Solubilizing agents, including for example, cremaphore and beta-cyclodextrins can also used in the pharmaceutical compositions herein.

Pharmaceutical compositions comprising the active compounds of the presently disclosed subject matter (or prodrugs thereof) can be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping or lyophilization processes. The compositions can be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Pharmaceutical compositions of the presently disclosed subject matter can take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, transdermal, rectal, vaginal, and the like, or a form suitable for administration by inhalation or insufflation.

For topical administration, the active compound(s) or prodrug(s) can be formulated as solutions, gels, ointments, creams, suspensions, and the like.

Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral, or pulmonary administration.

Useful injectable preparations include sterile suspensions, solutions or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions also can contain formulating agents, such as suspending, stabilizing and/or dispersing agent. The formulations for injection can be presented in unit dosage form (e.g., in ampules or in multidose containers) and can contain added preservatives.

Alternatively, the injectable formulation can be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer, dextrose solution, and the like, before use. To this end, the active compound(s) can be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

For oral administration, the pharmaceutical compositions can take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica);

disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets can be coated by methods well known in the art with, for example, sugars or enteric coatings.

Liquid preparations for oral administration can take the form of, for example, elixirs, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). The preparations also can contain buffer salts, preservatives, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration can be suitably formulated to give controlled release of the active compound or prodrug, as is well known.

For buccal administration, the compositions can take the form of tablets or lozenges formulated in a conventional manner.

For rectal and vaginal routes of administration, the active compound(s) can be formulated as solutions (for retention enemas), suppositories, or ointments containing conventional suppository bases, such as cocoa butter or other glycerides.

For nasal administration or administration by inhalation or insufflation, the active compound(s) or prodrug(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example capsules and cartridges comprised of gelatin) can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

A specific example of an aqueous suspension formulation suitable for nasal administration using commercially-available nasal spray devices includes the following ingredients: active compound or prodrug (0.5-20 mg/ml); benzalkonium chloride (0.1-0.2 mg/mL); polysorbate 80 (TWEEN® 80; 0.5-5 mg/ml); carboxymethylcellulose sodium or microcrystalline cellulose (1-15 mg/ml); phenylethanol (1-4 mg/ml); and dextrose (20-50

mg/ml). The pH of the final suspension can be adjusted to range from about pH5 to pH7, with a pH of about pH 5.5 being typical.

For ocular administration, the active compound(s) or prodrug(s) can be formulated as a solution, emulsion, suspension, and the like, suitable for administration to the eye. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in U.S. Patent No. 6,261,547; U.S. Patent No. 6,197,934; U.S. Patent No. 6,056,950; U.S. Patent No. 5,800,807; U.S. Patent No. 5,776,445; U.S. Patent No. 5,698,219; U.S. Patent No. 5,521,222; U.S. Patent No. 5,403,841; U.S. Patent No. 5,077,033; U.S. Patent No. 4,882,150; and U.S. Patent No. 4,738,851, each of which is incorporated herein by reference in its entirety.

For prolonged delivery, the active compound(s) or prodrug(s) can be formulated as a depot preparation for administration by implantation or intramuscular injection. The active ingredient can be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, e.g., as a sparingly soluble salt. Alternatively, transdermal delivery systems manufactured as an adhesive disc or patch which slowly releases the active compound(s) for percutaneous absorption can be used. To this end, permeation enhancers can be used to facilitate transdermal penetration of the active compound(s). Suitable transdermal patches are described in for example, U.S. Patent No. 5,407,713; U.S. Patent No. 5,352,456; U.S. Patent No. 5,332,213; U.S. Patent No. 5,336,168; U.S. Patent No. 5,290,561; U.S. Patent No. 5,254,346; U.S. Patent No. 5,164,189; U.S. Patent No. 5,163,899; U.S. Patent No. 5,088,977; U.S. Patent No. 5,087,240; U.S. Patent No. 5,008,110; and U.S. Patent No. 4,921,475, each of which is incorporated herein by reference in its entirety.

Alternatively, other pharmaceutical delivery systems can be employed. Liposomes and emulsions are well-known examples of delivery vehicles that can be used to deliver active compound(s) or prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) also can be employed.

The pharmaceutical compositions can, if desired, be presented in a pack or dispenser device which can contain one or more unit dosage forms containing the active compound(s). The pack can, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

The active compound(s) or prodrug(s) of the presently disclosed subject matter, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being

treated. The compound(s) can be administered therapeutically to achieve therapeutic benefit or prophylactically to achieve prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient can still be afflicted with the underlying disorder. For example, administration of a compound to a patient suffering from an allergy provides therapeutic benefit not only when the underlying allergic response is eradicated or ameliorated, but also when the patient reports a decrease in the severity or duration of the symptoms associated with the allergy following exposure to the allergen. As another example, therapeutic benefit in the context of asthma includes an improvement in respiration following the onset of an asthmatic attack, or a reduction in the frequency or severity of asthmatic episodes. Therapeutic benefit also includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

For prophylactic administration, the compound can be administered to a patient at risk of developing one of the previously described diseases. A patient at risk of developing a disease can be a patient having characteristics placing the patient in a designated group of at risk patients, as defined by an appropriate medical professional or group. A patient at risk may also be a patient that is commonly or routinely in a setting where development of the underlying disease that may be treated by administration of a metalloenzyme inhibitor according to the invention could occur. In other words, the at risk patient is one who is commonly or routinely exposed to the disease or illness causing conditions or may be acutely exposed for a limited time. Alternatively, prophylactic administration can be applied to avoid the onset of symptoms in a patient diagnosed with the underlying disorder.

The amount of compound administered will depend upon a variety of factors, including, for example, the particular indication being treated, the mode of administration, whether the desired benefit is prophylactic or therapeutic, the severity of the indication being treated and the age and weight of the patient, the bioavailability of the particular active compound, and the like. Determination of an effective dosage is well within the capabilities of those skilled in the art.

Effective dosages can be estimated initially from *in vitro* assays. For example, an initial dosage for use in animals can be formulated to achieve a circulating blood or serum concentration of active compound that is at or above an IC50 of the particular compound as measured in as *in vitro* assay, such as the *in vitro* fungal MIC or MFC and other *in vitro* assays described in the Examples section. Calculating dosages to achieve such circulating blood or

serum concentrations taking into account the bioavailability of the particular compound is well within the capabilities of skilled artisans. For guidance, see Fingl & Woodbury, "General Principles," In: *Goodman and Gilman's The Pharmaceutical Basis of Therapeutics*, Chapter 1, pp. 1-46, latest edition, Pagamonon Press, and the references cited therein, which are incorporated herein by reference.

Initial dosages also can be estimated from *in vivo* data, such as animal models. Animal models useful for testing the efficacy of compounds to treat or prevent the various diseases described above are well-known in the art.

Dosage amounts will typically be in the range of from about 0.0001 or 0.001 or 0.01 mg/kg/day to about 100 mg/kg/day, but can be higher or lower, depending upon, among other factors, the activity of the compound, its bioavailability, the mode of administration, and various factors discussed above. Dosage amount and interval can be adjusted individually to provide plasma levels of the compound(s) which are sufficient to maintain therapeutic or prophylactic effect. In cases of local administration or selective uptake, such as local topical administration, the effective local concentration of active compound(s) cannot be related to plasma concentration. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

The compound(s) can be administered once per day, a few or several times per day, or even multiple times per day, depending upon, among other things, the indication being treated and the judgment of the prescribing physician.

Preferably, the compound(s) will provide therapeutic or prophylactic benefit without causing substantial toxicity. Toxicity of the compound(s) can be determined using standard pharmaceutical procedures. The dose ratio between toxic and therapeutic (or prophylactic) effect is the therapeutic index. Compounds(s) that exhibit high therapeutic indices are preferred.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Agricultural applications

The compounds and compositions herein can be used in methods of modulating metalloenzyme activity in a microorganism on a plant comprising contacting a compound herein with the plant (e.g., seed, seedling, grass, weed, grain). The compounds and compositions herein can be used to treat a plant, field or other agricultural area (e.g., as herbicides, pesticides, growth regulators, etc.) by administering the compound or composition (e.g., contacting, applying, spraying, atomizing, dusting, etc.) to the subject plant, field or other agricultural area. The administration can be either pre- or post-emergence. The administration can be either as a treatment or preventative regimen.

One aspect is a method of treating or preventing a fungal disease or disorder in or on a plant comprising contacting a compound of any of the formulae herein with the plant. Another aspect is a method of treating or preventing fungi growth in or on a plant comprising contacting a compound of any of the formulae herein with the plant. Another aspect is a method of inhibiting microorganisms in or on a plant comprising contacting a compound of any of the formulae herein with the plant.

The compositions comprising compounds herein can be employed, for example, in the form of directly sprayable aqueous solutions, powders, suspensions, also highly-concentrated aqueous, oily or other suspensions or dispersions, emulsions, oil dispersions, pastes, dusts, materials for spreading or granules, by means of spraying, atomizing, dusting, spreading or pouring.

Aqueous use forms can be prepared from emulsion concentrates, suspensions, pastes, wettable powders or water-dispersible granules by adding water. To prepare emulsions, pastes or oil dispersions, the substances, as such or dissolved in an oil or solvent, can be homogenized in water by means of wetting agent, tackifier, dispersant or emulsifier. However, it is also possible to prepare concentrates composed of active substance, wetting agent, tackifier, dispersant or emulsifier and, if appropriate, solvent or oil, and these concentrates are suitable for dilution with water.

Granules, e.g. coated granules, impregnated granules and homogeneous granules, can be prepared by binding the active ingredients (e.g., compounds herein) to solid carriers. Solid carriers are mineral earths such as silicas, silica gels, silicates, talc, kaolin, limestone, lime, chalk, bole, loess, clay, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic material, fertilizers such as ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas and products of vegetable origin such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders or other solid carriers.

The compounds herein can be formulated as ordinary tablets, capsules, solids, liquids, emulsions, slurries, oils, fine granules or powders, which are suitable for administration to plants, fields or other agricultural areas. In preferred embodiments, the preparation includes between 1 and 95% (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 25%, 75%, 80%, 90%, 95%) compound herein in a carrier or diluent. The compositions delineated herein include the compounds of the formulae delineated herein, as well as additional agricultural agents if present, in amounts effective for controlling (e.g., modulating, inhibiting) a metalloenzyme-mediated agricultural disease or disorder.

In one approach, a compound herein is provided in an encapsulated formulation (liquid or powder). Specific materials suitable for use in capsule materials include, but are not limited to, porous particulates or substrates such as silica, perlite, talc, clay, pyrophyllite, diatomaceous earth, gelatin and gels, polymers (e.g., polyurea, polyurethane, polyamide, polyester, etc.), polymeric particles, or cellulose. These include, for example, hollow fibers, hollow tubes or tubing which release a compound specified herein through the walls, capillary tubing which releases the compound out of an opening in the tubing, polymeric blocks of different shapes, e.g., strips, blocks, tablets, discs, which release the compound out of the polymer matrix, membrane systems which hold the compound within an impermeable container and release it through a measured permeable membrane, and combinations of the foregoing. Examples of such dispensing compositions are polymer laminates, polyvinyl chloride pellets, and microcapillaries.

Encapsulation processes are typically classified as chemical or mechanical. Examples of chemical processes for encapsulation include, but are not limited to, complex coacervation, polymer-polymer incompatibility, interfacial polymerization in liquid media, *in situ* polymerization, in-liquid drying, thermal and ionic gelation in liquid media, desolvation in liquid media, starch-based chemistry processes, trapping in cyclodextrins, and formation of liposomes. Examples of mechanical processes for encapsulation include, but are not limited to, spray drying, spray chilling, fluidized bed, electrostatic deposition, centrifugal extrusion, spinning disk or rotational suspension separation, annular-jet encapsulation, polymerization at liquid-gas or solid-gas interface, solvent evaporation, pressure extrusion or spraying into solvent extraction bath.

Microcapsules are also suitable for the long-term release of active compound herein. Microcapsules are small particles that contain a core material or active ingredient surrounded by a coating or shell. The size of the microcapsule typically varies from 1 to 1000 microns with capsules smaller than 1 micron classified as nanocapsules and capsules larger than 1000

microns as macrocapsules. Core payload usually varies from 0.1 to 98 weight percent. Microcapsules can have a variety of structures (continuous core/shell, multinuclear, or monolithic) and have irregular or geometric shapes.

In another approach, the compound herein is provided in an oil-based delivery system. Oil release substrates include vegetable and/or mineral oils. In one embodiment, the substrate also contains a surface active agent that renders the composition readily dispersable in water; such agents include wetting agents, emulsifying agents, dispersing agents, and the like.

Compounds of the invention can also be provided as emulsions. Emulsion formulations can be found as water in oil (w/o) or oil in water (o/w). Droplet size can vary from the nanometer scale (colloidal dispersion) to several hundred microns. A variety of surfactants and thickeners are usually incorporated in the formulation to modify the size of the droplets, stabilize the emulsion, and modify the release.

Alternatively, compounds of the invention may also be formulated in a solid tablet and comprise (and preferably consist essentially of) an oil, a protein/carbohydrate material (preferably vegetable based), a sweetener and an active ingredient useful in the prevention or treatment of a metalloenzyme-mediated agricultural disease or disorder. In one embodiment the invention provides a solid tablet and comprises (and preferably consist essentially of) an oil, a protein/carbohydrate material (preferably vegetable based), a sweetener and an active ingredient (e.g., compound herein or combinations or derivatives thereof) useful in the prevention or treatment a metalloenzyme-mediated agricultural disease or disorder. Tablets typically contain about 4-40% (e.g., 5%, 10%, 20%, 30%, 40%) by weight of an oil (e.g., plant oil, such as corn, sunflower, peanut, olive, grape seed, tung, turnip, soybean, cotton seed, walnut, palm, castor, earth almond, hazelnut, avocado, sesame, croton tiglium, cacao, linseed, rape-seed, and canola oils and their hydrogenated derivatives; petroleum derived oils (e.g., paraffins and petroleum jelly), and other water immiscible hydrocarbons (e.g., paraffins). The tablets further contain from about 5-40% (e.g., 5%, 10%, 20%, 30%, 40%) by weight of a vegetable-based protein/carbohydrate material. The material contains both a carbohydrate portion (e.g., derived from cereal grains, such as wheat, rye, barley, oat, corn, rice, millet, sorghum, birdseed, buckwheat, alfalfa, mielga, corn meal, soybean meal, grain flour, wheat middlings, wheat bran, corn gluten meal, algae meal, dried yeast, beans, rice) and a protein portion.

Optionally, various excipients and binders can be used in order to assist with delivery of the active ingredient or to provide the appropriate structure to the tablet. Preferred excipients and binders include anhydrous lactose, microcrystalline cellulose, corn starch,

magnesium estearate, calcium estearate, zinc estearate, sodic carboxymethylcellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and mixtures thereof.

The invention provides kits for the treatment or prevention of agricultural or plant disease or disorders. In one embodiment, the kit includes a composition containing an effective amount of a compound herein in a form suitable for delivery to a site plant. In some embodiments, the kit comprises a container which contains a compound of any of the formulae herein (e.g., formulae I-V); such containers can be boxes, ampules, bottles, vials, tubes, bags, pouches, blister-packs, or other suitable container forms known in the art. Such containers can be made of plastic, glass, laminated paper, metal foil, or other materials suitable for holding compounds.

If desired the compound(s) of the invention is provided together with instructions for administering it to a plant, field, or other agricultural area. The instructions will generally include information about the use of the composition for the treatment or prevention of a metalloenzyme-mediated agricultural disease or disorder. In other embodiments, the instructions include at least one of the following: description of the compound; dosage schedule and administration for treatment or prevention of a metalloenzyme-mediated agricultural disease or disorder; precautions; warnings; description of research studies; and/or references. The instructions may be printed directly on the container (when present), or as a label applied to the container, or as a separate sheet, pamphlet, card, or folder supplied in or with the container.

Examples

The present invention will now be demonstrated using specific examples that are not to be construed as limiting.

General Experimental Procedures

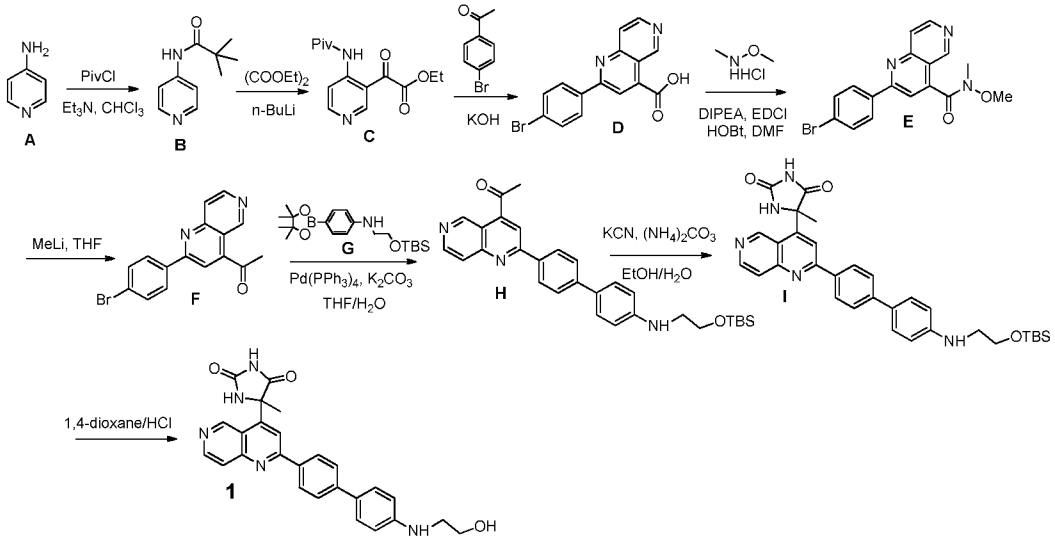
Definitions of variables in the structures in schemes herein are commensurate with those of corresponding positions in the formulae delineated herein.

In embodiments, the invention provides for the intermediate compounds of the formulae delineated herein and methods of converting such compounds to compounds of the formulae herein (e.g., in Scheme 1, E to 1; F to H; H to 1) comprising reacting a compound herein with one or more reagents in one or more chemical transformations (including those provided herein) to thereby provide the compound of any of the formulae herein or an intermediate compound thereof.

The synthetic methods described herein may also additionally include steps, either before or after any of the steps described in any scheme, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compound of the formulae described herein. The methods delineated herein contemplate converting compounds of one formula to compounds of another formula (e.g., in Scheme 1, in Scheme 1, E to 1; F to H; H to 1). The process of converting refers to one or more chemical transformations, which can be performed *in situ*, or with isolation of intermediate compounds. The transformations can include reacting the starting compounds or intermediates with additional reagents using techniques and protocols known in the art, including those in the references cited herein. Intermediates can be used with or without purification (e.g., filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

Synthesis of Inhibitors

Scheme 1



EXAMPLE 1

5-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-5-methylimidazolidine-2,4-dione hydrochloride (1)

To a stirred solution of 4-amino pyridine (**A**; 5 g, 53.12 mmol) in $CHCl_3$ (200 mL) were added triethylamine (TEA or Et_3N) (11.5 mL, 106.2 mmol) followed by pivaloyl chloride (7.15 mL, 69 mmol) dropwise at 0°C over a period of 10 minutes (min). The reaction mixture was warmed to RT and stirred for 1.5 hours (h). The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was washed with saturated sodium bicarbonate ($NaHCO_3$) solution, dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 10% methanol (MeOH)/dichloromethane (CH_2Cl_2) to afford **B** (7 g, 73.9%) as an off-white solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.54 (bs, NH), 8.40 (d, J = 5.8 Hz, 2H), 7.67 (d, J = 6.4 Hz, 2H), 1.23 (s, 9H). MS (ESI): m/z 179 [M^++1].

To a stirred solution of **B** (3 g, 16.83 mmol) in dry THF (30 mL) was added *n*-BuLi (21.5 mL, 50.5 mmol, 2.3M in hexane) dropwise at -78°C under an inert atmosphere. After being stirred for 30 min at 0°C, a solution of diethyl oxalate (5.6 mL, 42 mmol) in dry tetrahydrofuran (THF) (5.6 mL) was added to reaction mixture at -78°C. The resulting reaction mixture was warmed to room temperature (RT) and the stirring was continued for another 2 h. The reaction mixture was diluted with cold water (100 mL) and extracted with diethyl ether (2x20 mL). The combined organic phases were dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography eluting with 30% ethyl aceate (EtOAc)/hexane to afford **C** (1.2g, 25.6%) as a thick syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.47 (bs, NH), 8.92 (s, 1H), 8.74 (d, J = 5.5 Hz, 1H), 8.66 (d, J = 5.5 Hz, 1H), 4.51 (q, J = 7.5 Hz, 2H), 1.45 (t, J = 7.5 Hz, 3H), 1.36 (s, 9H).

To a stirred solution of **C** (14 g, 50.35 mmol) in EtOH:H_2O (200 mL, 1:15) was added potassium hydroxide (KOH; 11.3g, 0.2 mol). The reaction mixture was heated at reflux for 2 h. 4-Bromo propiophenone (20 g, 0.1 mol) was added to the reaction mixture and stirred for another 16 h. After consumption of the starting material by TLC, ethanol was distilled off. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (2x100 mL) to remove excess 4-bromo-propiophenone. The aqueous layer was acidified to pH~2 using acetic acid. The precipitated solid was filtered and dried *in vacuo* to afford acid **D** (13 g, 78.7%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 14.3 (bs, 1H), 10.01 (s, 1H), 8.83 (d, J = 5.5 Hz, 1H), 8.58 (s, 1H), 8.31 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 5.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 2H), 2.33 (s, 3H).

To a stirred solution of acid **D** (2 g, 6.11 mmol) in DMF (20 mL) were added diisopropylethylamine (DIPEA; 2.3 g, 18.3 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1.75 g, 9.16 mmol) at 0 °C. The reaction was stirred for 15 min. Hydroxybenzotriazole (HOBt; 1.4 g, 9.16 mmol) was added to the reaction mixture at 0 °C. After being stirred for 15 min, N,O-dimethylhydroxylamine hydrochloride (1.19 g, 12.2 mmol) was added to the reaction mixture at 0 °C and stirring was continued for another 16 h at RT. After consumption of the starting material by TLC, the reaction was quenched with cold water (20 mL) and extracted with ethyl acetate (2x20 mL). The combined

organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2. The obtained material was triturated with isopropanol (IPA):pentane (10 mL, 2:8) and dried *in vacuo* to afford **E** (1.6 g, 70.4%) as an off-white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.80 (d, *J* = 6.0 Hz, 1H), 8.11 (d, *J* = 6.8 Hz, 2H), 8.00 (d, J = 6.0 Hz, 1H), 7.97 (s, 1H), 7.69 (d, *J* = 6.8 Hz, 2H), 3.53-3.44 (m, 6H). MS (ESI): 374 [M^++2].

To a stirred solution of **E** (1.75 g, 4.7 mmol) in dry THF (50 mL) was added methyllithium (7.11 mL, 11.75 mmol, 1.6M in THF) at -78 °C and stirred for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with an aqueous ammonium chloride (NH_4Cl) solution (20 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography eluting with 40% EtOAc/hexane to afford ketone **F** (1.04 g, 67.9%) as a pale orange liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.12-8.09 (m, 3H), 8.00 (d, *J* = 6.0 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 2.85 (s, 3H). MS (ESI): 327 [M^+], 329 [M^++2].

To a stirred solution of ketone **F** (0.2 g, 0.61 mmol) and N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**G**; 0.34 g, 0.91 mmol; synthesis described below) in THF:H_2O (25 mL, 4:1) was added potassium carbonate (K_2CO_3; 0.25 g, 1.83 mmol) at RT under inert atmosphere. After purging with nitrogen over a period of 30 min, tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$; 0.07 g, 0.06 mmol) was added to reaction mixture and then stirred for 12 h at 80 °C. The reaction mixture was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography eluting with 40% EtOAc/hexane to afford **H** (0.2 g, 66%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.63 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.66 (s, 1H), 8.44 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 6.0 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 6.72 (d, *J* = 6.0 Hz, 2H), 5.88 (t, *J* = 6.0 Hz, 1H, NH), 3.74 (t, *J* = 5.5 Hz, 2H), 3.23 (q, *J* = 5.5 Hz, 2H), 2.91 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). MS (ESI): 498 [M^++1].

To a stirred solution of **H** (0.2 g, 0.4 mmol) in EtOH:H_2O (14 mL, 1:1) was added potassium cyanide (KCN; 52.4 mg, 0.8 mmol) followed by ammonium carbonate (0.25 g, 1.6 mmol) at RT. The reaction mixture was heated in a sealed tube at 80 °C for 48 h. The volatiles were

evaporated under reduced pressure and the residue was washed with 20% MeOH/CH_2Cl_2 (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 to afford compound **I** (16 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H, NH), 9.65 (s, 1H, NH), 8.97 (s, 1H), 8.76 (d, *J* = 6.0 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 2H), 8.28 (s, 1H), 8.01 (d, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.87 (bt, NH), 3.74 (t, *J* = 5.5 Hz, 2H), 3.23 (q, *J* = 6.0 Hz, 2H), 2.07 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). MS (ESI): 568 [M^++1].

A mixture of compound **I** (16 mg, 0.028 mmol) in 1,4-dioxane/HCl (5 mL) at 0 °C was warmed to RT and stirred for 1 h. After consumption of the starting material by TLC, the volatiles were evaporated under reduced pressure. The residue was co-distilled with diisopropyl ether (2x2 mL), filtered, washed with *n*-pentane (2x2 mL) and dried *in vacuo* to afford **1** (9.9 mg as an HCl salt, 70.8%) as a brown syrup. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.34 (s, 1H, NH), 9.88 (s, 1H, NH), 9.06 (s, 1H), 8.82 (d, *J* = 6.5 Hz, 1H), 8.40-8.38 (m, 3H), 8.21 (d, *J* = 5.5 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 3.51-3.46 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.07 (s, 3H). MS (ESI): 454.6 [M^++1]. HPLC: 83.6%.

Synthesis of intermediate **G [N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline]**

To a stirred solution of 4-iodoaniline (10 g, 45.6 mmol) in CH_2Cl_2 (500 mL) was added pyridine (7.3 mL, 91.2 mmol) at RT. After the reaction mixture was cooled to 0 °C, 2-chloroethyl chloroformate (5.2 mL, 50.1 mmol) was added dropwise to the reaction mixture and stirred for 2 h at RT. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and was washed with water (50 mL), a saturated aqueous $CuSO_4$ solution (2x30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 8% EtOAc/hexane to afford 2-chloroethyl(4-iodophenyl) carbamate (12.8 g, 86.4%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63-7.57 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.66 (bs, *NH*), 4.42 (t, *J* = 5.4 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H). MS (ESI): m/z 236 [M^++1].

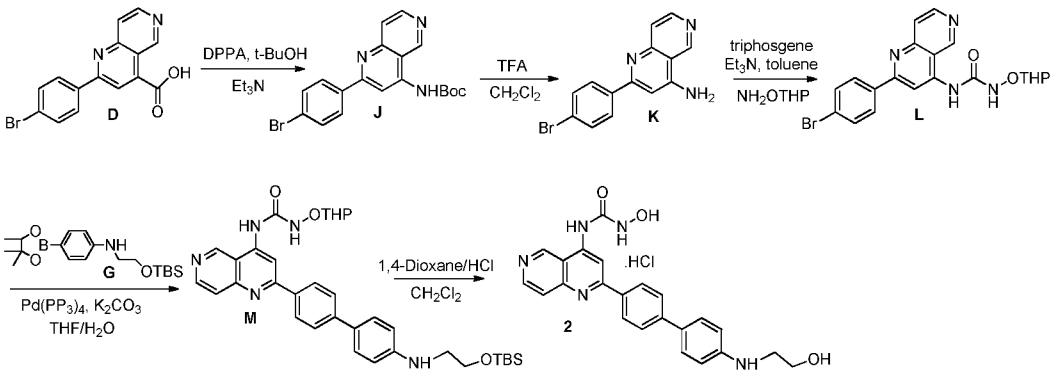
To a stirred solution of 2-chloroethyl(4-iodophenyl)carbamate (0.1 g, 0.307 mmol) in ethanol (4 mL) was added KOH pellets (85.7 mg, 1.53 mmol) at RT. The reaction mixture was gradually heated to reflux for 12 h. After consumption of the starting material (by TLC), the

volatiles were removed under reduced pressure. The obtained residue was diluted with water and extracted with EtOAc (2x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 40% EtOAc/hexane to afford 2-((4-iodophenyl) amino) ethanol (40 mg, 49%) as an off-white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 8.6 Hz, 2H), 5.77 (bt, NH), 4.68 (t, *J* = 5.4 Hz, 1H, OH), 3.53 (q, *J* = 5.6 Hz, 2H), 3.06 (q, *J* = 5.6 Hz, 2H). MS (ESI): m/z 263.9 [M^++1].

To a stirred solution of 2-((4-iodophenyl)amino)ethanol (24 g, 91.2 mmol) in DMSO (400 mL) was added bis(pinacolato)diboron (25.6 g, 0.1 mol) followed by potassium acetate (KOAc; 26.8 g, 0.27 mol) at RT under argon atmosphere. After purging with argon over a period of 1 h, [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)_2Cl_2$; 6.8 g, 9.12 mmol) was added to reaction mixture under argon atmosphere. The resulting mixture was stirred at 100 °C for 14 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The obtained residue was diluted with water (100 mL) and extracted with EtOAc (2x250 mL). The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 40% EtOAc/hexane to afford 2-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethanol (12 g, 50%) as a sticky solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68-7.60 (m, 2H), 6.68-6.59 (m, 2H), 3.82 (t, *J* = 5.0 Hz, 2H), 3.32 (q, *J* = 5.4 Hz, 2H), 2.28-2.22 (m, 1H), 1.31-1.29 (m, 12H). MS (ESI): m/z 264 [M^++1].

To a stirred solution of 2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethanol (2 g, 7.6 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.03 g, 15.2 mmol) followed by *tert*-butylchlorodimethylsilane (1.72 g, 11.4 mmol) at 0 °C and stirred for 2 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted in CH_2Cl_2 (2x20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 8% EtOAc/hexane to afford TBS-boronate **G** (0.9 g, 32%) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 2H), 6.59 (d, *J* = 8.41Hz, 2H), 4.23 (bs, 1H), 3.80 (t, *J* = 5.5 Hz, 2H), 3.24-3.23 (m, 2H), 1.31 (s, 12H), 0.90 (s, 9H), 0.06 (s, 6H). MS (ESI): m/z 378 [M^++1].

Scheme 2



EXAMPLE 2

1-Hydroxy-3-(2-(4'-(2-hydroxyethylamino)biphenyl-4-yl)-1,6-naphthyridin-4-yl)urea (2)

To a stirred solution of 2-(4-bromophenyl)-1, 6-naphthyridine-4-carboxylic acid (**D**; 3 g, 9.1 mmol) in *t*-BuOH (50 mL) was added Et_3N (2.5 mL, 18.2 mmol) followed by diphenylphosphoryl azide (DPPA; 4.2 mL, 18.2 mmol) at RT. The reaction mixture was heated to reflux for 18 h. The progress of the reaction was monitored by TLC. The volatiles were removed under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 to afford **J** (2.1 g, 58%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.32 (s, 1H), 9.73 (s, 1H), 8.69 (d, J = 5.5 Hz, 1H), 8.63 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 5.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 1.58 (s, 9H). MS (ESI): 400 [M^+], 402 [M^++2].

To a stirred solution of **J** (2 g, 5.01 mmol) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (TFA; 15 mL, 5.01 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 12 h. After consumption of the starting material by TLC, the volatiles were evaporated under reduced pressure. To the obtained residue diluted with CH_2Cl_2 (50 mL), was added Et_3N (5 mL) at RT and stirred for another 15 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to afford **K** (0.9 g, 60%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 6.0 Hz, 1H), 7.46 (s, 2H), 7.17 (s, 1H). MS (ESI): 301.7 [M^++2].

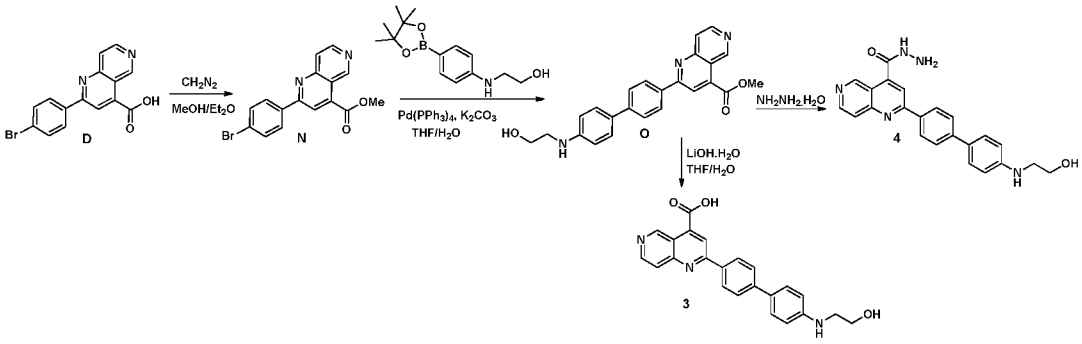
To a stirred solution of **K** (0.4 g, 1.33 mmol) in toluene (25 mL) was added Et_3N (0.6 mL, 4.01 mmol) followed by triphosgene (0.59 g, 2.00 mmol) at 0 °C. The reaction mixture was heated at 100 °C for 4 h. After consumption of the starting material by TLC, the reaction mixture was cooled to 0 °C and NH_2-OTHP (0.47 g, 4.01 mmol) was added to the reaction mixture and stirring was continued for another 14 h at RT. The precipitated solid was filtered

off and the filtrate was concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **L** (20 mg, 3.38%) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.14 (s, 1H, NH), 9.62 (s, 1H), 9.50 (s, 1H), 8.75 (s, 1H), 8.73 (d, J = 6.0 Hz, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 6.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 4.96 (s, 1H), 4.01-3.97 (m, 1H), 3.62-3.60 (m, 1H), 1.79-1.74 (m, 3H), 1.57-1.56 (m, 3H). MS (ESI): 443 [M^+], 445 [M^++2].

To a stirred solution of **L** (0.12 g, 0.27 mmol) in THF:H_2O (11 mL, 10:1) was added N-(2-(tert-butyldimethylsilyloxy) ethyl)-4-(4, 4, 5-trimethyl-1, 3, 2-dioxaborolan-2-yl) aniline (**G**; 51 mg, 0.40 mmol) followed by potassium carbonate (K_2CO_3; 37 mg, 0.81 mmol) at RT under argon atmosphere. After purging with argon over a period of 1 h, $Pd(PPh_3)_4$ (10 mg, 0.027 mmol) was added to the reaction mixture and then continued purging with argon for another 15 min. The resulting reaction mixture was heated at 70 °C for 2 h. After consumption of the starting material by TLC, the reaction mixture was filtered through a pad of Celite. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **M** (10 mg, 18%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.12 (s, 1H), 9.57 (s, 1H), 9.47 (s, 1H), 8.78 (s, 1H), 8.71 (d, J = 6.0 Hz, 1H), 8.20 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 5.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 6.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.84 (t, J = 6.0 Hz, 1H, NH), 4.97 (s, 1H), 4.00-3.99 (m, 1H), 3.74 (t, J = 6.0 Hz, 2H), 3.63-3.61 (m, 1H), 3.24-3.20 (m, 2H), 1.80-1.78 (m, 3H), 1.57 (bs, 3H), 0.88 (s, 9H), 0.05 (s, 6H). MS (ESI): 614 [M^++1].

To a mixture of **M** (40 mg, 0.096 mmol) in CH_2Cl_2 (10 mL) was added 1,4-dioxane/HCl (0.1 mL) at 0 °C. The reaction was warmed to RT and stirred for 4 h. After consumption of the starting material by TLC, the volatiles were evaporated under reduced pressure. The obtained crude was washed with CH_2Cl_2, ether and n-pentane to afford **2** (16.4 mg, 60.74%) as a green solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.56 (bs, NH), 10.10 (bs, 2H), 8.96 (s, 1H), 8.83 (d, J = 6.5 Hz, 1H), 8.27-8.24 (m, 3H), 7.89 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 6.8 Hz, 2H), 6.91 (bs, 2H), 3.61 (t, J = 5.5 Hz, 2H), 3.22 (d, J = 5.5 Hz, 2H). MS (ESI): 416 [M^++1]. HPLC: 93.73%.

Scheme 3



EXAMPLE 3

2-(4'-((2-Hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carboxylic acid (3)

To a stirred solution of acid **D** (50 mg, 0.15 mmol) in MeOH/Et_2O (1:4, 20 mL) was added freshly prepared diazomethane [N-nitroso-N-methylurea (78 mg, 0.75 mmol) in 40% aqueous KOH (10 mL)/Et_2O (20 mL)] at 0 °C and stirred for 1 h. After consumption of the starting material by TLC, the solvent was evaporated under reduced pressure. The obtained crude product was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 to afford ester **N** (40 mg, 76.9%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.84 (d, *J* = 6.0 Hz, 1H), 8.47 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 6.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 4.12 (s, 3H). MS (ESI): m/z 342.9 [M^++1].

To a stirred solution of ester **N** (0.4 g, 1.16 mmol) and 2-((4-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethanol (0.37 g, 1.40 mmol) in THF:H_2O (25 mL, 4:1) was added K_2CO_3 (0.484 g, 3.48 mmol) at RT under inert atmosphere. After purging with nitrogen over a period of 30 min, $Pd(PPh_3)_4$ (67 mg, 0.06 mmol) was added to reaction mixture and then stirred for 5 h at 80 °C. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The obtained residue was diluted with water (25 mL) and extracted with EtOAc (2x25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 to afford **O** (0.25 g, 53.6%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.91 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.62 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 5.5 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.88 (t, *J* = 5.5 Hz, 1H), 4.71 (t, *J* = 5.5 Hz, 1H), 4.07 (s, 3H), 3.58 (q, *J* = 6.0 Hz, 2H), 3.17 (q, *J* = 6.0 Hz, 2H). MS (ESI): m/z 400 [M^++1]. HPLC: 97.49%.

To a stirred solution of **O** (0.1 g, 0.25 mmol) in THF/H_2O (4:1, 10 mL) was added LiOH·H_2O (31 mg, 0.75 mmol) at RT and the reaction mixture was stirred for 2 h. After the consumption

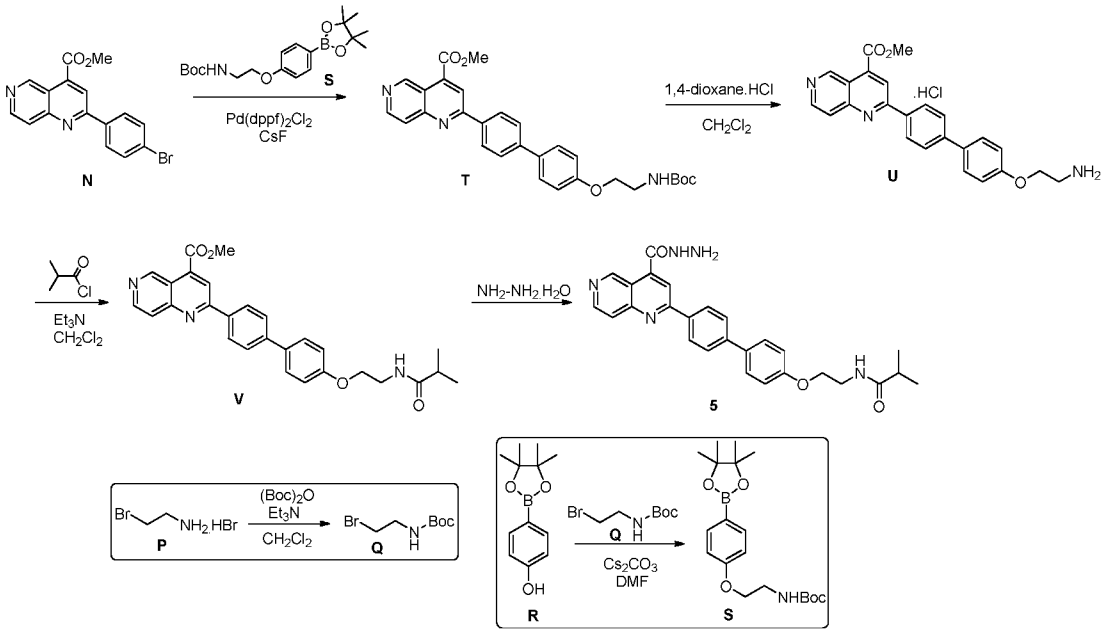
of the starting material by TLC, the volatiles were evaporated under reduced pressure. The residue was diluted with water and acidified to pH ~ 2 using 1N HCl. The precipitated solid was filtered, washed with H_2O and dried to afford **3** (75 mg, 78.1%) as a brown solid. ^1H NMR (500 MHz, DMSO-d_6): δ 10.03 (s, 1H), 8.64 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 8.5 Hz, 2H), 8.23 (s, 1H), 7.86 (d, J = 6.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 5.83 (bs, 1H), 4.72 (bs, 1H), 3.58 (t, J = 6.0 Hz, 2H), 3.16 (t, J = 6.0 Hz, 2H). MS (ESI): 386.2 [M^++1]. HPLC: 97.41%.

EXAMPLE 4

2-(4'-((2-Hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (4)

A mixture of **O** (0.1 g, 0.25 mmol) and hydrazine hydrate (NH_2-NH_2·H_2O; 2 mL) was heated at 90 °C for 5 h. After consumption of the starting material by TLC, the reaction mixture was concentrated *in vacuo* to remove the excess hydrazine hydrate. The crude material was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 to afford **4** (50 mg, 50%) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 11.32 (s, 1H), 9.65 (s, 1H), 8.97 (d, J = 6.1 Hz, 1H), 8.76 (d, J = 8.0 Hz, 2H), 8.28 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.87 (bt, NH), 4.82 (bs, 2 H), 4.72-4.6 (m, 1H), 3.74-3.73 (m, 2H), 3.23-3.22 (m, 2H). MS (ESI): 400.2 [M^+]. HPLC: 91.12%.

Scheme 4



EXAMPLE 5

N-(2-((4'-(4-(Hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl) isobutyramide (5)

To a stirred solution of 2-bromoethanamine hydrobromide (**P**; 10.0 g, 48.78 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (17.1 mL, 121.95 mmol) followed by Boc-anhydride (12.7g, 58.53 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 3 h at RT. After complete consumption of the starting material (by TLC), the reaction mixture was extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford **Q** (7.0 g, 31.23 mmol, 64%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (bs, NH), 3.54-3.53 (m, 2H), 3.46-3.45 (m, 2H), 1.45 (s, 9H).

To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**R**) (1.0 g, 4.54 mmol) in DMF (15 mL) was added Cs_2CO_3 (3.25 g, 9.99 mmol) at RT under inert atmosphere. After being stirred for 20 min, **Q** (1.52 g, 6.78 mmol) was added at RT and the resulting reaction mixture was heated to 65 °C and stirred for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then allowed to RT, diluted with water (20 mL) and extracted with EtOAc (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford **S** (0.8 g, 2.20 mmol, 48%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74

(d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.98 (bs , 1H), 4.04 (t, J = 5.0 Hz, 2H), 3.54-3.53 (m, 2H), 1.46 (s, 12H), 1.33 (s, 9H).

A solution of methyl 2-(4-bromophenyl)-1,6-naphthyridine-4-carboxylate (**N**; 2.8 g, 8.18 mmol) in THF/toluene (300 mL, 1:1 *v/v*) was degassed by purging with argon for 15 min. To the resulting reaction mixture were added boronate **S** (2.97 g, 8.18 mmol), CsF (3.7 g, 24.56 mmol) and $Pd(dppf)_2Cl_2$ (598 mg, 0.81 mmol) and degassed for another 5 min. The resulting reaction mixture was then stirred for 14 h at reflux. Progress of the reaction was monitored by TLC. The reaction mixture was filtered through a pad of Celite and the bed was washed with CH_3OH. The collected filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 30% EtOAc/hexane as eluent to afford **T** (2.8 g, 5.61 mmol, 70%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 8.83 (d, J = 5.6 Hz, 1H), 8.64 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 5.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.04 (t, J = 6.0 Hz, NH), 4.08 (s, 3H), 4.03 (t, J = 6.0 Hz, 2H), 3.34 (t, J = 6.0 Hz, 2H), 1.40 (s, 9H). LC-MS: *m/z* 500 $[M+1]^+$ at 4.35 min (94.4% purity).

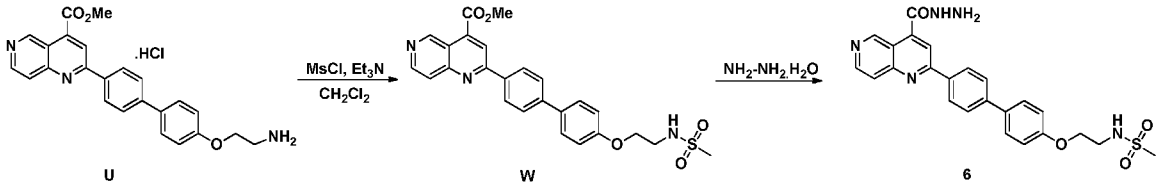
To a stirred solution of **T** (0.16 g, 0.32 mmol) in CH_2Cl_2 (5 mL) was added 4N hydrochloric acid (HCl) in 1,4-dioxane (3 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was allowed to warm to RT and stirred for 2 h. Progress of the reaction was monitored by TLC. The volatiles were then evaporated under reduced pressure to afford amine **U** (0.12 g, crude) as a pink solid. The crude product was used in the next step without any further purification.

To a stirred solution of amine **U** (0.12 g, 0.30 mmol; crude) in CH_2Cl_2 (15 mL) were added Et_3N (1.6 mL, 1.20 mmol) and isobutyryl chloride (38 mg, 0.36 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was allowed to warm to RT and stirred for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was then diluted with ice-cold water and extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was triturated with MeOH/diisopropyl ether to afford **V** (0.1 g, 0.21 mmol, 70.9%) as a yellow solid. The product was confirmed by LC-MS analysis and taken forward to the next step. LC-MS: *m/z* 470.6 $[M+1]^+$ at 3.73 min (96.1% purity).

A mixture of ester **V** (0.1 g, 0.21 mmol) and hydrazine hydrate (3 mL) was heated to 100 °C and stirred for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to RT, diluted with ice-cold water and stirred for 5 min. The precipitated solid

was filtered and dried under reduced pressure to obtain the crude. The crude material was purified by trituration with MeOH/diisopropyl ether to afford **5** (80 mg, 0.17 mmol, 80%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (bs, 1H), 9.63 (s, 1H), 8.79 (d, J = 5.5 Hz, 1H), 8.43 (d, J = 7.5 Hz, 2H), 8.33 (s, 1H), 8.01 (d, J = 6.5 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 4.78 (bs, 2H), 4.06 (t, J = 5.5 Hz, 2H), 3.44 (t, J = 5.5 Hz, 2H), 2.41-2.38 (m, 1H), 1.01 (d, J = 7.0 Hz, 6H). MS (ESI): m/z 470 $[M+1]^+$. HPLC: 97.2%.

Scheme 5



EXAMPLE 6

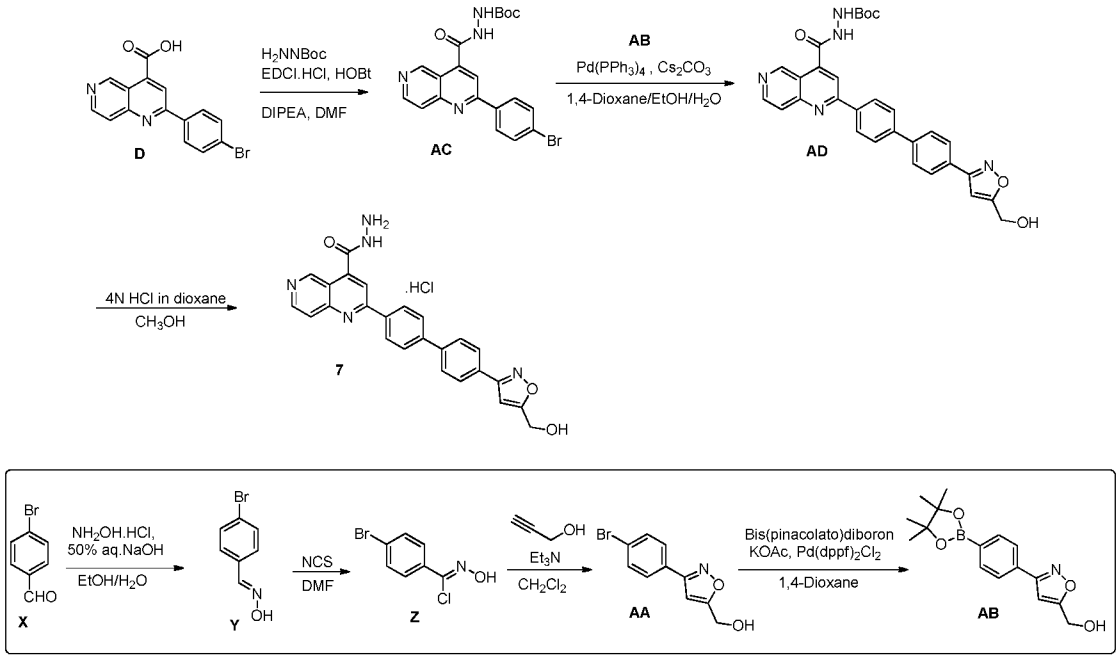
N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl) methanesulfonamide (6)

To a stirred solution of methyl 2-(4'-(2-aminoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carboxylate HCl salt (**U**; 0.15 g, 0.37 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.16 mL, 1.12 mmol) followed by methanesulfonyl chloride (47 mg, 0.40 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was allowed to warm to RT and stirred for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with ice-cold water and extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was triturated with MeOH/diisopropyl ether to afford **W** (80 mg, 0.16 mmol, 44%) as a yellow solid. The obtained product was confirmed by LC-MS analysis and taken forward to the next reaction. LC-MS: m/z 478.5 $[M+1]^+$ at 3.60 min (82.7% purity).

A mixture of **W** (80 mg, 0.16 mmol) and NH_2-NH_2·H_2O (4 mL) was heated to 100°C and stirred for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was then allowed to cool to RT, diluted with ice-cold water and stirred for 5 min. The precipitated solid was filtered and dried under reduced pressure to obtain the crude. The crude material was purified by trituration with MeOH/diisopropyl ether to afford **6** (70 mg, 0.14 mmol, 87%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (bs, 1H), 9.64 (s, 1H), 8.80 (d, J = 6.0

Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 2H), 8.34 (s, 1H), 8.02 (d, *J* = 6.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.32 (bs, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.79 (bs, 2H), 4.12 (t, *J* = 5.6 Hz, 2H), 3.38 (t, *J* = 5.6 Hz, 2H), 2.98 (s, 3H). MS (ESI): *m/z* 478 $[M+1]^+$. HPLC: 96.7%.

Scheme 6



EXAMPLE 7

2-(4'-(5-(Hydroxymethyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide HCl Salt (7)

To a stirred solution of 4-bromobenzaldehyde (**X**; 2.0 g, 10.75 mmol) in EtOH/H_2O (75 mL; 1:2 *v/v*) were added $NH_2OH{\cdot}HCl$ (821 mg, 11.83 mmol) and 50% aqueous sodium hydroxide (NaOH) solution (2.16 mL) at 5 °C. The resulting reaction mixture was stirred for 2 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was then acidified to pH ~6 with acetic acid (AcOH) and then extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 7-10% EtOAc/hexane as eluent to afford **Y** (1.2 g, 6.0 mmol, 57%) as white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H).

To a stirred solution of **Y** (600 mg, 3.0 mmol) in DMF (10 mL) were added N-chlorosuccinimide (NCS) (398mg, 3.0 mmol) at RT under inert atmosphere. The resulting reaction mixture was stirred for 1 h at 50 °C. Progress of the reaction was monitored by TLC. The reaction mixture was then quenched with crushed-ice and extracted with EtOAc (3×30 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 7-10% EtOAc/hexane as eluent to afford **Z** (500 mg, 2.132 mmol, 71%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.51 (s, 1H), 7.73–7.65 (m, 4H).

To a stirred solution of **Z** (500 mg, 2.132 mmol) in CH_2Cl_2 (10 ml) was added propargyl alcohol (120 mg, 2.132 mmol) and followed by Et_3N (0.34 ml 2.345 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 12 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 15-20% EtOAc/hexane as eluent to afford **AA** (400 mg, 1.57 mmol, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 6.54 (s , 1H), 4.83 (d, *J* = 4.5 Hz, 2H), 2.13 (bs, 1H). LC-MS: *m/z* 252 $[M-2]^-$ at 3.28 min (95.08% purity).

A stirred mixture of **AA** (200 mg, 0.787 mmol), bis(pinacalato)diboron (220 mg, 0.865 mmol) and anhydrous KOAc (231 mg, 2.36 mmol) in 1,4-dioxane (20 mL) was purged with argon for 30 min at RT. To the resulting reaction mixture was added $Pd(dppf)_2Cl_2$ (57 mg, 0.078 mmol) at RT and heated to 100 °C for 2 h. After completion of the starting material (by TLC), the reaction mass was brought to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography eluting with 35-50% EtOAc/hexane as eluent to afford **AB** (300 mg, 0.67 mmol) as a colorless sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 6.4 Hz, 2H), 6.60 (s , 1H), 4.83 (s, 2H), 4.15 (bs, 1H), 1.36 (s, 12H).

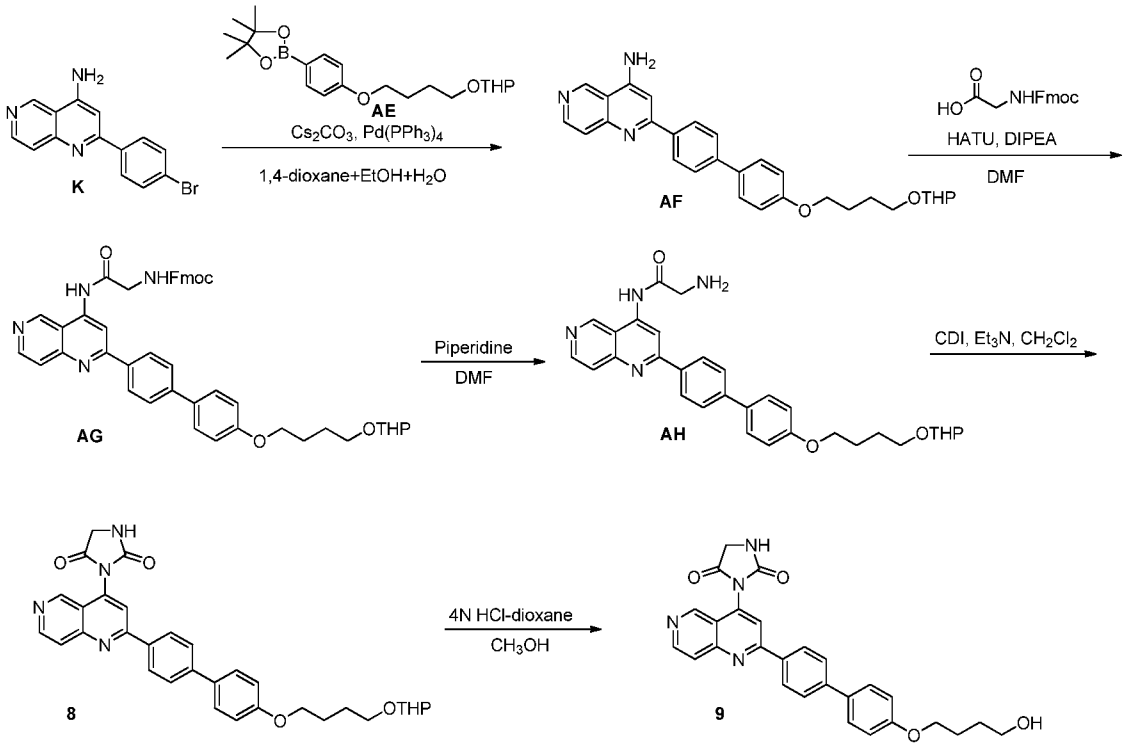
To a stirred solution of **D** (5.0 g, 15.24 mmol) in DMF (20 mL) was added DIPEA (8.5 mL, 45.72 mmol) followed by EDCI·HCl (4.4 g, 22.87 mmol) and HOBt (3.1 g, 22.87 mmol) at RT and continued stirring for another 20 min under inert atmosphere. To the resulting reaction mixture was added Boc-hydrazine (4.0 g, 30.48 mmol) at 0 °C and stirred for another 16 h at RT. After complete consumption of the starting material (by TLC), the reaction was quenched

with ice-cold water and extracted with EtOAc (2×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 3% CH_3OH/CH_2Cl_2 as eluent to afford **AC** (3.0 g, 6.77 mmol, 44%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.63 (bs, 1H), 9.70 (bs, 1H), 9.29 (s, 1H), 8.83 (d, J = 5.6 Hz, 1H), 8.31 (d, J = 8.4 Hz, 2H), 8.28 (s, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 1.49 (s, 9H). LC-MS: *m/z* 445 $[M+2]^+$ at 3.66 min (99.6% purity).

To a stirred solution of **AC** (150 mg, 0.338 mmol) and **AB** (122 mg, 0.406 mmol) dissolved in a mixture of 1,4-dioxane (8 mL):EtOH (4 mL):H_2O (2 mL) was added Cs_2CO_3 (326 mg, 1.015 mmol) at RT. The reaction was degassed by purging with inert gas for 1 h. To the resulting reaction mixture was added $Pd(PPh_3)_4$ (39 mg, 0.033 mmol) and then stirred at reflux temperature for 4 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (40 mL). The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 2-5% $MeOH/CH_2Cl_2$ as eluent to afford **AD** (25 mg, 0.046 mmol, 13%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.71 (s, 1H), 9.03 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.49 (d, J = 7.6 Hz, 2H), 8.34 (s , 1H), 8.06-7.95 (m, 7H), 7.02 (s, 1H), 5.73 (t, J = 6.0 Hz, *OH*), 4.64 (d, J = 6.0 Hz, 2H), 1.50 (s, 9H). MS (ESI): *m/z* 537 $[M]^+$.

To a stirred solution of **AD** (20 mg, 0.037 mmol) in MeOH (5 mL) was added 4N HCl in 1,4-dioxane (5 mL) at 0 °C under inert atmosphere and continued stirring for another 12 h at RT. After complete consumption of the starting material (by LC-MS), the volatiles were removed under reduced pressure to obtain the crude. The crude material was triturated with diisopropyl ether (2×2 mL) followed by n-pentane (2 mL) to afford the HCl salt of **7** (17.4 mg) as a brownish solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.95 (bs, 1H), 9.70 (s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.56 (s, 1H), 8.52 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 6.0 Hz, 1H), 8.03-7.94 (m, 6H), 7.01 (s, 1H), 4.63 (s, 2H), 3.68 (bs, 3H). MS (ESI): *m/z* 437 $[M]^+$. HPLC: 90.5%.

Scheme 7



EXAMPLE 8

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (8)

To a stirred solution of 2-(4-bromophenyl)-1,6-naphthyridin-4-amine (**K**; 3.0 g, 10.03 mmol) in 1,4-dioxane (40 mL): EtOH (20 mL):H_2O (8 mL) were added Cs_2CO_3 (9.8 g, 30.1 mmol), boronate **AE** (4.5 g, 12.04 mmol) and $Pd(PPh_3)_4$ (1.16 g, 1.003 mmol) at RT under inert atmosphere. The resulting reaction mixture was stirred for 16 h at reflux temperature. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to RT, filtered through a Celite bed and the filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 as eluent to afford **AF** (2.6 g, 5.53 mmol, 55.3%) as a brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.55 (d, J = 6.0 Hz, 1H), 8.17 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.69-7.61 (m, 3H), 7.37 (br s, 2H), 7.24 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 4.56 (s, 1H), 4.04 (t, J = 6.5 Hz, 2H), 3.76-3.67 (m, 2H), 3.44-3.39 (m, 2H), 1.82-1.77 (m, 2H), 1.72-1.60 (m, 4H), 1.47-1.44 (m, 4H).

To a stirred solution of Fmoc-glycine (5.6 g, 18.8 mmol) in DMF (50 mL) was added DIPEA (90.4 mL, 56.4 mmol) followed by HATU (11.0 g, 28.2 mmol) at RT under inert atmosphere. The reaction mixture was then cooled to 0 °C and **AF** (2.64 g, 5.63 mmol) was added. The resulting reaction mixture was stirred for 72 h at RT. After consumption of the starting

material by TLC, the reaction mixture was quenched with ice-cold water and extracted with EtOAc (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 as eluent to afford **AG** (1.7 g, 2.26 mmol, 40.9%) as a brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.76 (s, 1H), 8.86 (s, 1H), 8.75-74 (m, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.18 (br s, 1H), 7.91-7.84 (m, 5H), 7.88-7.71 (m, 5H), 7.44-7.34 (m, 4H), 7.06 (d, J = 9.0 Hz, 2H), 4.57 (s, 1H), 4.37 (d, J = 7.0 Hz, 1H), 4.28-4.26 (m, 2H), 4.13-4.06 (m, 1H), 3.76-3.60 (m, 2H), 3.43-3.41 (m, 2H), 3.16-3.11 (m, 2H), 1.81-1.59 (m, 6H), 1.47-1.45 (m, 4H). LCMS: *m/z* 749.0 [M^++1] at 5.42 min (83.59% purity)

To a stirred solution of **AG** (1.7 g, 2.26 mmol) in DMF (50 mL) was added piperidine (1 mL, 11.34 mmol) at RT under inert atmosphere. The resulting reaction mixture was stirred for 30 min at RT. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with ice-cold water and extracted with EtOAc (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 10% MeOH/CH_2Cl_2 as eluent to afford **AH** (0.7 g, 1.32 mmol, 58.8%) as a yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.69 (s, 1H), 8.88 (s, 1H), 8.76 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 6.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.79-7.77 (m, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 4.57 (s, 1H), 4.06 (t, J = 6.5 Hz, 2H), 3.76-3.67 (m, 4H), 3.44-3.40 (m, 2H), 2.99 (t, J = 5.5 Hz, 2H), 1.82-1.60 (m, 6H), 1.55-1.46 (m, 4H).

To a stirred solution of **AH** (0.3 g, 0.639 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (194 mg, 1.917 mmol) and N,N-carbonyl diimidazole (154 mg, 0.949 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 45 min at 0 °C and then stirred for 3 h at RT. After consumption of the starting material by TLC, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc (2×50 mL). The combined organic layer was washed with a brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 as eluent to afford **8** (110 mg, 0.22 mmol, 34.8%) as a pale-brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.38 (s, 1H), 8.81 (d, J = 5.5 Hz, 1H), 8.68 (s, 1H), 8.38 (s, 1H), 8.37 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H),

4.58-4.57 (m, 1H), 4.39 (d, *J* = 17.5 Hz, 1H), 4.19 (d, *J* = 17.5 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.76-3.67 (m, 2H), 3.44-3.39 (m, 2H), 1.83-1.59 (m, 6H), 1.47-1.46 (m, 4H).

EXAMPLE 9

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (13)

To a stirred solution of **8** (100 mg, 0.181 mmol) in CH_3OH (4 mL) was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C and stirring was continued for 30 min. After consumption of the starting material by TLC, the volatiles were evaporated under reduced pressure. The crude was triturated with 10% MeOH/CH_2Cl_2. The obtained solid was dissolved in CH_2Cl_2 and basified to pH~8 using Et_3N. The solid precipitate was filtered and dried under vacuum to afford **9** (60 mg, 0.128 mmol, 70.83%) as a yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.38 (s, 1H), 8.81 (d, *J* = 6.0 Hz, 1H), 8.67 (br s, 1H), 8.38-8.36 (m, 3H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 4.39 (d, *J* = 17.5 Hz, 1H), 4.20 (d, *J* = 17.5 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.33 (br s, 1H), 1.80-1.75 (m, 2H), 1.61-1.56 (m, 2H). LCMS: *m/z* 469 [M^++1] at 2.82 min (96.75% purity). HPLC: 97.07%.

Synthesis of intermediate AE **4,4,5,5-tetramethyl-2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,3,2-dioxaborolane**

To a stirred solution of 4-bromophenol (10 g, 57.80 mmol) in 1,4-dioxane (200 mL) was added bis(pinacolato)diborane (16.1 g, 63.38 mmol) followed by potassium acetate (16.9 g, 172.4 mmol) at RT and degassed by purging with N_2 for 15 min. To the resulting reaction mixture was added Pd(dppf)$_2$Cl$_2$ (4.2 g, 5.74 mmol) and then stirred at reflux temperature for 3 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through pad of Celite and the pad was washed with EtOAc (30 mL). The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (10.0 g, 45.45 mmol, 79.3%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.17 (brs, 1H), 1.33 (s, 12H). MS (ESI): m/z 218.9 [M^+-1]

To a stirred solution of tetrahydrofuran (50 mL) was added 48% HBr (23 mL) dropwise over a period of 2 h at reflux temperature. The stirring was continued for another 1.3 h at reflux

temperature and then cooled to RT. The reaction mixture was neutralized with a saturated $NaHCO_3$ solution, diluted with water and separated the organic layer. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to afford 4-bromobutanol (20 g, crude) as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$): δ 3.67-3.65 (m, 2H), 3.47-3.44 (m, 2H), 1.99-1.93 (m, 2H), 1.74-1.68 (m, 2H).

To a stirred solution of 4-bromobutanol (1 g, 6.53 mmol) in CH_2Cl_2 (15 mL) was added 3,4-dihydro-2H-pyran (824 mg, 9.79 mmol) followed by *p*-TSA (124 mg, 0.65 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 30 min at RT. After completion of the reaction (by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2x25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 5% EtOAc/hexane as eluent to afford 2-(4-bromobutoxy)tetrahydro-2H-pyran (0.9 g, 3.79 mmol, 58.4%) as a colorless syrupy mass. ^1H NMR (500 MHz, $CDCl_3$): δ 4.57-4.56 (m, 1H), 3.87-3.74 (m, 2H), 3.51-3.40 (m, 4H), 2.00-1.94 (m, 2H), 1.84-1.68 (m, 4H), 1.61-1.51 (m, 4H).

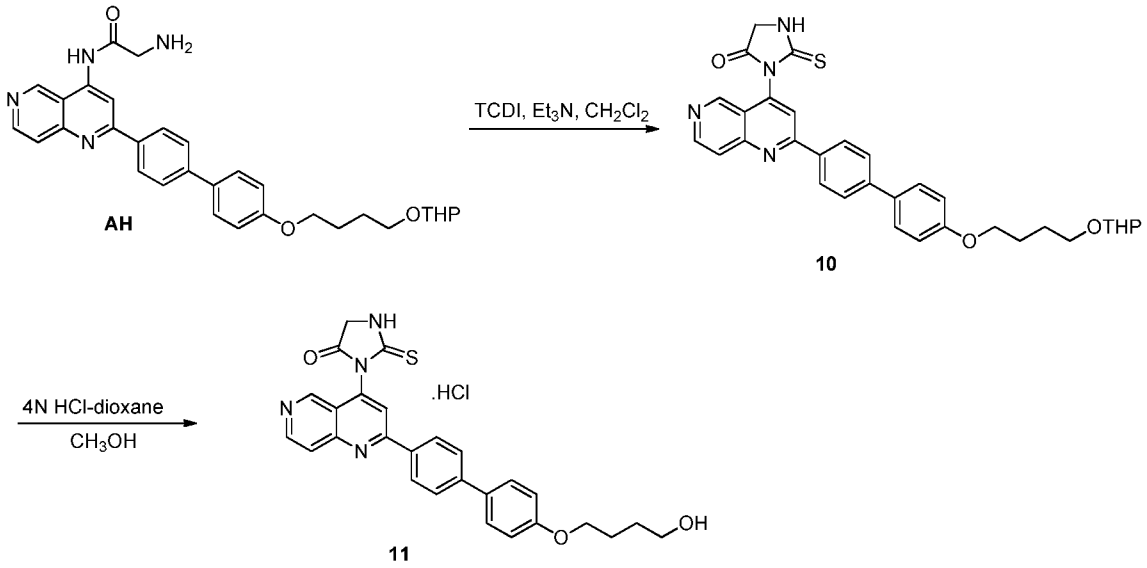
To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (4.0 g, 18.26 mmol) in DMF (10 mL) wad added K_2CO_3 (6.3 g, 45.65 mmol) at RT and stirred for 15 min. A solution of 2-(4-bromobutoxy)tetrahydro-2H-pyran (5.6 g, 23.62 mmol) in DMF (10 mL) was added to the reaction mixture and stirring was continued for another 16 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water and extracted with EtOAc (2x25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford 4,4,5,5-tetramethyl-2-(4-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)phenyl)-1,3,2-dioxaborolane (6.5 g, 17.3 mmol, 95.5%) as a colorless syrupy mass. ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.60-4.58 (m, 1H), 4.02 (t, J = 7.0 Hz, 2H), 3.88-3.78 (m, 2H), 3.51-3.43 (m, 2H), 1.90-1.69 (m, 4H), 1.60-1.58 (m, 4H), 1.57-1.52 (m, 2H), 1.33 (s, 12H).

To a stirred solution of 1-bromo-4-iodobenzene (14 g, 49.48 mmol) and 4,4,5,5-tetramethyl-2-(4-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)phenyl)-1,3,2-dioxaborolane (12.9 g, 34.6 mmol) dissolved in a mixture of toluene (250 mL):MeOH (40 mL) was added K_2CO_3 (20.4g, 148.2 mmol) at RT. The reaction was degassed by purging with N_2 for 1 h. To the resulting reaction mixture was added $Pd(PPh_3)_4$ (2.9 g, 2.47 mmol) and then stirred at reflux

temperature for 4 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (40 mL). The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 10% EtOAc/hexane as eluent to afford 2-(4-((4'-bromo-[1,1'-biphenyl]-4-yl)oxy)butoxy)tetrahydro-2H-pyran (10 g, 24.69 mmol, 50%) as an off-white semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 4.61-4.59 (m, 1H), 4.03 (t, *J* = 6.0 Hz, 2H), 3.89-3.80 (m, 2H), 3.52-3.44 (m, 2H), 1.93-1.70 (m, 6H), 1.61-1.51 (m, 4H). MS (ESI): m/z 406 [M^++1].

To a stirred solution of 2-(4-((4'-bromo-[1,1'-biphenyl]-4-yl)oxy)butoxy)tetrahydro-2H-pyran (10 g, 24.67 mmol) in 1,4-dioxane (250 mL) at RT degassed by purging with argon for 15 min were added bis(pinacolato)diboron (6.9 g, 27.2 mmol) followed by potassium acetate (7.3 g, 74.1 mmol). The degassing was continued for another 1 h. To the resulting reaction mixture was added $Pd(dppf)_2Cl_2$ (1.8 g, 2.47 mmol) and then stirred at reflux temperature for 12 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of Celite and the pad was washed with CH_2Cl_2 (50 mL). The collected filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 15% EtOAc/hexane to afford desired boronate 4,4,5,5-tetramethyl-2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,3,2-dioxaborolane (**AE**) (10 g, 22.1 mmol, 89%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.56-7.53 (m, 4H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.61-4.60 (m, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.89-3.80 (m, 2H), 3.52-3.45 (m, 2H), 1.92-1.70 (m, 7H), 1.56-1.52 (m, 3H), 1.33 (s, 12H). MS (ESI): m/z 452 [M^+].

Scheme 8



EXAMPLE 10

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (10)

To a stirred solution of **AH** (0.1 g, 0.213 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.064 mg, 0.639 mmol) and thiocarbonyl diimidazole (TCDI) (56.9 mg, 0.319 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred for 2 h at RT. After consumption of the starting material by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 as eluent to afford **10** (36.8 mg, 0.064 mmol, 30.6%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.78 (s, 1H), 9.38 (s, 1H), 8.81 (d, J = 6.0 Hz, 1H), 8.42 (s, 1H), 8.37 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.58 (d, J = 8.5 Hz, 2H), 4.44-4.40 (m, 1H), 4.07 (t, J = 6.5 Hz, 2H), 3.76-3.67 (m, 2H), 3.44-3.40 (m, 2H), 2.01-1.99 (m, 1H), 1.82-1.80 (m, 2H), 1.72-1.68 (m, 3H), 1.63-1.60 (m, 1H), 1.49-1.47 (m, 3H).

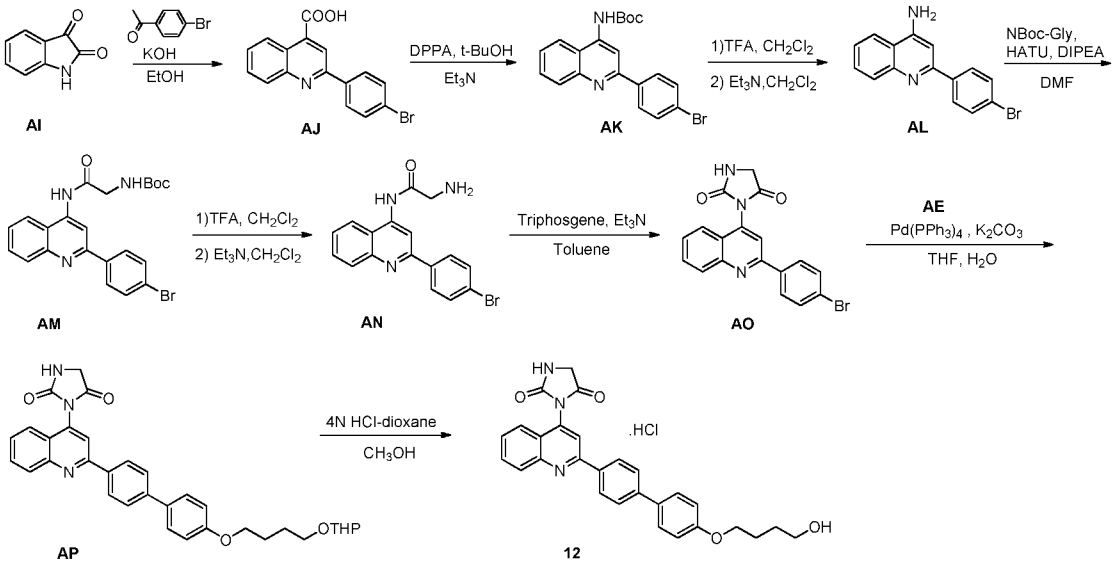
EXAMPLE 11

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one HCl Salt (11)

To a stirred solution of **10** (30 mg, 0.052 mmol) in 10% CH_3OH/CH_2Cl_2 (5 mL) was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was stirred for 2 h. After consumption of

the starting material by TLC, the volatiles were evaporated under reduced pressure and the crude was triturated with 10% MeOH/diethyl ether followed by n-pentane to obtain the HCl salt of **11** (15.5 mg) as a bright-yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.85 (s, 1H), 9.60 (br s, 1H), 8.86 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 8.0 Hz, 2H), 8.24 (br s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 4.58 (d, J = 20.0 Hz, 1H), 4.48 (d, J = 20.0 Hz, 1H), 4.07-4.04 (m, 3H), 3.47 (t, J = 6.5 Hz, 2H), 1.79-1.76 (m, 2H), 1.62-1.57 (m, 2H). MS (ESI): 485 [M^++1]. HPLC: 95.23%.

Scheme 9



EXAMPLE 12

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)imidazolidine-2,4-dione HCl salt (12)

To a stirred solution of indoline-2,3-dione (**AI**; 10.0 g, 68.03 mmol) and 1-(4-bromophenyl)ethanone (12.2 g, 61.3 mmol) dissolved in a 1:1 mixture of EtOH/H_2O (100 mL) was added KOH (15.3 g, 272.6 mmol) at RT. The resulting reaction mixture was heated at reflux and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were removed under reduced pressure and the aqueous layer was washed with CH_2Cl_2 (2×50 mL). The aqueous layer was separated and neutralized with acetic acid to precipitate the solid. The precipitated solid was filtered, azeotroped with toluene followed by drying the solid under reduced pressure to afford acid **AJ** (17.0 g, 51.8 mmol, 77%) as a pink solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.63 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H), 8.24 (d, J = 8.0 Hz, 2H), 8.11 (d, J

= 8.5 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz , 2H), 7.64 (t, *J* = 7.5 Hz, 1H). LCMS: m/z 328.8 [M^++1] at 4.83 min (64.89%).

To a stirred solution of **AJ** (1.4 g, 4.28 mmol) in *t*-BuOH (20 mL) were added Et_3N (1.2 mL, 8.56 mmol) followed by diphenyl phosphorazidate (DPPA) (1.8 mL, 8.56 mmol) at RT . The resulting reaction mixture was heated to reflux and stirred for 12 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure, the residue dissolved in CH_2Cl_2 (30 mL) and washed with water (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexane as eluent to afford **AK** (1.8 g, 4.51 mmol) as a pale yellow solid. This contained a small amount of impurity (in ^{1}H-NMR) and was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.05 (br s, 1H), 8.54 (s, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.10-8.06 (m, 3H), 7.83-7.78 (m, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H),1.57 (s, 9H). MS (ESI): m/z 399 [M^++1]

To a stirred solution of **AK** (5.0 g, 12.5 mmol) in CH_2Cl_2 (20 mL) was added TFA (20 mL) at 0 °C. The reaction mixture was slowly allowed to warm to RT and stirred for 8 h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure and the residue was triturated with CH_2Cl_2. The obtained solid was dissolved in CH_2Cl_2 and basified by using Et_3N (15 mL). The solid precipitate was filtered, washed with pentane and dried under reduced pressure to afford amine **AL** (2.5 g, 8.35 mmol, 67.5 mmol) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): 8.15 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 1H), 6.87 (s, 2H). LCMS: m/z 300.5 [M^++1] at 7.68 min (98.62%).

To a stirred solution N-Boc-glycine (1.7 g, 10.03 mmol) in DMF (20 mL) at 0 °C were added **AL** (1.0 g, 3.34 mmol) and HATU (5.9 g, 15.1 mmol) followed by DIPEA (2.59 g, 20.03 mmol) under inert atmosphere. The resulting reaction mixture was stirred for 12 h at RT. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (20 mL) and washed with water (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexane as eluent to afford **AM** (0.7 g, 1.53 mmol) as a pale yellow solid. This contained a small amount of impurity and was used in the next step without further purification. ^{1}H NMR (500

MHz, $CDCl_3$): δ 9.45 (br s, 1H), 8.82 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 5.41 (br s, 1H), 4.05 (d, *J* = 6.5 Hz, 2H), 1.56 (s, 9H). MS (ESI): m/z 459.0 [M^++2].

To a stirred solution of **AM** (0.7 g, 1.53 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 4 h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. To the residue dissolved in CH_2Cl_2 (50 mL) was added Et_3N (10 mL, 136.3 mmol) at 0 °C and the solution was stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford amine **AN** (0.35 g, 0.98 mmol, crude) as a yellow solid. This material was used in the next step without any further purification. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.83 (s, 1H), 8.17-8.07 (m, 4H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 5.02 (br s, 2H), 3.50 (s, 2H). MS (ESI): m/z 358 [M^++2].

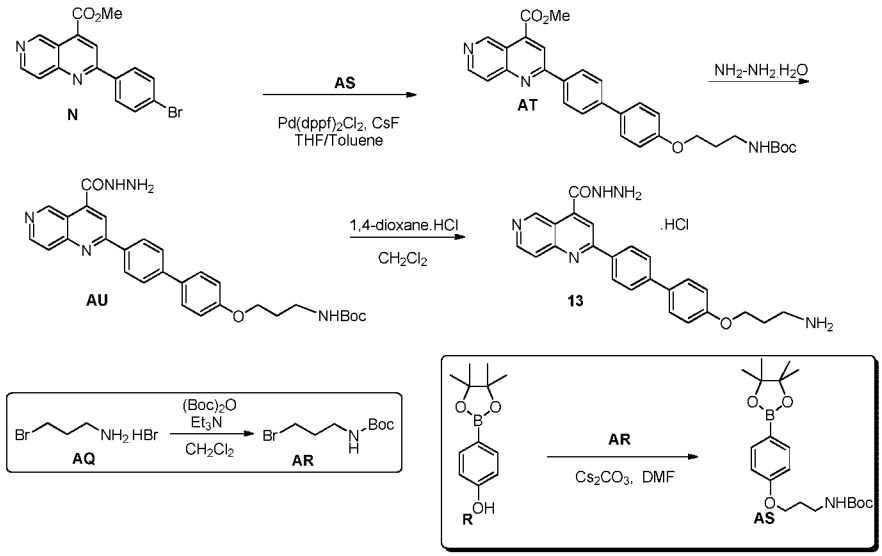
To a stirred solution of **AN** (50 mg, 0.14 mmol) in toluene (10 mL) was added Et_3N (0.03 mL, 0.21 mmol) followed by triphosgene (42 mg, 0.14 mmol) at 0 °C under inert atmosphere. The stirring was continued for 45 min. The resulting reaction mixture was heated to reflux and stirred for 12 h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 as eluent to afford **AO** (30 mg, 0.078 mmol, 56.6%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.58 (s, 1H), 8.24-8.22 (m, 3H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 4.38 (d, *J* = 18.0 Hz, 1H), 4.19 (d, *J* = 18.0 Hz, 1H). LCMS: m/z 382 [M^+] at 4.03 min (94.19%).

To a stirred solution of **AO** (150 mg, 0.392 mmol) in THF (20 mL):water (2 mL) degassed by purging with argon for 30 min were added **AE** (176 mg, 0.471 mmol) and K_2CO_3 (162 mg, 1.178 mmol) at RT. The degassing was continued for another 30 min. To the resulting reaction mixture was added $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) and the reaction was degassed for another 5 min. The reaction mixture was then slowly heated to reflux and stirred for 8.5 h. Progress of the reaction was monitored by TLC. The reaction mixture was then concentrated under reduced pressure and the obtained crude was purified by silica gel column chromatography eluting with 15% CH_3OH/CH_2Cl_2 as eluent to afford **AP** (30 mg, 0.054 mmol, 13.8%) as a white solid along with another 30 mg of product containing triphenylphosphine oxide as an

impurity. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.34 (d, J = 8.5 Hz, 2H), 8.25 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.88-7.84 (m, 3H), 7.73 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 4.58-4.57(m, 1H), 4.38 (d, J = 17.5 Hz, 1H), 4.20 (d, J = 17.5 Hz, 1H), 4.07 (t, J = 6.5 Hz, 2H), 3.76-3.69 (m, 2H), 3.45-3.41 (m, 2H), 1.84-1.80 (m, 2H), 1.73-1.62 (m, 4H), 1.49-1.46 (m, 4H). LC-MS: m/z 552 [M^++1] at 4.34 min (99.17% purity).

To a stirred solution of **AP** (30 mg, 0.054 mmol) in CH_3OH (1 mL) was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The stirring was continued for another 20 min. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to furnish the crude. The crude material was triturated with diisopropyl ether to afford the HCl salt of **12** (25 mg) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.34 (d, J = 8.0 Hz, 2H), 8.25 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.88-7.84 (m, 3H), 7.73 (d, J = 8.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 4.38 (d, J = 17.5 Hz, 1H), 4.20 (d, J = 17.5 Hz, 1H), 4.06-4.03 (m, 3H), 3.47 (t, J = 6.5 Hz, 2H), 1.81-1.76 (m, 2H), 1.62-1.56 (m, 2H). MS (ESI): m/z 468.6 [M^++1]. HPLC: 99.74%.

Scheme 10



EXAMPLE 13

2-(4'-(3-Aminopropoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide HCl salt

(13)

To a stirred solution of 3-bromopropan-1-amine hydrobromide (**AQ**; 1.0 g, 4.56 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (1.65 mL, 11.42 mmol) followed by Boc-anhydride (1.095 g, 5.02 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 8 h at RT. After complete consumption of the starting material (by TLC), the reaction mixture was extracted with CH_2Cl_2 (2x30 mL). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford **AR** (0.8 g, 3.35 mmol, 74%) as a pale-brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (bs, NH), 3.44 (t, *J* = 6.4 Hz, 2H), 3.28 (t, *J* = 6.4 Hz, 2H), 2.08-2.01 (m, 2H), 1.44 (s, 9H).

To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**R**; 5.4 g, 24.3 mmol) in DMF (54 mL) was added Cs_2CO_3 (17.4 g, 53.4 mmol) at RT under inert atmosphere. After being stirred for 20 min, **AR** (6.325 g, 26.56 mmol) was added to the above solution at RT. The resulting reaction mixture was heated to 65 °C and stirred for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then allowed to RT, diluted with water (20 mL) and extracted with EtOAc (2×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 15% EtOAc/hexane as eluent to afford **AS** (6.7 g, 17.6 mmol, 72%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 6.8, 2.0 Hz, 2H), 6.88 (dd, *J* = 6.8, 2.0 Hz, 2H), 4.73 (bs , NH), 4.04 (t, *J* = 6.4 Hz, 2H), 3.33-3.31 (m, 2H), 2.05-1.94 (m, 2H), 1.43 (s, 9H), 1.33 (s, 12H).

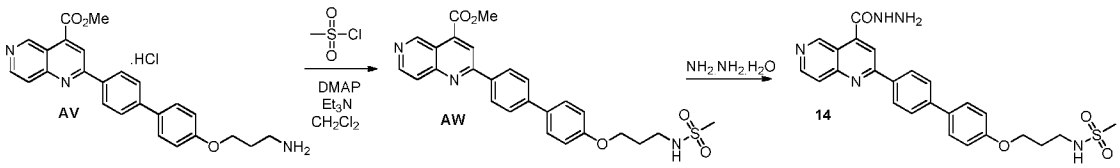
To a solution of **N** (2.0 g, 5.83 mmol) in THF/toluene (100 mL, 1:1 *v/v*) were added boronate **AS** (2.2 g, 5.80 mmol), CsF (2.6 g, 17.19 mmol) at RT. The reaction was degassed by purging with inert gas for 10 min. To the resulting reaction mixture was added $Pd(dppf)_2Cl_2$ (426 mg, 0.58 mmol) and the reaction was degassed for another 15 min. The reaction mixture was then stirred for 24 h at reflux temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then allowed to cool to RT and filtered through a pad of Celite. The Celite bed was washed with CH_3OH and the collected filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 50% EtOAc/hexane as eluent to afford **AT** (1.72 g, 2.80 mmol, 48%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.55 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 2H), 8.02 (dd, *J* = 6.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.62

(d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 4.76 (bs, NH), 4.11 (s, 3H), 4.09 (t, J = 6.0 Hz, 2H), 3.38-3.34 (m, 2H), 2.02 (t, J = 6.0 Hz, 2H), 1.45 (s, 9H). LC-MS: m/z 514 $[M+1]^+$ at 4.32 min (98.4% purity).

A mixture of ester **AT** (88 mg, 0.17 mmol) and hydrazine hydrate (3 mL) was heated to 100 °C and stirred for 2 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to 0 °C, diluted with ice-cold water and stirred for 5 min. The precipitated solid was filtered and dried under reduced pressure to obtain the crude. The crude material was purified by trituration with IPA/pentane to afford **AU** (50 mg, 0.097 mmol, 56%) as a pale-green solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.63 (s, 1H), 8.79 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 8.4 Hz, 2H), 8.33 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.91 (bs, 1H), 4.78 (bs, 2H), 4.04 (t, J = 6.4 Hz, 2H), 3.13-3.08 (m, 2H), 1.86 (t, J = 6.4 Hz, 2H), 1.38 (s, 9H). LC-MS: m/z 514 $[M+1]^+$ at 3.54 min (79.1% purity).

To a stirred solution of **AU** (88 mg, 0.17 mmol) in CH_3OH (1 mL) was added 4N HCl in 1,4-dioxane (2 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was allowed to warm to RT and stirred for 2 h. Progress of the reaction was monitored by TLC. The volatiles were then evaporated under reduced pressure to obtain the crude. The crude product was triturated with diisopropylether followed by 10% CH_3OH/diisopropylether to afford the HCl salt of **13** (40 mg) as an orange colored solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (bs, 1H), 9.73 (s, 1H), 8.87 (d, J = 6.0 Hz, 1H), 8.59 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.17 (d, J = 6.0 Hz, 1H), 8.02 (bs, 3H), 7.91 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 9.2 Hz, 2H), 4.15 (t, J = 6.4 Hz, 2H), 3.01-2.96 (m, 2H), 2.09 (t, J = 6.4 Hz, 2H). MS (ESI): m/z 412 $[M-1]^-$, 448 [M+HCl]. HPLC: 94.47%.

Scheme 11



EXAMPLE 14

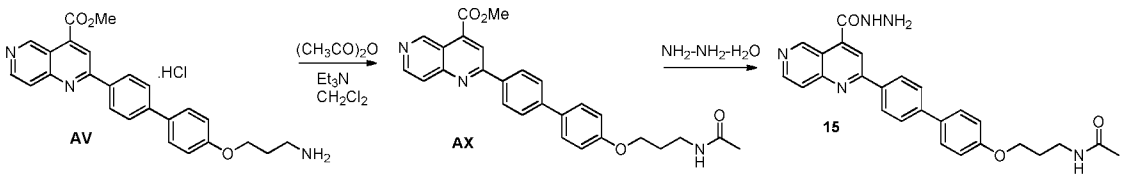
N-(3-((4'-(4-(Hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl) methanesulfonamide (14)

To a stirred solution of methyl 2-(4'-(3-aminopropoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carboxylate HCl salt (**AV**; 60 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added

Et_3N (0.083 mL, 0.51 mmol) followed by DMAP (1.7 mg, 0.013 mmol) at 0 °C under inert atmosphere. After being stirred for 15 min, methanesulfonyl chloride (0.017 mL, 0.21 mmol) was added to the reaction mixture at 0 °C. The resulting reaction mixture was stirred for 2 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was then diluted with ice-cold water and extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with 10% $NaHCO_3$ solution followed by water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was triturated with IPA/pentane to afford **AW** (27 mg, 0.054 mmol, 38%) as a pale-brown solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.02 (bs, 1H), 8.89 (d, J = 6.0 Hz, 1H), 8.75 (s, 1H), 8.47 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 4.11 (t, J = 6.4 Hz, 2H), 3.16-3.13 (m, 2H), 2.91 (s, 3H), 2.32 (s, 3H), 1.98-1.90 (m, 2H). LC-MS: *m/z* 492.7 $[M+1]^+$ at 3.74 min (88.6% purity).

A mixture of **AW** (27 mg, 0.054 mmol) and $NH_2NH_2 \cdot H_2O$ (2 mL) was heated to 100 °C and stirred for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to RT, diluted with ice-cold water and stirred for 5 min. The precipitated solid was filtered and dried *in vacuo* to obtain the crude. The crude material was purified by trituration with MeOH/diisopropyl ether to afford **14** (9 mg, 0.018 mmol, 33%) as a pale-brown solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.19 (bs, 1H), 9.63 (s, 1H), 8.79 (d, J = 6.0 Hz, 1H), 8.43 (d, J = 8.4 Hz, 2H), 8.33 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.09-7.07 (m, 3H), 4.78 (bs, 2H), 4.09 (t, J = 6.4 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 2.91 (s, 3H), 1.96 (t, J = 6.4 Hz, 2H). MS (ESI): 492.7 $[M+1]^+$. HPLC: 90%.

Scheme 12



EXAMPLE 15

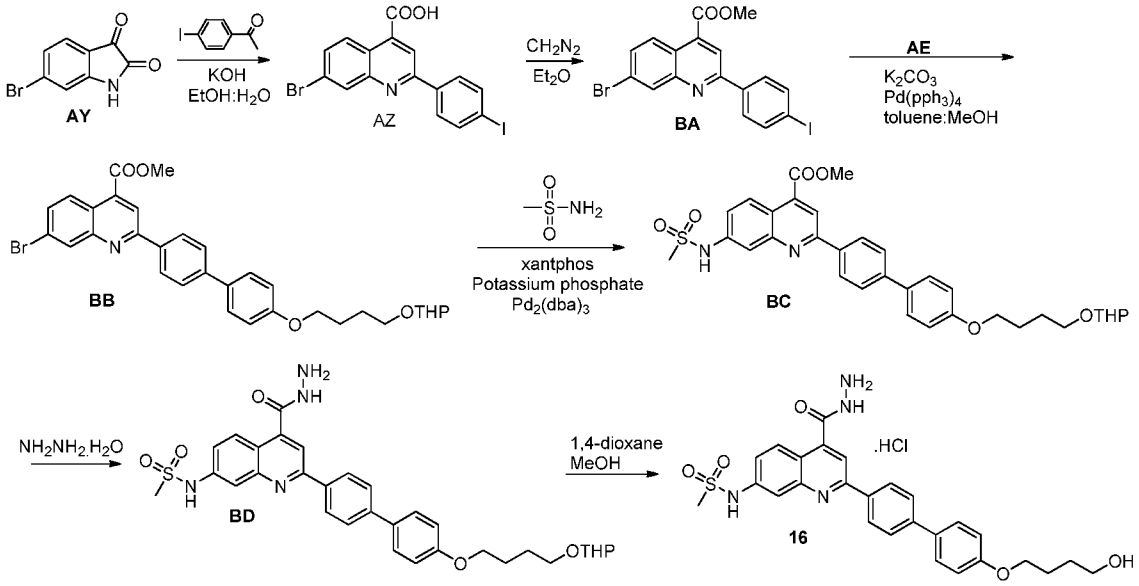
***N*-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl) acetamide (15)**

To a stirred solution of methyl 2-(4'-(3-aminopropoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carboxylate HCl salt (**AV**; 0.15 g, 0.28 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.16 mL, 1.12 mmol) followed by DMAP (3.4 mg, 0.027 mmol) at 0 °C under inert

atmosphere. A solution of acetic anhydride (23 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture dropwise at 0 °C. The resulting reaction mixture was allowed to warm to RT and stirred for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to 0 °C, diluted with 10% $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was triturated with IPA/pentane (4:1) to afford **AX** (0.1 g, 0.21 mmol, 83%) as a pale-green solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 8.82 (d, J = 6.0 Hz, 1H), 8.64 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 8.04 (dd, J = 6.0Hz, 1H), 7.89 (bs, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 4.04 (s, 3H), 4.02 (t, J = 6.4 Hz, 2H), 3.22-3.17 (m, 2H), 1.87 (t, J = 6.4 Hz, 2H), 1.82 (s, 3H). LC-MS: m/z 456 $[M+1]^+$ at 3.40 min (98.8% purity).

A mixture of **AX** (0.03 g, 0.065 mmol) and hydrazine hydrate (2 mL) was heated to 100 °C and stirred for 1 h. Progress of the reaction was monitored by TLC. The reaction mixture was then allowed to cool to RT, diluted with ice-cold water and stirred for 5 min. The precipitated solid was dissolved in 30% MeOH/CH_2Cl_2 (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was triturated with CH_3OH and diisopropyl ether to afford **15** (25 mg, 0.054 mmol, 83%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (bs, 1H), 9.63 (s, 1H), 8.79 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 8.4 Hz, 2H), 8.33 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.92-7.81 (m, 3H), 7.75 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.78 (bs, 2H), 4.05 (t, J = 6.4 Hz, 2H), 3.25-3.15 (m, 2H), 1.87 (t, J = 6.4 Hz, 2H), 1.81 (s, 3H). MS (ESI): 456.7 $[M+1]^+$. HPLC: 97.2%.

Scheme 13



EXAMPLE 16

N-(4-(Hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-7-yl)methanesulfonamide HCl salt (16)

To a stirred solution of 6-bromoindoline-2,3-dione (**AY**; 5.0 g, 22.12 mmol) in EtOH:H_2O (100 mL, 1:1 *v/v*) were added 1-(4-iodophenyl)ethanone (5.4 g, 21.94 mmol) and KOH (4.96 g, 88.39 mmol) at RT under inert atmosphere. The resulting reaction mixture was stirred for 4 h at 110 °C. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to RT and the volatiles were evaporated under reduced pressure. The residue obtained was diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL). The aqueous layer was then separated, washed with CH_2Cl_2 (100 mL), and acidified to pH~2 using AcOH. After being stirred for 5 min, the precipitated solid was filtered, washed with water (50 mL) and dried under vacuum. To remove the water traces, the obtained solid residue was distilled twice with toluene (2x20 mL). The crude material was finally triturated with Et_2O and pentane to afford **AZ** (2.5 g, 5.50 mmol, 25%) as a pale-orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (d, *J* = 9.2 Hz, 1H), 8.45 (s, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.84 (dd, *J* = 9.2, 2.0 Hz, 1H).

To a stirred solution of **AZ** (2.5 g, 5.50 mmol) in ether (100 mL) was added freshly prepared diazomethane [prepared by using dissolving NMU (2.8 g, 27.18 mmol) in a 1:1 mixture of 30% KOH solution (50 mL) and ether (50 mL) at 0 °C followed by separation and drying of the organic layer using KOH pellets] and stirred for 1 h at 0 °C. The progress of the reaction was monitored by TLC. The reaction mixture was then concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting

with 5-10% EtOAc/hexane as eluent to afford **BA** (2.4 g, 5.12 mmol, 96%) as a pale-green solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.39 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.71 (dd, *J* = 9.0, 2.0 Hz, 1H), 4.07 (s, 3H). LCMS: m/z 470 $[M+2]^+$ at 5.74 min (98.6%).

A stirred solution of **BA** (1.8 g, 3.84 mmol) in toluene/CH_3OH (100 mL, 4:1 *v/v*) was degassed by purging with argon for 15 min. To the resulting reaction mixture were added **AE** (1.44 g, 3.84 mmol), K_2CO_3 (1.59 g, 11.53 mmol) and $Pd(PPh_3)_4$ (0.44 g, 0.38 mmol) and degassed for another 5 min. The resulting reaction mixture was then stirred for 6 h at reflux temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to RT, filtered through a pad of Celite and the bed was washed with EtOAc (2x20 mL). The collected filtrate was then concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane as eluent to afford **BB** (0.62 g, 1.04 mmol, 27%) as a pale-brown thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 9.2 Hz, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 2H), 7.74-7.68 (m, 3H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.08-4.05 (m, 5H), 3.89-3.81 (m, 3H), 3.53-3.46 (m, 3H), 1.94-1.79 (m, 7H), 1.76-1.70 (m, 2H).

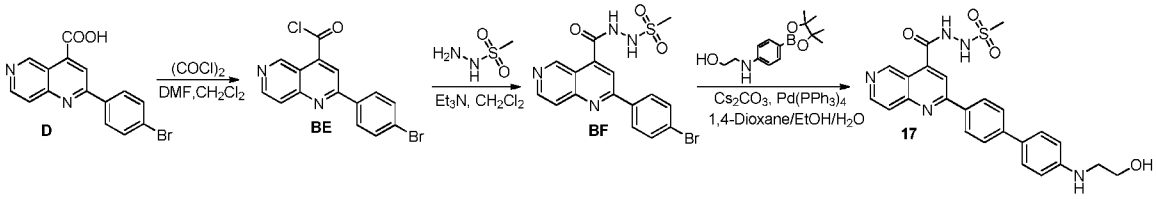
A stirred mixture of **BB** (0.62 g, 1.049 mmol), methane sulfonamide (119 mg, 1.25 mmol), potassium phosphate (0.33g, 1.57 mmol), xantphos (32.6 mg, 0.062 mmol) and $Pd_2(dba)_3$ (28.8 mg, 0.031 mmol) in 1,4-dioxane (50 mL) at RT was degassed for 30 min by purging with nitrogen. The resulting reaction mixture was then heated to 100 °C, and stirred for 12 h stirring. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude. The crude compound was purified by silica gel column chromatography eluting with 30% EtOAc/hexane as eluent to afford **BC** (0.11 g, 0.18 mmol, 17.4%) as a pale-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 9.2 Hz, 1H), 8.41 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.46 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.79 (bs, 1H), 4.61-4.60 (m, 1H), 4.08-4.05 (m, 5H), 3.91-3.82 (m, 2H), 3.81 (s, 1H), 3.53-3.46 (m, 2H), 3.16 (s, 3H), 2.04-2.01 (m, 4H), 1.94-1.89 (m, 3H), 1.84-1.79 (m, 2H). LCMS: *m/z* 605 $[M+1]^+$ at 4.62 min (92.5%).

A mixture of **BC** (0.11 g, 0.18 mmol) and hydrazine hydrate (2 mL) was heated to 100 °C and stirred for 1 h under inert atmosphere. Progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to RT, diluted with ice-cold water and extracted with 10% MeOH/EtOAc (2x10 mL). The combined organic layer was dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was triturated with IPA/pentane to afford **BD** (82 mg, 0.13 mmol, 74%) as a pale brown-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (bs, 1H), 10.02 (bs, 1H), 8.35 (d, *J* = 8.4 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.04 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.48 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.69 (bs, 2H), 4.58-4.57 (m, 1H), 4.08-4.05 (m, 2H), 3.78-3.67 (m, 2H), 3.45-3.39 (m, 2H), 3.15 (s, 3H), 1.74-1.59 (m, 6H), 1.59-1.45 (m, 4H).

To a stirred solution of **BD** (82 mg, 0.13 mmol) in MeOH (0.5 mL) was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was allowed to warm to RT and stirred for 1.5 h. Progress of the reaction was monitored by TLC. The volatiles were then evaporated under reduced pressure. The crude material was triturated with MeOH/diisopropyl ether to afford **16** (75 mg, 0.14 mmol, 94%) as an orange colored solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (bs, 1H), 10.42 (bs, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.16 (s, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.54 (dd, *J* = 2.0, 8.8 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.54 (bs, 1H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.17 (s, 3H), 1.80-1.74 (m, 2H), 1.62-1.58 (m, 2H). MS (ESI): 521 $[M+1]^+$. HPLC: 95.03%.

Scheme 14



EXAMPLE 17

N'-(2-(4'-((2-Hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbonyl) methanesulfonohydrazide (17)

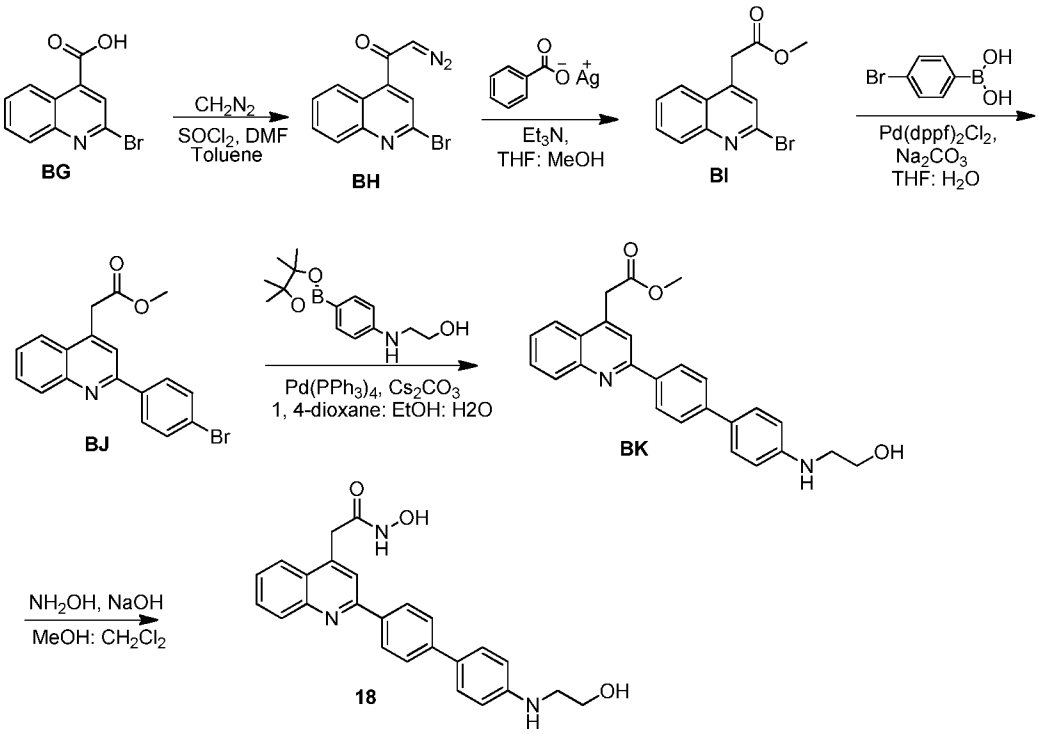
To a stirred solution of 2-(4-bromophenyl)-1,6-naphthyridine-4-carboxylic acid (**D**; 0.5 g, 1.52 mmol) in dry CH_2Cl_2 (20 mL) was added oxalyl chloride (0.54 mL, 6.08 mmol) followed by a catalytic amount of DMF at 0 °C and the reaction was stirred for 1 h at RT. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to half the original volume. This was followed by the addition of dry CH_2Cl_2 (20 mL) and the mixture was concentrated to half the volume under reduced pressure to afford **BE** (416

mg, crude). This crude material was used directly in the next step without any further purification.

To a stirred solution of methanesulfonohydrazide (264 mg, 2.40 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.5 mL, 3.54 mmol) at 0 °C under inert atmosphere. A solution of **BE** (416 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was added to the above reaction mixture dropwise at 0 °C for 5 min. The resulting reaction mixture was allowed to warm to RT and stirred for 1 h. Progress of the reaction was monitored by TLC. The separated organic layer was washed with 10% a $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the crude. The crude material was purified by silica gel column chromatography eluting with 5-10% MeOH/CH_2Cl_2 as eluent to afford **BF** (0.3 g, 0.71 mmol, 59%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.20 (bs, 1H), 9.94 (bs, 1H), 9.58 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.40 (s, 1H), 8.33 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 3.18 (s, 3H). MS (ESI): m/z 421 $[M]^+$.

To a mixture of **BF** (0.16 g, 0.37 mmol) and 2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethanol (149 mg, 0.56 mmol) in 1,4-dioxane/EtOH/H_2O (20 mL) was added Cs_2CO_3 (0.37g, 1.13 mmol). The reaction mixture was degassed by purging with inert atmosphere for 20 min. To the resulting reaction mixture was added $Pd(PPh_3)_4$ (65.8 mg, 0.05 mmol) and the reaction was degassed for another 5 min. The resulting reaction mixture was stirred for 12 h at reflux temperature. Progress of the reaction was monitored by TLC. The volatiles were then evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 8% MeOH/CH_2Cl_2 as eluent to afford **17** (12 mg, 0.025 mmol, 6.6%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.22 (bs, 1H), 9.96 (bs, 1H), 9.55 (s, 1H), 8.81 (d, J = 6.0 Hz, 1H), 8.39 (d, J = 9.0 Hz, 2H), 8.02 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.90 (t, J = 5.5 Hz, 1H), 4.73 (t, J = 5.5 Hz, 2H), 3.60-3.56 (m, 2H), 3.19-3.14 (m, 5H). MS (ESI): 477 $[M]^+$. HPLC: 93.19%

Scheme 15



Example 18

***N*-hydroxy-2-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)quinolin-4-yl)acetamide (18)**

To a stirred solution of 2-bromoquinoline-4-carboxylic acid (**BG**; 200 mg, 0.79 mmol) in toluene (10 mL) under inert atmosphere were added thionyl chloride (0.22 mL, 3.17 mmol) and DMF (0.01 mL, catalytic) at RT. The reaction was heated to reflux for 1 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was dissolved in toluene (10 mL) under inert atmosphere and diazomethane in ether (10 mL) was added at 0 °C and stirred for 30 min. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with *n*-hexane (2x5 mL) to afford **BH** (170 mg, 80%) as a pale brown solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.34-8.32 (m, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 5.78 (br s, 1H).

To a stirred solution of **BH** (170 mg, 0.61 mmol) in THF:MeOH (1:1, 5 mL) under inert atmosphere was added a solution of silver benzoate (32.4 mg, 0.14 mmol) in triethylamine (0.3 mL, 1.97 mmol) dropwise at RT and stirred for 12 h. The reaction was monitored by TLC, after complete consumption of the starting material, the reaction mass was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude.

The crude was purified by silica gel column chromatography eluting with 10-15% EtOAc/hexanes to afford **BI** (110 mg, 64%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 4.04 (s, 2H), 3.71 (s, 3H).

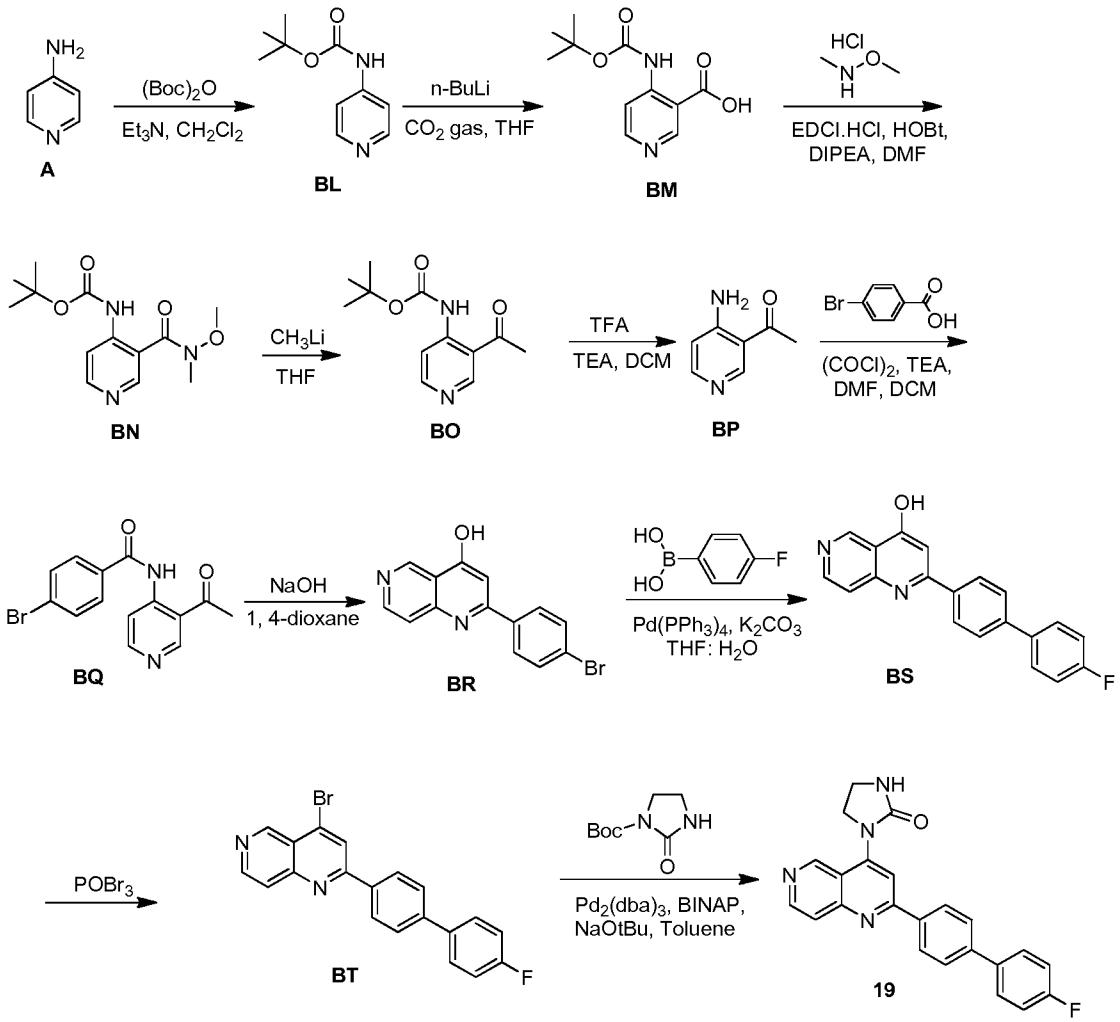
To a stirred solution of **BI** (100 mg, 0.35 mmol) in THF: H_2O (4: 1, 20 mL) under inert atmosphere were added (4-bromophenyl) boronic acid (86 mg, 0.42 mmol) and sodium carbonate (150 mg, 1.42 mmol) at RT and purged with argon for 20 min. Then $Pd(dppf)_2Cl_2$ (39 mg, 0.05 mmol) was added to the reaction mixture and the reaction mixture was heated to reflux and stirred for 16 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT, diluted with water (10 mL) and the compound was extracted with EtOAc (2x10 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-5% EtOAc/hexanes to afford **BJ** (50 mg, 39%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22-8.17 (m, 1H), 8.06-7.98 (m, 3H), 7.85-7.70 (m, 3H), 7.65 (d, J = 8.5 Hz, 2H), 4.15-4.13 (m, 2H), 3.72 (s, 3H).

To a stirred solution of **BJ** (100 mg, 0.28 mmol) in 1,4-dioxane:ethanol:water (3:1:1, 20 mL) under inert atmosphere were added 2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl amino)ethanol (110 mg, 0.42 mmol) and cesium carbonate (366 mg, 1.12 mmol) at RT. Theb reaction mixture was purged with argon for 30 min. Then $Pd(PPh_3)_4$ (32 mg, 0.02 mmol) was added to the reaction mixture and the reaction mixture was heated to reflux and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 40% EtOAc/hexanes to afford **BK** (20 mg, 13%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.29 (d, *J* = 8.0 Hz, 2H), 8.10-8.05 (m, 3H), 7.79-7.70 (m, 3H), 7.60 (t, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 5.80 (t, *J* = 6.0 Hz, 1H), 4.70 (t, *J* = 6.0 Hz, 1H), 3.60-3.57 (m, 2H), 3.17-3.14 (m, 2H), 2.79-2.77 (m, 3H).

To a stirred solution of **BK** (100 mg, 0.24 mmol) in MeOH:CH_2Cl_2 (3:1, 12 mL) under inert atmosphere was added 50% aq. hydroxyl amine solution (2.4 mL) at 0 °C and the reaction mixture was stirred for 10 min. Then a sodium hydroxide solution (77 mg in 1 mL water, 1.94 mmol) was added to the reaction mixture and stirred for 30 min. The reaction was warmed to RT and stirred for 2 h. After complete consumption of the starting material, the volatiles were

evaporated under reduced pressure. The residue was diluted with water (20 mL) and the aqueous layer was acidified with acetic acid to pH~6. The compound was extracted with 20% MeOH/CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and dried under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (8-10% MeOH/CH_2Cl_2) to afford **18** (48 mg, 48%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.95 (s, 1H), 8.27 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 1H), 8.09-8.06 (m, 2H), 7.76 (d, J = 8.5 Hz, 3H), 7.60 (t, J = 7.0 Hz, 2H), 7.55 (d, J = 9.0 Hz, 1H), 6.71 (d, J = 8.5 Hz, 2H), 5.79 (t, J = 5.5 Hz, 1H), 4.70 (t, J = 5.5 Hz, 1H), 3.92 (s, 2H), 3.60-3.57 (m, 2H), 3.18-3.14 (m, 2H). MS (ESI): m/z 414.2 $[M+1]^+$. HPLC Purity: 92.63%

Scheme 16



Example 19

1-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidin-2-one (19)

To a stirred solution of pyridin-4-amine (**A**; 100 g, 1.06 mol) in CH_2Cl_2 (1 L) under inert atmosphere were added triethylamine (161.47 g, 1.59 mol) and Boc-anhydride (255 g, 1.17 mol) at 0 °C. The reaction was warmed to RT and stirred for 3 h. After complete consumption of the starting material, the reaction mixture was diluted with water (400 mL) and the compound was extracted with CH_2Cl_2 (2x500 mL). The combined organic extracts were washed with water (300 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **BL** (190 g, 90%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.80 (s, 1H), 8.33 (d, J = 5.5 Hz, 2H), 7.41 (d, J = 6.5 Hz, 2H), 1.48 (s, 9H).

To a stirred solution of **BL** (12 g, 0.06 mol) in dry THF (200 mL) under inert atmosphere was added *n*-butyl lithium (79.12 mL, 0.18 mol) at -78 °C. The reaction was warmed to 0 °C and stirred for 30 min. Carbon dioxide gas was added to the reaction mass at -78 °C for 1 h, then at RT for 1 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was diluted with water (200 mL) and washed with diethyl ether (2x150 mL). The aqueous layer was acidified with citric acid to pH~4. The obtained solid was filtered and dried under vacuum to afford **BM** (5.1 g, 35%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.76 (br s, 1H), 8.96 (s, 1H), 8.52 (d, J = 15.0 Hz, 1H), 8.22 (d, J = 15.0 Hz, 1H), 1.49 (s, 9H).

To a stirred solution of **BM** (5.1 g, 0.02 mol) in DMF (10 mL) under inert atmosphere were added EDCI·HCl (6.14 g, 0.03 mol), HOBt (4.33 g, 0.03 mol), diisopropylethyl amine (5.53 g, 0.04 mol) and N,O-dimethylhydroxylamine hydrochloride (4.18 g, 0.04 mol) at 0 °C. The reaction was warmed to RT and stirred for 16 h. After complete consumption of the starting material, the reaction mixture was diluted with water (40 mL) and the compound was extracted with diethyl ether (3x40 mL). The combined organic extracts were washed with water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **BN** (2.5 g, 42%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 8.74 (s, 1H), 8.47 (d, J = 15.0 Hz, 1H), 8.25 (d, J = 15.0 Hz, 1H), 3.58 (s, 3H), 3.41 (s, 3H), 1.52 (s, 9H).

To a stirred solution of **BN** (12 g, 42.70 mol) in THF (150 mL) under inert atmosphere was added methyl lithium (4.05 g, 0.19 mol) at -78 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the reaction mixture was diluted with a saturated ammonium chloride solution (80 mL) and the compound was extracted with

diethyl ether (3x60 mL). The combined organic extracts were washed with water (60 mL), brine (60 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 40% EtOAc/hexanes to afford **BO** (11.5 g, 58%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.04 (br s, 1H), 9.03 (s, 1H), 8.53 (d, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 6.0 Hz, 1H), 2.68 (s, 3H), 1.53 (s, 9H).

To a stirred solution of **BO** (11.5 g, 48.72 mmol) in CH_2Cl_2 (120 mL) under inert atmosphere was added trifluoroacetic acid (55.8 mL, 730.8 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure, co-distilled with toluene (2x20 mL) and triturated with diethyl ether (2x20 mL). The residue was dissoved in CH_2Cl_2 (60 mL), triethylamine (60 mL) was added and stirred for 30 min. The volatiles were evaporated under reduced pressure and triturated with diethyl ether (2x40 mL) to obtain the crude. The crude was purified through column chromatography eluting with 60% EtOAc/hexanes to afford **BP** (4 g, 60%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.18 (br s, 1H), 9.06 (br s, 1H), 8.98 (s, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 2.50 (s, 3H).

To a stirred solution of *p*-bromo benzoic acid (12 g, 59.70 mmol) in CH_2Cl_2 (50 mL) under inert atmosphere were added oxalyl chloride (6.5 mL, 71.64 mmol) and DMF (0.3 mL, catalytic) at 0 °C. The reaction was warmed to RT and stirred for 1 h. The volatiles were evaporated under reduced pressure to obtain the acid chloride. To a stirred solution of **BP** (4 g, 29.41 mmol) in CH_2Cl_2 (25 mL) under inert atmosphere at -20 °C were added the freshly prepared acid chloride (12.9 g, 58.76 mmol) in CH_2Cl_2 (25 mL) dropwise for 15 min and triethylamine (12.7 mL, 88.24 mmol). The reaction was warmed to RT and and stirred for 2 h. After complete consumption of the starting material, the reaction mixture was diluted with saturated sodium bicarbonate solution (50 mL) and the compound was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **BQ** (8 g, 85%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.80 (br s, 1H), 9.17 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.68 (d, *J* = 6.0 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 2.77 (s, 3H).

To a stirred solution of **BQ** (8 g, 25.07 mmol) in 1,4-dioxane (70 mL) under inert atmosphere was added sodium hydroxide (3.51 g, 87.75 mmol) at RT in a sealed tube. The reaction was heated at 100 °C and stirred for 2 h. After complete consumption of the starting material, the

volatiles were evaporated under reduced pressure. The residue was diluted with water (50 mL) and washed with diethyl ether (2x40 mL). The aqueous layer was acidified with 2 N HCl to pH~6-7. The obtained solid was filtered, triturated with methanol (2x10 mL), diethyl ether (2x10 mL), pentane (2x10 mL) and dried under vacuum to afford **BR** (7 g, 93%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.03 (br s, 1H), 9.22 (s, 1H), 8.64 (d, J = 6.0 Hz, 1H), 7.87-7.81 (m, 4H), 7.70-7.64 (m, 1H), 6.52 (br s, 1H).

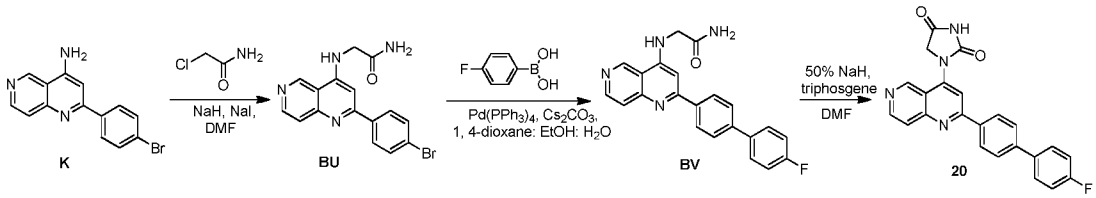
To a stirred solution of **BR** (7 g, 23.25 mmol) in THF:water (3:1, 280 mL) under inert atmosphere were added *p*-fluoro benzene boronic acid (3.90 g, 27.87 mmol) and potassium carbonate (9.62g, 69.71 mmol) at RT and purged under argon for 30 min. Then tetrakis(triphenylphosphino) palladium (0) (2.68 g, 2.32 mmol) was added to the reaction mass and again purged for 10 min. The reaction mixture was heated to reflux and stirred for 12 h. After complete consumption of the starting material, the reaction mass was filtered and washed with 50% MeOH:CH_2Cl_2 (2x40 mL). The aqueous layer was acidified with 2 N HCl to pH~6-7. The precipitate was filtered, triturated with methanol (2x10 mL), diethyl ether (2x10 mL), pentane (2x10 mL) and dried under vacuum to afford **BS** (5.2 g, 71%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.97 (br s, 1H), 9.22 (s, 1H), 8.64 (d, J = 6.0 Hz, 1H), 7.96-7.82 (m, 6H), 7.64 (d, J = 6.0 Hz, 1H), 7.35 (t, J = 9.0 Hz, 2H), 6.56 (s, 1H).

A stirred solution of **BS** (1 g, 3.16 mmol) in phosphorous oxybromide (1.8g, 9.49 mmol) under inert atmosphere was heated to 110 °C and stirred for 2 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was basified with solid sodium bicarbonate to pH~6-7. Then the reaction mass was diluted with water (30 mL) and the compound was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with water (30 mL), a brine solution (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **BT** (550 mg, 46%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.29 (s, 1H), 8.26 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 6.0 Hz, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.63 (t, J = 9.0 Hz, 2H), 7.18 (t, J = 9.0 Hz, 2H).

To a stirred solution of **BT** (100 mg, 0.26 mmol) in dry toluene (20 mL) under inert atmosphere were added tert-butyl 2-oxoimidazolidine-1-carboxylate (58 mg, 0.31 mmol), BINAP (25 mg, 0.03 mmol) and sodium tert-butoxide (38 mg, 0.39 mmol) at RT and purged under argon for 30 min. Then $Pd_2(dba)_3$ (12 mg, 0.013 mmol) was added to the reaction mass and again purged for 15 min. The reaction mass was heated to reflux and stirred for 20 h. The reaction was monitored by TLC. After complete consumption of the starting material, the

volatiles were evaporated under reduced pressure. The residue was diluted with water (15 mL) and the compound was extracted with 10% MeOH:CH_2Cl_2 (3x15 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5-8% MeOH/CH_2Cl_2 to afford **19** (10 mg, 8%) as a pale brown liquid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.38 (br s, 1H), 8.67 (br s, 1H), 8.42 (d, J = 8.5 Hz, 2H), 8.06 (s, 1H), 7.93-7.83 (m, 4H), 7.56 (s, 1H), 7.35 (t, J = 9.0 Hz, 2H), 4.25 (t, J = 7.5 Hz, 2H), 3.61 (t, J = 7.5 Hz, 2H). Mass: m/z 385.7 $[M+1]^+$. HPLC Purity: 95.92%

Scheme 17



Example 20

1-(2-(4'-fluoro-[1, 1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (20)

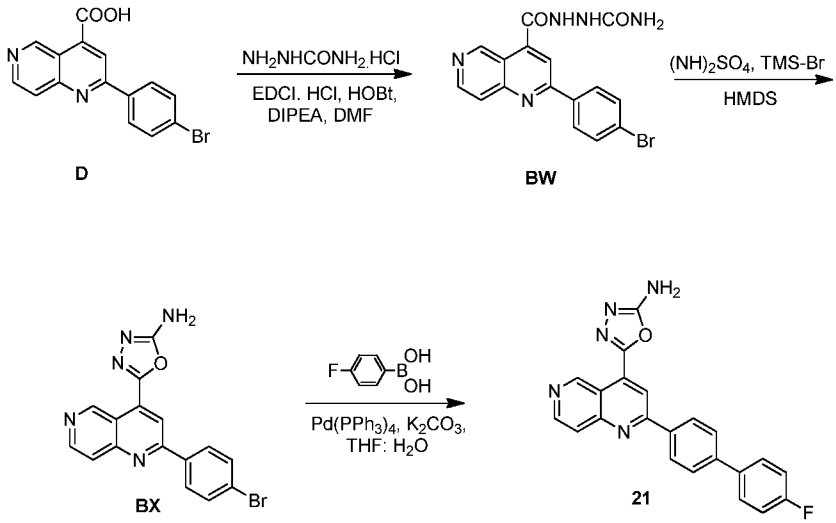
To a stirred solution of 50% sodium hydride (0.8 g, 33.33 mmol) in DMF (60 mL) under inert atmosphere was added 2-(4-bromophenyl)-1,6-naphthyridin-4-amine (**K**; 2 g, 6.68 mmol) portionwise for 10 min at 0 °C. The reaction was warmed to RT and stirred for 2 h. To the reaction mass cooled to 0 °C were added 2-chloro acetamide (1.87 g, 20.00 mmol) and sodium iodide (1.0026 g, 6.68 mmol). The reaction was then heated to 100 °C and stirred for 3 h. After complete consumption of the starting material, the reaction mass was diluted with ice cold water (40 mL) and the compound was extracted with EtOAc (2x40 mL). The combined organic extracts were washed with water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 10% MeOH/CH_2Cl_2 to afford **BU** (510 mg, 21%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.56 (s, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.23 (t, J = 6.0 Hz, 1H), 8.13 (t, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 6.0 Hz, 2H), 7.22 (br s, 1H), 6.94 (s, 1H), 4.06 (d, J = 6.0 Hz, 2H).

To a stirred solution of **BU** (510 mg, 1.43 mmol) in 1,4-dioxane:methanol:water (4:2:1, 50 mL) under inert atmosphere were added 4-fluorobenzeneboronic acid (240 mg, 1.71 mmol) and cesium carbonate (1.4g, 4.29 mmol) After purging the reaction under argon for 30 min, tetrakis(triphenylphosphino) palladium(0) (160 mg, 0.13 mmol) was added to the reaction. The reaction was heated to 90 °C and stirred for 5 h. After complete consumption of the

starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 10% MeOH/CH_2Cl_2 to afford **BV** (350 mg, 66%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.59 (d, J = 6.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.19 (br s, 1H), 7.81 (t, J = 8.0 Hz, 4H), 7.69 (d, J = 6.0 Hz, 1H), 7.65 (s, 1H), 7.33 (t, J = 8.5 Hz, 2H), 7.22 (s, 1H), 6.98 (s, 1H), 4.07 (d, J = 7.0 Hz, 2H).

To a stirred solution of **BV** (250 mg, 0.67 mmol) in DMF (10 mL) under inert atmosphere was added 50% sodium hydride (129 mg, 2.68 mmol) portionwise for 5 min at 0 °C. After stirring for 15 min, the reaction was warmed to RT and stirred for 30 min. Then triphosgene (398 mg, 1.34 mmol) was added at 0 °C and the reaction was stirred for 30 min at 0 °C and at RT for 30 min. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction was diluted with ice cold water (20 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **20** (6 mg, 3%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.53 (s, 1H), 9.48 (br s, 1H), 8.78 (br s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.40 (s, 1H), 8.00 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.86 (t, J = 8.5 Hz, 2H), 7.35 (t, J = 8.5 Hz, 2H), 4.85 (s, 2H). MS (ESI): m/z 399.4 $[M+1]^+$. HPLC Purity: 82.78%

Scheme 18



Example 21

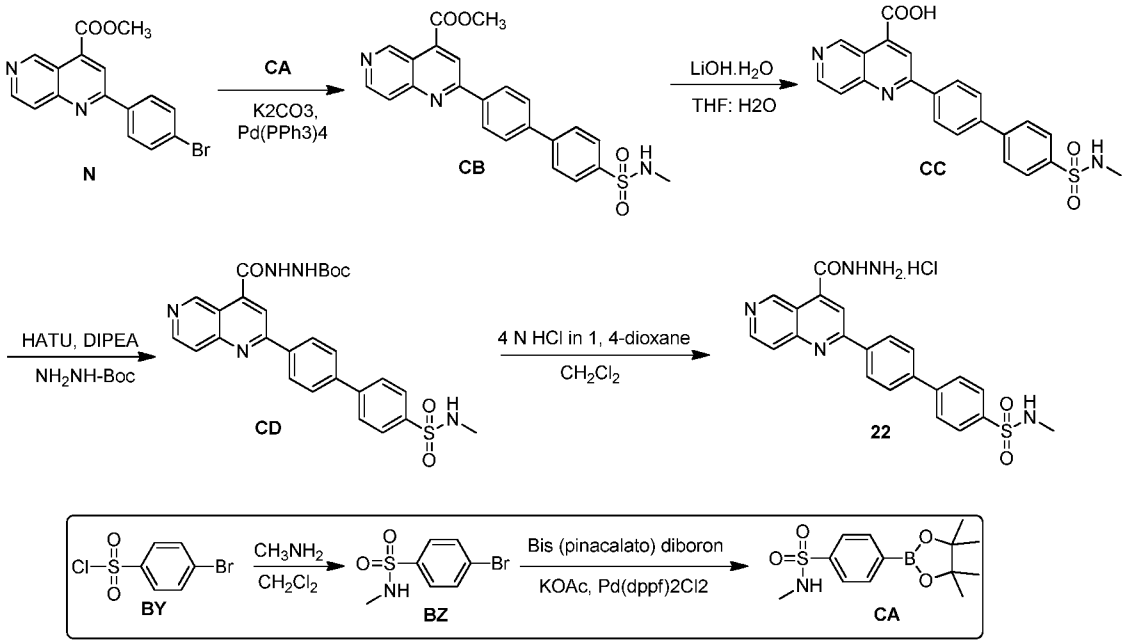
5-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-1,3,4-oxadiazol-2-amine (21)

To a stirred solution of 2-(4-bromophenyl)-1,6-naphthyridine-4-carboxylic acid (**D**; 2 g, 6.09 mmol) in DMF (20 mL) under inert atmosphere were added EDCI·HCl (1.5g, 7.85 mmol), HOBt (900mg, 6.66 mmol) and diisopropylethyl amine (3.91 g, 30.22 mmol) at RT. The reaction was stirred for 30 min. Then semicarbazide hydrochloride (1.35 g, 12.10 mmol) was added to the reaction mass and again stirred at RT for 24 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was diluted with water (40 mL) and the compound was extracted with EtOAc (2x40 mL). The combined organic extracts were washed with water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified via column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **BW** (1 g, 43%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.55 (s, 1H), 9.69 (s, 1H), 8.81 (d, J = 6.0 Hz, 1H), 8.46 (br s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1H), 8.15 (br s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 6.26 (br s, 2H).

To a stirred solution of **BW** (300 mg, 0.77 mmol) in HMDS (10 mL) under inert atmosphere were added TMS-bromide (1.19 g, 7.77 mmol) and ammonium sulphate (41 mg, 0.31 mmol) at RT. The reaction mixture was heated to reflux and stirred for 12 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified via column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **BX** (100 mg, 35%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.42 (s, 1H), 8.25 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.77 (s, 2H).

To a stirred solution of **BX** (50 mg, 0.13 mmol) in THF:water (10:1, 11 mL) under inert atmosphere were added (4-fluorophenyl)boronic acid (28.6 mg, 0.20 mmol) and potassium carbonate (56 mg, 0.40 mmol) at RT. The reaction was purged under argon for 1 h. Then $Pd(PPh_3)_4$ (15.7 mg, 0.001 mmol) was added to the reaction mass and the reaction was heated to reflux and stirred for 8 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified through column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **21** (25 mg, 48%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.85 (d, J = 6.0 Hz, 1H), 8.46 (s, 1H), 8.38 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.85 (t, J = 8.0 Hz, 2H), 7.77 (s, 2H), 7.35 (t, J = 8.0 Hz, 2H). Mass: m/z 384.4 $[M+1]^+$. HPLC Purity: 99.10%

Scheme 19



Example 22

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-*N*-methyl-[1,1'-biphenyl]-4-sulfonamide hydrochloride (22)

To a stirred solution of 4-bromobenzene-1-sulfony chloride (**BY**; 2.5 g, 9.78 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere was added 2M methylamine in THF (10 mL, 19.56 mmol) at 0 °C. The reaction was then warmed to RT and stirred for 2 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was neutralized with saturated sodium bicarbonate solution (30 mL) and the compound was extracted with CH_2Cl_2 (3x25 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was triturated with diethyl ether/pentane (3x15 mL) to afford **BZ** (2 g, 94%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.83 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.54 (s, 1H), 2.41 (d, J = 13.5 Hz, 3H). MS (ESI): m/z 250 $[M+1]^+$

To a stirred solution of **BZ** (500 mg, 2.00 mmol) in 1,4-dioxane (20 mL) under inert atmosphere were added bis(pinacalato)diboron (561 mg, 2.20 mmol) and fused potassium acetate (590 mg, 6.02 mmol) at RT. The reaction was purged with argon for 30 min. Then $Pd(dppf)_2Cl_2$ (146 mg, 0.2 mmol) was added to the reaction mixture and the reaction was heated to 100 °C and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (30-40% EtOAc/hexanes) to afford

CA (400 mg, 67%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 4.27 (d, *J* = 5.5 Hz, 1H), 2.65 (d, *J* = 5.5 Hz, 3H), 1.35 (s, 12H). MS (ESI): *m/z* 298 $[M+1]^+$

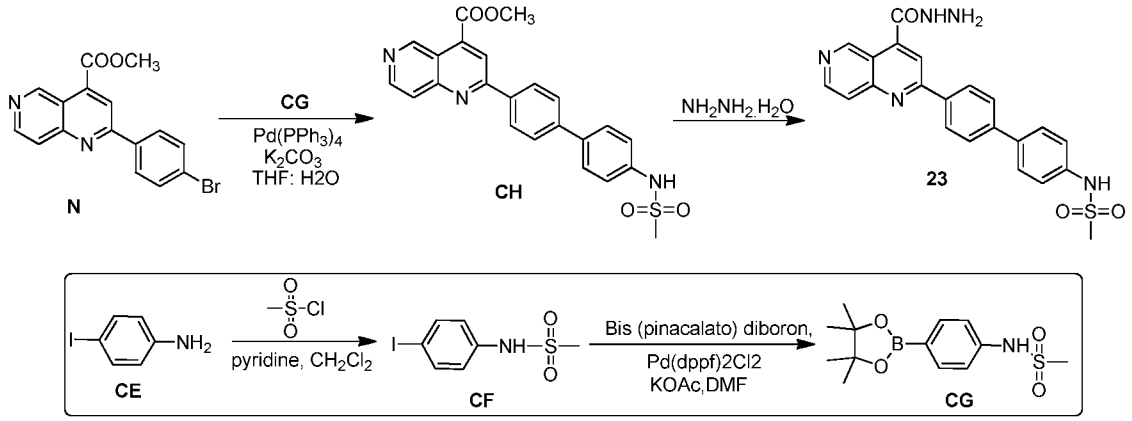
To a stirred solution **N** (370 mg, 1.07 mmol) in THF:H_2O (1:1, 10 mL) under inert atmosphere were added **CA** (384 mg, 1.29 mmol) and potassium carbonate (446 mg, 3.23 mmol) at RT. The reaction was purged with argon for 30 min. Then $Pd(PPh_3)_4$ (63 mg, 0.053 mmol) was added to the reaction mixture and the reaction was heated to reflux and stirred for 8 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by preparative HPLC to afford **CB** (250 mg, 54%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.69 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 6.0 Hz, 1H), 8.04-8.00 (m, 4H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.55-7.52 (m, 1H), 4.08 (s, 3H), 2.47 (d, *J* = 12.0 Hz, 3H). MS (ESI): *m/z* 434 $[M+1]^+$

To a stirred solution of **CB** (100 mg, 0.23 mmol) in THF:H_2O (1:1, 5 mL) under inert atmosphere was added lithium hydroxide monohydrate (40 mg, 0.69 mmol) at 0 °C. The reaction was warmed to RT and stirred for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was diluted with water (10 mL) and acidified with a glacial acetic acid solution to pH~4 and then filtered. The obtained solid was triturated with toluene (2x5 mL) to afford **CC** (80 mg, 83%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.03 (s, 1H), 8.81 (d, *J* = 5.5 Hz, 1H), 8.62 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 2H), 8.03 (d, *J* = 7.5 Hz, 3H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.54 (s, 1H), 2.47 (d, *J* = 13.5 Hz, 3H). MS (ESI): *m/z* 420 $[M+1]^+$

To a stirred solution of **CC** (80 mg, 0.18 mmol) in DMF (2 mL) under inert atmosphere were added HATU (144 mg, 0.36 mmol), diisopropyl ethyl amine (0.08 mL, 0.55 mmol) and Boc-hydrazine (48 mg, 0.36 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mixture was diluted with water (10 mL) and the compound was extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by preparative HPLC to afford **CD** (40 mg, 15%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.72 (s, 1H), 9.59 (s, 1H), 9.48 (s, 1H), 9.30 (s, 1H), 8.84 (d, *J* = 5.5 Hz, 1H), 8.50 (d, *J* = 7.5 Hz, 3H), 8.35-8.33 (m, 1H), 8.06-7.98 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 4.5 Hz, 1H), 2.87 (s, 3H), 1.38 (s, 9H). MS (ESI): *m/z* 534 $[M+1]^+$

To a stirred solution of **CD** (20 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere was added 4 N HCl in 1, 4-dioxane (1 mL) at 0 °C. The reaction was warmed to RT and stirred for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with IPA:diethyl ether (2x4 mL) followed by pentane (2x4 mL) to afford **22** (20 mg as HCl salt) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.10-11.90 (br s, 1H), 9.72 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.58 (s, 1H), 8.55 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 6.0 Hz, 1H), 8.04 (t, J = 8.5 Hz, 4H), 7.91 (d, J = 8.5 Hz, 2H), 7.56 (s, 1H), 2.46 (d, J = 13.0 Hz, 3H). MS (ESI): m/z 434 $[M+1]^+$. HPLC Purity: 96.02%

Scheme 20



Example 23

***N*-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)methane sulfonamide (23)**

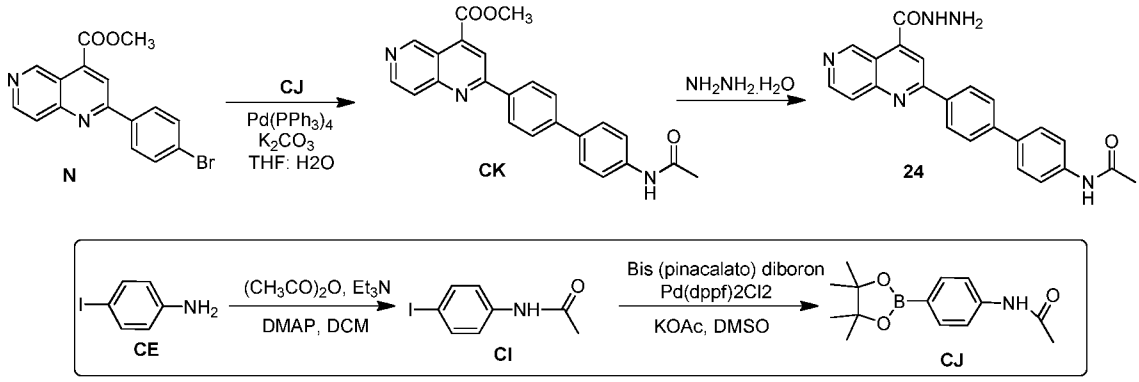
To a stirred solution of 4-iodoaniline (**CE**; 2 g, 9.13 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere were added pyridine (1.47 mL, 18.26 mmol), methane sulfonyl chloride (1.06 mL, 13.69 mmol) at 0 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the reaction mass was quenched with a 1 N HCl solution (30 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **CF** (2.2 g, 81%) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 3.68 (s, 1H), 3.02 (s, 3H).

To a stirred solution of **CF** (500 mg, 1.68 mmol) in DMF (20 mL) under inert atmosphere were added bis(pinacalato)diboron (470 mg, 1.85 mmol) and fused potassium acetate (495 mg, 5.05 mmol) at RT and purged with argon for 30 min. Then $Pd(dppf)_2Cl_2$ (123 mg, 0.16 mmol) was added to the reaction mixture and the reaction was heated to 100°C and stirred for 4 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT, diluted with water (20 mL) and the compound was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) to afford **CG** (320 mg, 64%) as a colorless sticky solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.95 (s, 3H), 1.33 (s, 12H).

To a stirred solution of **N** (150 mg, 0.43 mmol) in THF:H_2O (10:1, 11 mL) under inert atmosphere were added **CG** (300 mg, 1.00 mmol) and potassium carbonate (181 mg, 1.31 mmol) at RT. The reaction was purged with argon for 30 min. Then tetrakis(triphenyl phosphine) palladium(0) (50mg, 0.04 mmol) was added to the reaction mixture and the reaction was heated to reflux and stirred for 4 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (5% $MeOH/CH_2Cl_2$) to afford **CH** (100 mg, 52.9%) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.92 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.65 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.62-7.53 (m, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.06 (s, 3H), 3.04 (s, 3H).

A stirred solution of **CH** (100 mg, 0.23 mmol) in hydrazine hydrate (4 mL) under inert atmosphere was heated to 70 °C and stirred for 30 min. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and the reaction mass was diluted with water (15 mL). The compound was extracted with IPA/CH_2Cl_2 (3x20 mL) to afford **23** (15 mg, 15%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.19 (br s, 1H), 9.80 (br s, 1H), 9.63 (s, 1H), 8.79 (d, *J* = 6.0 Hz, 1H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.34 (s, 1H), 8.01 (d, *J* = 6.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.78 (s, 2H), 3.04 (s, 3H). MS (ESI): *m/z* 432.5 $[M-1]^+$. HPLC Purity: 90.88%

Scheme 21



Example 24

***N*-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl) acetamide (24)**

To a stirred solution of 4-iodoaniline (**CE**; 1 g, 4.56 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere were added triethylamine (1.6 mL, 11.41 mmol), *p*-dimethylaminopyridine (10 mg, catalytic) and acetic anhydride (0.51 mL, 5.47 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction was warmed to RT and stirred for 2 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was diluted with water (30 mL) and the compound was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **CI** (850 mg, 71%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.16 (br s, 1H), 2.17 (s, 3H). MS (ESI): *m/z* 262 $[M+1]^+$

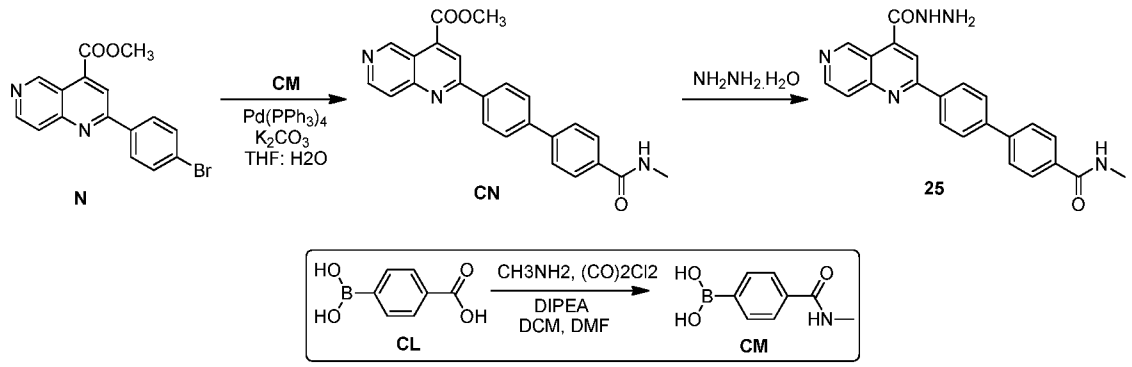
To a stirred solution of **CI** (300 mg, 1.14 mmol) in DMSO (15 mL) under inert atmosphere were added bis(pinacalato)diboron (321 mg, 1.26 mmol) and fused potassium acetate (338 mg, 3.44 mmol) at RT. The reaction was purged with argon for 30 min. Then $Pd(dppf)_2Cl_2$ (84 mg, 0.11 mmol) was added to the reaction mixture and the reaction was heated to 100 °C and stirred for 4 h. After complete consumption of the starting material, the reaction mass was cooled to RT, was diluted with water (20 mL), and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to afford **CJ** (150 mg, 50%) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.17 (br s, 1H), 2.18 (s, 3H), 1.33 (s, 12H). MS (ESI): *m/z* 262 $[M+1]^+$

To a stirred solution of **N** (150 mg, 0.43 mmol) in THF:H_2O (10:1, 11 mL) under inert atmosphere were added **CJ** (149 mg, 0.57 mmol) and potassium carbonate (181 mg, 1.31

mmol) at RT. The reaction was purged with argon for 30 min. Then tetrakis(triphenylphosphine) palladium(0) (50 mg, 0.04 mmol) was added to the reaction mixture and the reaction was heated to reflux and stirred for 4 h. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (3% MeOH/CH_2Cl_2) to afford **CK** (75 mg, 43%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 9.92 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.64 (s, 1H), 8.42 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.76-7.71 (m, 4H), 4.07 (s, 3H), 2.07 (s, 3H). MS (ESI): m/z 396.5 $[M-1]^+$

A stirred solution of **CK** (75 mg, 0.18 mmol) was dissolved in hydrazine hydrate (3 mL) under inert atmosphere. The reaction was heated to 90 °C and stirred for 30 min. After complete consumption of the starting material, the reaction mass was cooled to RT and the reaction mass was filtered under reduced pressure. The obtained solid was triturated with CH_2Cl_2 (2x5 mL) to afford **24** (35 mg, 47%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.20 (br s, 1H), 10.08 (s, 1H), 9.63 (s, 1H), 8.79 (d, J = 6.0 Hz, 1H), 8.43 (d, J = 8.0 Hz, 2H), 8.33 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.77-7.72 (m, 4H), 4.78 (br s, 2H), 2.08 (s, 3H). MS (ESI): m/z 398 $[M+1]^+$. HPLC Purity: 98.04%

Scheme 22



Example 25

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-*N*-methyl-[1,1'-biphenyl]-4-carboxamide (25)

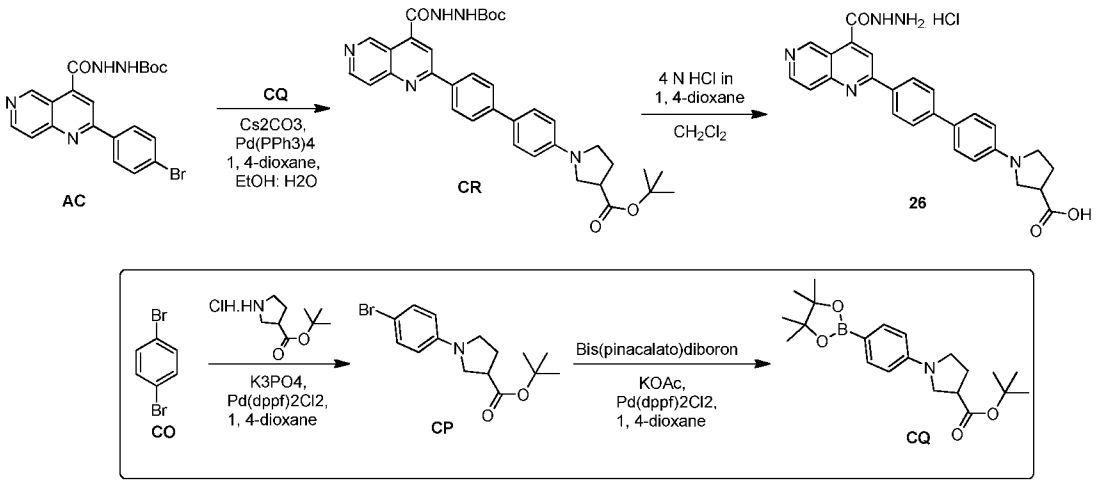
To a stirred solution of 4-boronobenzoic acid (**CL**; 1.5 g, 9.03 mmol) in CH_2Cl_2 (50 mL) under inert atmosphere were added DMF (1.5 mL) and oxalyl chloride (1.77 mL, 19.88 mmol) at 0 °C. After stirring for 15 min at 0 °C, the reaction was warmed to RT and stirred for 30 min. Then the reaction mixture was heated to 40 °C and stirred for 3 h. After complete

consumption of the starting material, the volatiles were removed under reduced pressure. To the residue dissolved in DMF (5 mL) under inert atmosphere were added diisopropylamine (4.05 mL, 22.59 mmol) and methyl amine solution in 2 M THF (6 mL) at 0 °C. The reaction was warmed to RT and stirred for 16 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were removed under reduced pressure. The residue was diluted with water (25 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), 1 N HCl solution (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude **CM** (1.1 g, 68%) as a colorless sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (br s, 1H), 8.42 (br s, 1H), 8.14 (s, 1H), 7.83-7.75 (m, 2H), 3.62-3.55 (m, 3H), 2.77-2.76 (m, 2H).

To a stirred solution of **N** (300 mg, 0.87 mmol) in THF:H_2O (10:1, 22 mL) under inert atmosphere were added **CM** (314 mg, 1.75 mmol) and potassium carbonate (363 mg, 2.63 mmol) at RT. The reaction was purged with argon for 30 min. Then tetrakis(triphenylphosphine) palladium(0) (101 mg, 0.08 mmol) was added to the reaction mixture and the reaction was heated to reflux and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction was cooled to RT, diluted with water (15 mL), and extracted with EtOAc (2x15 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to afford **CN** (100 mg, 29%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.85 (d, J = 6.0 Hz, 1H), 8.67 (s, 1H), 8.53-8.52 (m, 1H), 8.47 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 6.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 4.08 (s, 3H), 2.82 (s, 3H). MS (ESI): m/z 398 $[M+1]^+$

A stirred solution of **CN** (100 mg, 0.25 mmol) in hydrazine hydrate (3 mL) under inert atmosphere was heated to 90 °C and stirred for 30 min. The reaction was monitored by TLC After complete consumption of the starting material, the reaction mass was cooled to RT and the reaction mass was filtered under reduced pressure. The obtained solid was triturated with CH_2Cl_2 (2x5 mL) to afford **25** (90 mg, 90%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (br s, 1H), 9.65 (s, 1H), 8.80 (d, J = 6.0 Hz, 1H), 8.53-8.52 (m, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.36 (s, 1H), 8.03-7.97 (m, 6H), 7.91 (d, J = 8.4 Hz, 1H), 4.80-4.78 (m, 2H), 2.83-2.82 (m, 3H). MS (ESI): m/z 398 $[M+1]^+$. HPLC Purity: 97.04%

Scheme 23



Example 26

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-3-carboxylic acid hydrochloride (26)

To a stirred solution of tert-butyl pyrrolidine-3-carboxylate hydrochloride (**CO**; 500 mg, 2.40 mmol) in 1,4-dioxane (40 mL) under inert atmosphere were added potassium phosphate (2.6 g, 12.03 mmol) and 1,4-dibromo benzene (681 mg, 2.88 mmol). The reaction was purged with argon for 30 min. To the reaction mixture was added $Pd(dppf)_2Cl_2$ (121 mg, 0.166 mmol) and the reaction was heated to 100 °C and stirred for 16 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (10-20% EtOAc/hexanes) to afford **CP** (350 mg, with a minor impurity) as a sticky white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 6.42 (d, J = 8.5 Hz, 2H), 3.49-3.41 (m, 2H), 3.36-3.27 (m, 2H), 3.12-3.09 (m, 1H), 2.26-2.22 (m, 2H), 1.45 (s, 9H). MS (ESI): *m/z* 326 $[M+1]^+$

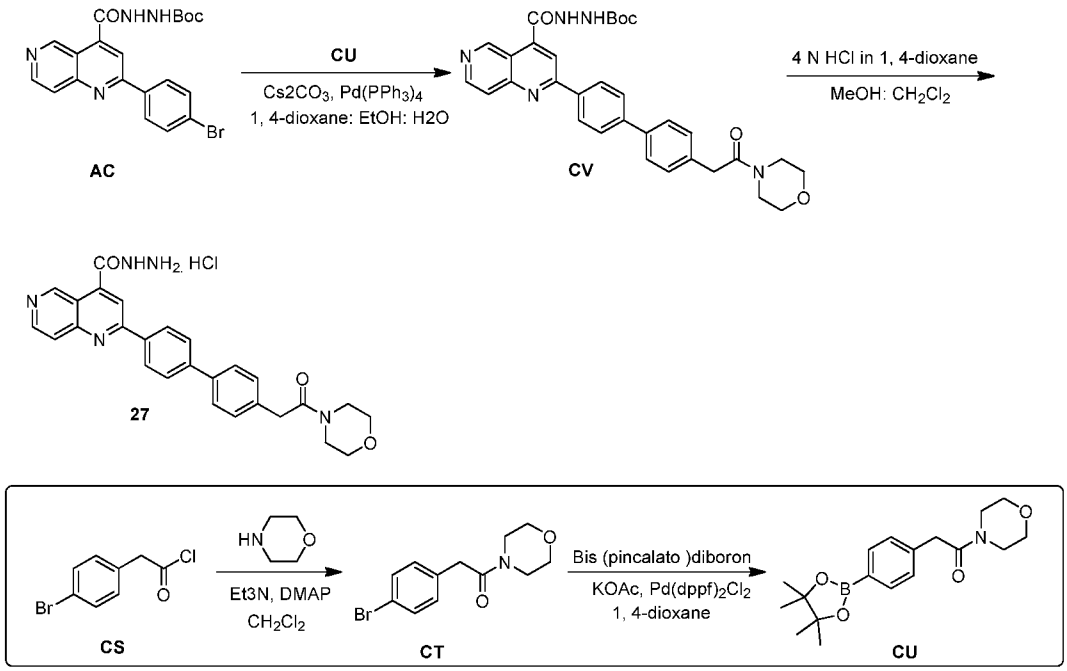
A stirred solution of **CP** (350 mg, 1.66 mmol) in 1,4-dioxane (20 mL) under inert atmosphere were added bis(pinacalato)diboron (300 mg, 1.81 mmol) and fused potassium acetate (316 mg, 3.22 mmol) at RT. The reaction was purged with argon for 30 min followed by the addition of $Pd(dppf)_2Cl_2$ (79 mg, 0.1 mmol). The reaction was heated to 100 °C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **CQ** (170 mg, 43%) as a sticky brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 3.55 (d, J = 8.5 Hz, 1H), 3.49 (d, J = 7.0 Hz, 1H), 3.45-3.42

(m, 1H), 3.35-3.33 (m, 1H), 3.12-3.09 (m, 1H), 2.60-2.21 (m, 2H), 1.54 (s, 9H), 1.34 (s, 12H). MS (ESI): *m/z* 374 $[M+1]^+$

To a stirred solution of **AC** (181 mg, 0.41 mmol) in 1,4-dioxane:ethanol:H_2O (4:2:1) under inert atmosphere was added **CQ** (170 mg, 0.45 mmol) and cesium carbonate (405 mg, 1.24 mmol) at RT. The reaction was purged with argon for 30 min followed by the addition of $Pd(PPh_3)_4$ (48 mg, 0.04 mmol). The reaction was heated to reflux and stirred for 8 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by preparative HPLC to afford **CR** (60 mg, 25%) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.72 (br s, 1H), 9.74 (br s, 1H), 9.25 (br s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 2H), 8.29 (s, 1H), 8.00 (d, *J* = 5.6 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.54-3.46 (m, 1H), 3.44-3.42 (m, 1H), 3.38-3.33 (m, 1H), 3.22-3.18 (m, 1H), 2.26-2.12 (m, 2H), 1.86 (s, 9H), 1.52 (s, 9H). MS (ESI): *m/z* 610 $[M+1]^+$

To a stirred solution of **CR** (60 mg, 0.09 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. The reaction was warmed to RT, stirred for 4 h. The reaction was monitored by TLC; after complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with IPA:diethyl ether (2x10 mL) followed by pentane (2x5 mL) to afford **26** (42mg as HCl salt) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.37 (br s, 1H), 9.77 (s, 1H), 8.89 (d, *J* = 6.4 Hz, 1H), 8.65 (s, 1H), 8.48 (d, *J* = 4.8 Hz, 2H), 8.26 (d, *J* = 6.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 3.56-3.46 (m, 2H), 3.39-3.34 (m, 2H), 3.25-3.21 (m, 1H), 2.26-2.17 (m, 2H). MS (ESI): *m/z* 510 $[M+1]^+$. HPLC Purity: 97.76 %

Scheme 24



Example 27

2-(4'-(2-morpholino-2-oxoethyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (27)

To a stirred solution of morpholine (1g, 11.47 mmol) in CH_2Cl_2 (40 mL) under inert atmosphere was added triethylamine (2.3g, 22.92 mmol) and *p*-dimethyl amino pyridine (140mg, 1.14 mmol) at 0 °C. To this was added 2-(4-bromophenyl) acetyl chloride (**CS**; 3.2g, 13.77 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the reaction was warmed to RT and stirred for 2 h. The reaction was monitored by TLC, after complete consumption of the starting material, the reaction mass was diluted with (30 mL) and the compound was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 1-2% MeOH/CH_2Cl_2 to afford **CT** (1.4 g, 45%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.66-3.64 (m, 6H), 3.54-3.52 (m, 2H), 3.43-3.42 (m, 2H).

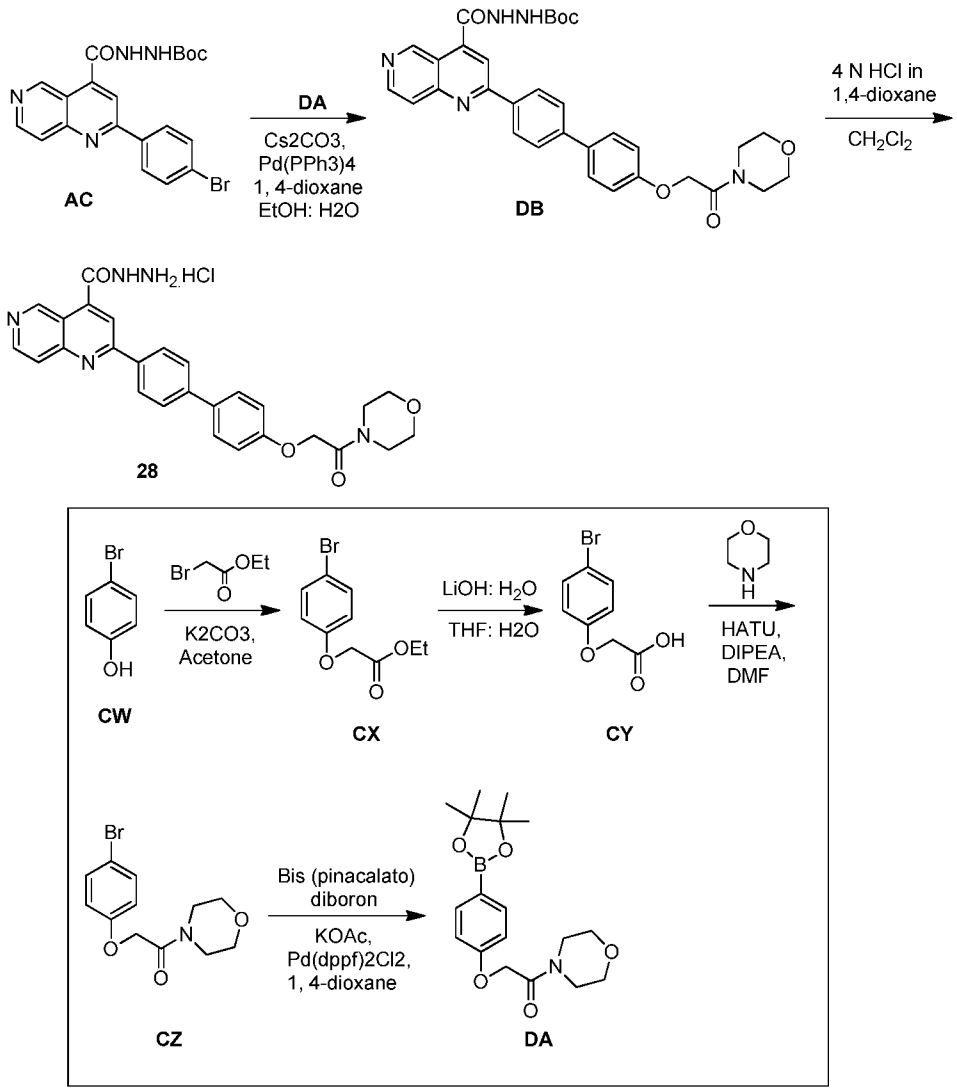
To a stirred solution of **CT** (1.4 g, 5.68 mmol) in 1,4-dioxane (30 mL) under inert atmosphere were added bis(pinacalato)diboron (1.56 g, 6.14 mmol) and fused potassium acetate (1.51 g, 15.41 mmol) at RT. The reaction was purged with argon for 20 min followed by the addition of $Pd(dppf)_2Cl_2$ (370 mg, 0.50 mmol). The reaction was heated to reflux and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and

filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 50-70% EtOAc/hexanes to afford **CU** (1.1 g, 66%) as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 2H), 3.63 (s, 4H), 3.43-3.41 (m, 2H), 3.39-3.38 (m, 2H), 1.34 (s, 12 H).

To a stirred solution of **AC** (300 mg, 0.67 mmol) in 1,4-dioxane:ethanol:H_2O (4:2:1; 21 mL) under inert atmosphere were added **CU** (260 mg, 0.78 mmol) and cesium carbonate (660 mg, 2.02 mmol) at RT. The reaction was then purged with argon for 20 min followed by the addition of $Pd(PPh_3)_4$ (78mg, 0.06 mmol). The reaction was heated to reflux and stirred for 7 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 3-4% MeOH:CH_2Cl_2 to afford **CV** (260 mg, 68%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.70 (br s, 1H), 9.29 (br s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 2H), 8.32 (br s, 1H), 8.04 (d, *J* = 6.0 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.79 (s, 2H), 3.56-3.47 (m, 8H), 1.49 (s, 9H).

To a stirred solution of **CV** (150 mg, 0.26 mmol) in MeOH:CH_2Cl_2 (1:4, 2 mL) under inert atmosphere was added a 4N HCl solution in 1,4-dioxane (3 mL) at 0 °C. The reaction was warmed to RT and stirred for 45 min. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with diisopropyl ether (2x10 mL) to afford **27** (100 mg as an HCl salt) as an orange solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.50 (br s, 1H), 9.67 (s, 1H), 8.84 (d, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 8.5 Hz, 3H), 8.10 (d, *J* = 6.0 Hz,1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.79 (s, 2H), 3.55-3.52 (m, 6H), 3.48-3.46 (m, 2H). MS (ESI): *m/z* 468.3 $[M+1]^+$. HPLC Purity: 98.25%

Scheme 25



Example 28

2-(4'-(2-morpholino-2-oxoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (28)

To a stirred solution of 4-bromophenol (**CW**; 10 g, 57.80 mmol) in acetone (150 mL) under inert atmosphere were added potassium carbonate (12 g, 86.70 mmol) and bromo ethyl acetate (7.7 mL, 69.40 mmol) at 0 °C. The reaction was warmed to RT and stirred for 16 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with water (40 mL) and was extracted with diethyl ether (2x50 mL). The combined organic extracts were washed with an aqueous 10% NaOH solution (40 mL), water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was recrystallized with ethanol (20 mL) to afford **CX** (13 g, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 9.5 Hz, 2H), 6.89 (d,

J = 9.0 Hz, 2H), 4.58 (s, 2H), 4.29-4.24 (m, 2H), 1.31-1.28 (m, 3H). MS (ESI): *m/z* 260 $[M+1]^+$

To a stirred solution of **CX** (7 g, 27.02 mmol) in THF:H_2O (1:1, 50 mL) under inert atmosphere was added lithium hydroxide monohydrate (11.3 g, 41.90 mmol) at 0 °C. The reaction was warmed to RT for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with water (40 mL) and acidified with HCl to pH~2 and filtered. The obtained solid was triturated with toluene (2x30 mL) to afford **CY** (4.5 g, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 13.03 (br s, 1H), 7.44 (d, *J* = 6.8 Hz, 2H), 6.89 (d, *J* = 6.8 Hz, 2H), 4.66 (s, 2H). MS (ESI): *m/z* 231 $[M+1]^+$

To a stirred solution of **CY** (500 mg, 2.16 mmol) in DMF (10 mL) under inert atmosphere were added HATU (2.1 g, 5.41 mmol) and diisopropylethylamine (0.04 mL, 0.27 mmol) at 0 °C. After the addition of morpholine (282mg, 3.24 mmol) at 0 °C, the reaction was warmed to RT and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (70-80% EtOAc/hexanes) to afford **CZ** (500 mg, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.0 Hz, 2H), 6.84 (d, *J* = 7.0 Hz, 2H), 4.67 (s, 2H), 3.67-3.63 (m, 4H), 3.62-3.57 (m, 4H). MS (ESI): *m/z* 301 $[M+1]^+$

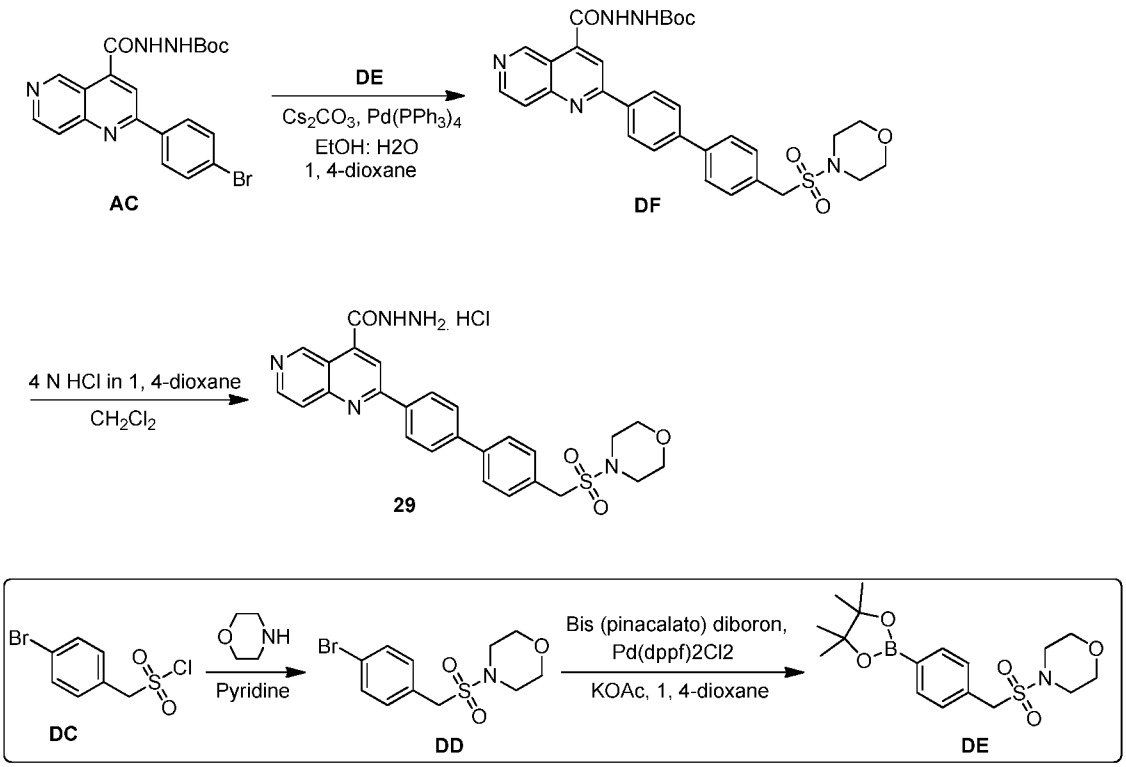
To a stirred solution of **CZ** (500 mg, 1.66 mmol) in 1,4-dioxane (20 mL) were added bis(pinacalato)diboron (634 mg, 2.49 mmol) and fused potassium acetate (489 mg, 4.99 mmol) at RT. After the reaction was purged with argon for 30 min, $Pd(dppf)_2Cl_2$ (121mg, 0.166 mmol) was added to the reaction. The reaction mixture was then heated to 100°C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography (50-70% EtOAc/hexanes) to afford **DA** (450 mg, 78%) as a sticky white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.71 (s, 2H), 3.64-3.60 (m, 8H), 1.26 (s, 12H). MS (ESI): *m/z* 348 $[M+1]^+$

To a stirred solution of **AC** (384 mg, 0.84 mmol) in 1,4-dioxane:ethanol:H_2O (4:2:1, 14 mL) under inert atmosphere were added **DA** (350 mg, 1.00 mmol) and cesium carbonate (808 mg, 2.52 mmol) at RT. After the reaction mixture was purged with argon for 30 min, $Pd(PPh_3)_4$

(97mg, 0.08 mmol) was added. The reaction was heated to reflux and stirred for 8 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography (2-5% CH_2Cl_2/MeOH) to afford **DB** (200 mg, 52%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.69 (br s, 1H), 9.29 (br s, 1H), 8.82 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 8.0 Hz, 2H), 8.31 (s, 1H), 8.03 (d, J = 6.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.91 (s, 2H), 3.63-3.58 (m, 4H), 3.50-3.48 (m, 4H), 1.49 (s, 9H). MS (ESI): m/z 584 $[M+1]^+$

To a stirred solution of **DB** (100 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C and stirred for 4 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with IPA:diethyl ether (2x10 mL) followed by pentane (2x5 mL) to afford **28** (28.7 mg as an HCl salt) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 9.75 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.61 (s, 1H), 8.50 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.92 (s, 2H), 3.63-3.58 (m, 4H), 3.50-3.48 (m, 4H). MS (ESI): m/z 484 $[M+1]^+$. HPLC Purity: 96.37%

Scheme 26



Example 29

2-(4'-((morpholinosulfonyl)methyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (29)

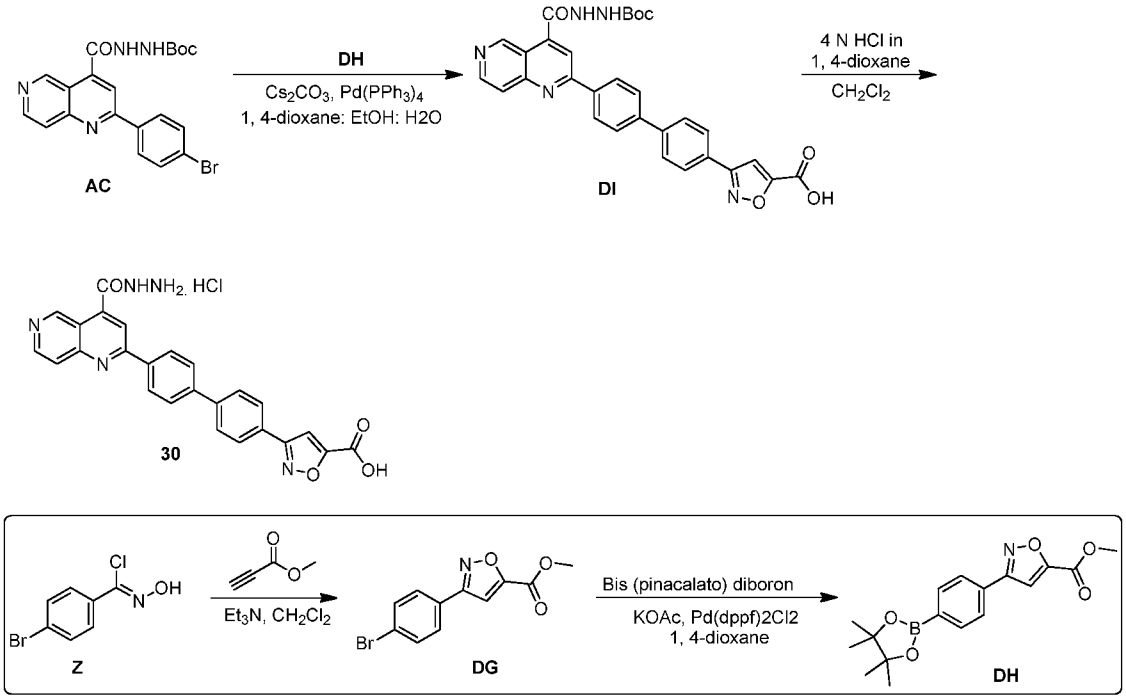
To a stirred solution of (4-bromophenyl)methanesulfonyl chloride (**DC**; 500 mg, 1.85 mmol) in pyridine (10 mL) under inert atmosphere was added morpholine (712 mg, 2.22 mmol) at RT and stirred for 16 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was diluted with water (30 mL) and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **DD** (360 mg, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.16 (s, 2H), 3.65 (t, *J* = 4.8 Hz, 4H), 3.13 (t, *J* = 4.8 Hz, 4H).

To a stirred solution of **DD** (250 mg, 0.78 mmol) in 1,4-dioxane (15 mL) under inert atmosphere were added bis(pinacalato)diboron (238 mg, 0.93 mmol) and fused potassium acetate (230 mg, 2.34 mmol) at RT. After the reaction was purged with argon for 30 min, $Pd(dppf)_2Cl_2$ (57mg, 0.07 mmol) was added to the reaction mixture. The reaction was then heated to 90°C and stirred for 16 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (30-40% EtOAc/hexanes) to afford **DE** (210 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.25 (s, 2H), 3.60 (t, *J* = 4.8 Hz, 4H), 3.08 (t, *J* = 4.8 Hz, 4H), 1.35 (s, 12H).

To a stirred solution of **AC** (200 mg, 0.45 mmol) in 1,4-dioxane:ethanol:H_2O (20:10:3, 33 mL) under inert atmosphere were added **DE** (215 mg, 0.58 mmol) and cesium carbonate (442 mg, 1.35 mmol) at RT. After the reaction was purged with argon for 30 min, tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.05 mmol) was added to the reaction mixture. The reaction was heated to reflux and stirred for 5 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (5-10% MeOH/CH_2Cl_2) to afford **DF** (110 mg, 40%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H), 9.69 (s, 1H), 9.29 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 2H), 8.32 (s, 1H), 8.04 (d, *J* = 6.0 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 4.52 (s, 2H), 3.60 (t, *J* = 4.5 Hz, 4H), 3.14 (t, *J* = 4.5 Hz, 4H), 1.48 (s, 9H).

To a stirred solution of **DF** (60 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (0.6 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with diethyl ether (2x5 mL) to afford **29** (40 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 9.75 (s, 1H), 8.89 (d, J = 6.0 Hz, 1H), 8.63 (s, 1H), 8.54 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 6.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 4.53 (s, 2H), 3.62-3.60 (m, 4H), 3.17-3.15 (m, 4H). MS (ESI): m/z 504 $[M+1]^+$. HPLC Purity: 94.51%

Scheme 27



Example 30

3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carboxylic acid hydrochloride (30)

To a stirred solution **Z** (8 g, 34.17 mmol) in dry CH_2Cl_2 (100 mL) under inert atmosphere were added triethylamine (5.38 mL, 101.19 mmol) and methylpropiolate (3.05 mL, 34.17 mmol) dropwise at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (50 mL) and the compound was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were washed with water (50 mL), dried over sodium sulfate, filtered and concentrated under

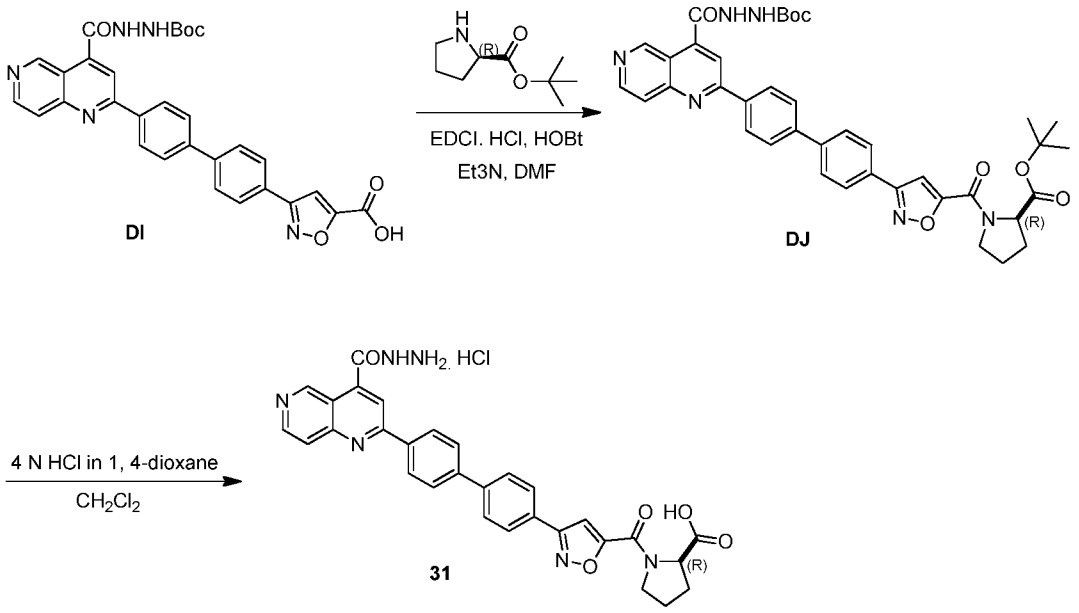
reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 8-10% EtOAc/hexanes to afford **DG** (3.1 g, 32%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 1H), 4.00 (s, 3H).

To a stirred solution of **DG** (2 g, 7.08 mmol) in 1,4-dioxane (100 mL) under inert atmosphere were added bis(pinacalato)diboron (2.15 g, 8.50 mmol) and fused potassium acetate (2.08 g, 21.24 mmol) at RT. After the reaction mixture was purged with argon for 20 min, $Pd(dppf)_2Cl_2$ (518mg, 0.70 mmol) was added. The reaction was then heated to 90 °C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 8-10% EtOAc/hexanes to afford **DH** (1.4 g, 60%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 1H), 4.00 (s, 3H), 1.36 (s, 12H).

To a stirred solution of **AC** (1.5 g, 3.39 mmol) in 1,4-dioxane:EtOH:H_2O (4:2:1, 50 mL) were added **DH** (1.3 g, 4.06 mmol) and cesium carbonate (3.3 g, 10.17 mmol) at RT. After the reaction was purged with argon for 30 min, $Pd(PPh_3)_4$ (390mg, 0.33 mmol) was added. The reaction was then heated to 90 °C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure. The residue was diluted with water (40 mL) and the compound was extracted with ethyl acetate (3x30 mL). The aqueous layer was acidified with glacial acetic acid to pH~2 (20 mL) and the resulting solid was filtered under vacuum to afford **DI** (1.1 g, 59%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (br s, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 2H), 8.35 (s, 1H), 8.10-7.91 (m, 8H), 7.64 (s, 1H), 1.50 (s, 9H).

To a stirred solution of **DI** (70 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with diisopropyl ether (2x8 mL) and pentane (2x8 mL) to afford **30** (50 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.02 (br s, 1H), 9.73 (s, 1H), 8.88 (d, *J* = 6.0 Hz, 1H), 8.60 (s, 1H), 8.55 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H). MS (ESI): *m/z* 452.3 $[M+1]^+$

Scheme 28



Example 31

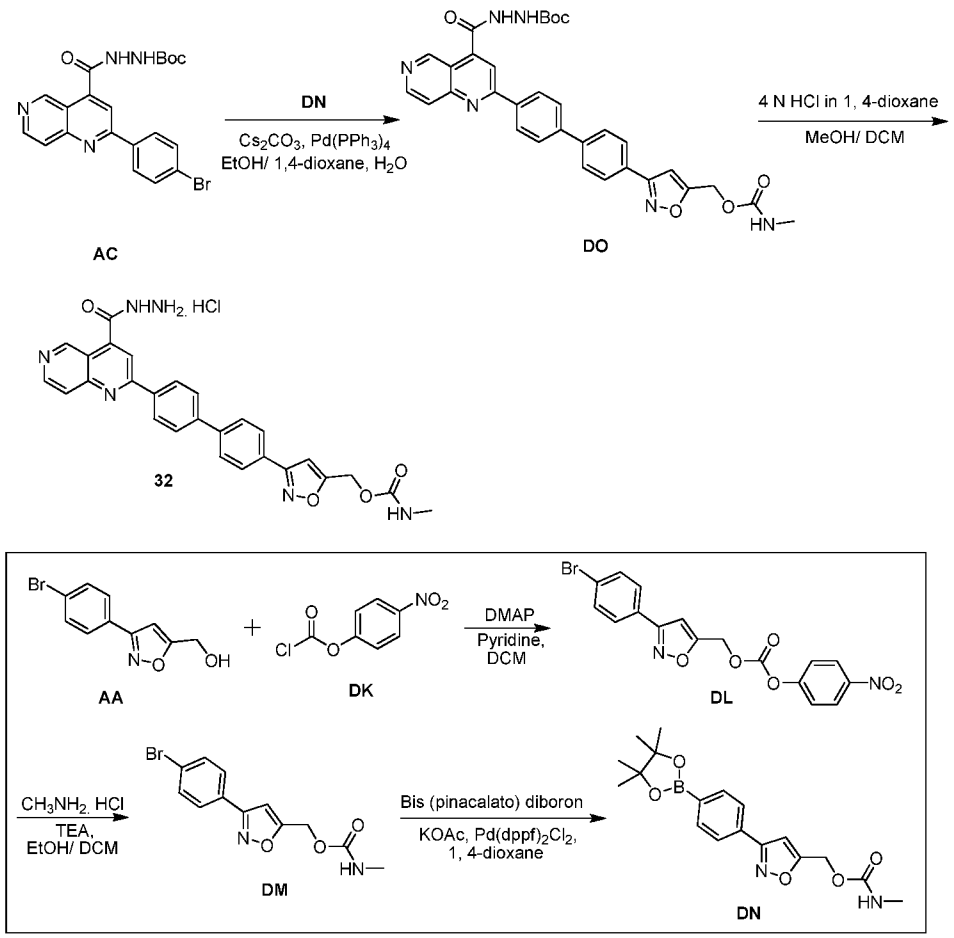
(*R*)-1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)pyrrolidine-2-carboxylic acid hydrochloride (31)

To a stirred solution of **DI** (300 mg, 0.54 mmol) in DMF (10 mL) under inert atmosphere were added EDCI·HCl (260 mg, 1.36 mmol), HOBt (132 mg, 0.97 mmol), triethylamine (220 mg, 2.17 mmol) and (R)-tert-butyl pyrrolidine-2-carboxylate (226 mg, 1.08 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (20 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (25 mL), a brine solution (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-4% MeOH/CH_2Cl_2 to afford **DJ** (115 mg, 39%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (br s, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.49 (d, J = 7.6 Hz, 2H), 8.35 (s, 1H), 8.14-7.99 (m, 7H), 7.81 (s, 1H), 4.98-4.95 (m, 0.4H), 4.45-4.42 (m, 0.6H), 3.92 (t, J = 6.8 Hz, 1H), 3.68-3.30 (m, 1H), 2.49-2.30 (m, 1H), 2.06-1.88 (m, 3H), 1.50 (s, 9H), 1.43 (s, 6H), 1.33 (s, 3H). MS(ESI): *m/z* 550.5 $[M-1]^+$

To a stirred solution of **DJ** (60 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. The reaction was warmed to RT and stirred for 16 h. After complete consumption of the starting material, the volatiles were

evaporated under reduced pressure to obtain the crude. The crude was triturated with isopropyl ether (2x5 mL), 20% isopropyl alcohol:CH_2Cl_2 (1:4, 2x5 mL):*n*-pentane (2x5 mL) to afford **31** (22 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (br s, 1H), 9.69 (s, 1H), 8.86 (d, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 5.6 Hz, 3H), 8.15-8.00 (m, 8H), 7.80 (s, 1H), 5.05-5.02 (m, 0.2H), 4.51-4.47 (m, 0.8H), 3.94-3.91 (m, 1H), 3.67-3.65 (m, 1H), 2.32-2.26 (m, 1H), 2.03-1.93 (m, 3H). MS (ESI): *m/z* 549.3 $[M+1]^+$. HPLC Purity: 92.71%

Scheme 29



Example 32

(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl methylcarbamate hydrochloride (32)

To a stirred solution of (3-(4-bromophenyl)isoxazol-5-yl)methanol (**AA**; 0.5 g, 1.96 mmol) in CH_2Cl_2 (15 mL) under inert atmosphere were added pyridine (0.39 mL, 4.91 mmol) and *p*-dimethylaminopyridine (0.024 mg, 0.19 mmol) at 0 °C. After the addition of 4-nitrophenyl carbonochloridate (**DK**; 0.39 g, 1.93 mmol) at 0 °C, the reaction mixture was warmed to RT

and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was diluted with a saturated ammonium chloride solution (20 mL) and the compound was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was triturated with pentane (2x15 mL) to afford crude **DL** (710 mg) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.5 Hz, 2H), 8.17 (d, *J* = 6.8 Hz, 1H), 7.70-7.59 (m, 5H), 7.40 (d, *J* = 9.5 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.73 (s, 1H), 5.43 (s, 2H), 5.34 (s, 1H).

To a stirred solution of **DL** (710 mg, 1.70 mmol) in CH_2Cl_2 (50 mL) under inert atmosphere were added methylamine hydrochloride (229 mg, 3.40 mmol) in ethanol (10 mL) and triethylamine (2.46 mL, 17.01 mmol) at RT. The reaction was stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with a saturated ammonium chloride solution (30 mL) and was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with water (30 mL), a brine solution (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexanes to afford **DM** (450 mg, 86%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.29-7.28 (m, 1H), 7.09 (s, 1H), 5.18 (s, 2H), 2.60-2.59 (m, 3H).

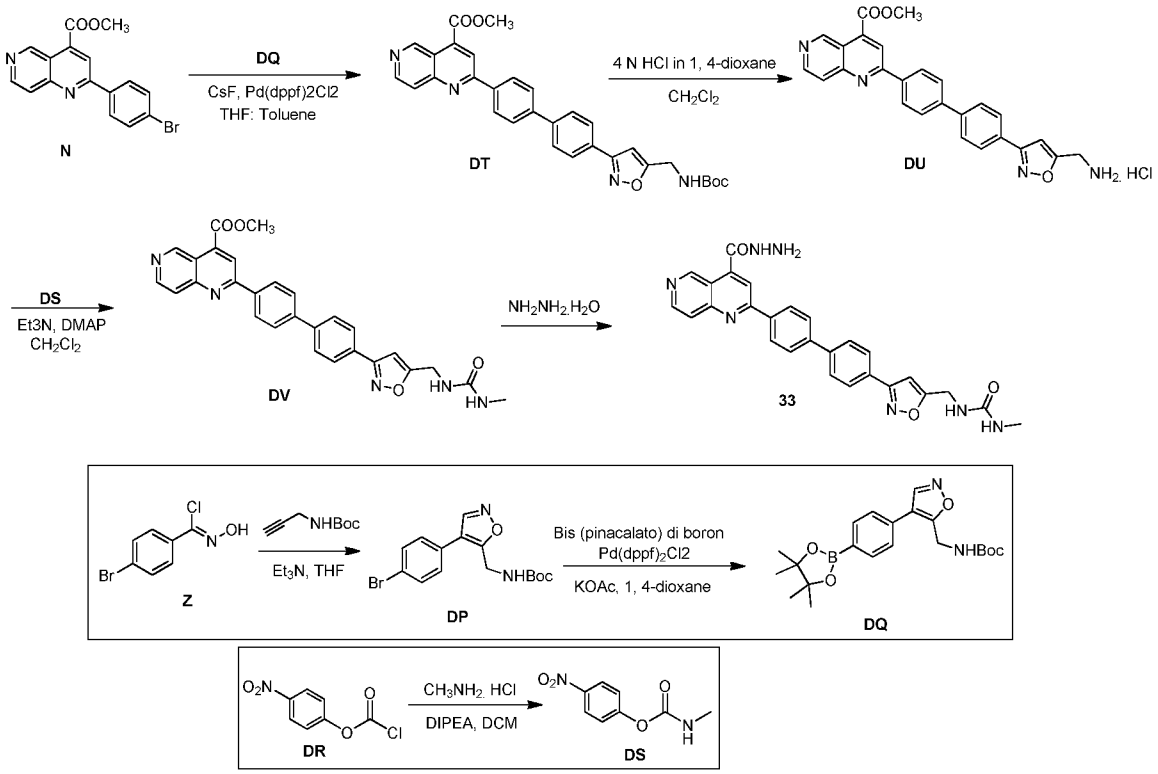
To a stirred solution of **DM** (420 mg, 1.34 mmol) in 1,4-dioxane (30 mL) under inert atmosphere were added fused potassium acetate (411 mg, 1.61 mmol), bis(pinacalato)diboron (393 mg, 4.02 mmol). After the reaction was purged with argon for 30 min, $Pd(dppf)_2Cl_2$ was added and the reaction was again purged with argon for 15 min. The reaction mixture was heated to 90 °C and stirred for 3 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 30% EtOAc/hexanes to afford **DN** (320 mg, 66%) as a colorless thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 11.2 Hz, 2H), 6.64 (s, 1H), 5.22 (s, 2H), 2.84 (s, 3H), 1.36 (s, 12H). MS (ESI): *m/z* 359.3 $[M+1]^+$

To a stirred solution of **AC** (60 mg, 0.13 mmol) in 1,4-dioxane:ethanol (2:1, 30 mL) and water (1 mL) under inert atmosphere were added cesium carbonate (130 mg, 0.40 mmol) and **DN** (58 mg, 0.16 mmol) at RT. After the reaction was purged with argon for 20 min, $Pd(PPh_3)_4$ (15mg, 0.013 mmol) was added. The reaction was heated to reflux and stirred for 6 h. After complete consumption of the starting material, the volatiles were evaporated under reduced

pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 3-4% MeOH/CH_2Cl_2 to afford **DO** (10 mg, 12%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 8.83 (d, J = 5.6 Hz, 1H), 8.49 (d, J = 7.6 Hz, 2H), 8.34 (s, 1H), 8.06-7.95 (m, 7H), 7.31-7.30 (m, 1H), 7.16 (s, 1H), 5.21 (s, 2H), 2.62 (s, 3H), 1.50 (s, 9H). MS (ESI): *m/z* 595.4 $[M+1]^+$

To a stirred solution of **DO** (7 mg, 0.011 mmol) in CH_2Cl_2 (1 mL) and methanol (0.2 mL) under inert atmosphere was added a 4N HCl solution in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with diisopropyl ether (2x3 mL) and *n*-pentane (2x3 mL) to afford **32** (5 mg as an HCl salt) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (br s, 1H), 9.69 (s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.52 (t, J = 4.4 Hz, 3H), 8.13 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 4H), 7.97 (d, J = 8.4 Hz, 2H), 7.29-7.28 (m, 1H), 7.15 (s, 1H), 5.22 (s, 2H), 2.60 (s, 3H). MS (ESI): *m/z* 495.2 $[M+1]^+$. HPLC Purity: 86.47%

Scheme 30



Example 33

1-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)-3-methylurea (33)

To a stirred solution **Z** (3 g, 12.93 mmol) in THF (40 mL) under inert atmosphere were added triethylamine (1.86 mL, 12.93 mmol) and tert-butylprop-2-yn-1-ylcarbamate (12 g, 12.93 mmol) at 0 °C. The reaction was then warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (30 mL) and the compound was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **DP** (3.2 g, 70%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.81 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.55-7.53 (m, 1H), 6.84 (s, 1H), 4.30-4.29 (m, 2H), 1.39 (s, 9H).

To a stirred solution of **DP** (2 g, 5.68 mmol) in 1,4-dioxane (30 mL) under inert atmosphere were added bis(pinacalato)diboron (1.73 g, 6.81 mmol) and fused potassium acetate (1.67 g, 17.04 mmol) at RT. After the reaction was purged with argon for 20 min, $Pd(dppf)_2Cl_2$ (415mg, 0.56 mmol) was added. The reaction was heated to 90 °C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT, filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (20-30% EtOAc/hexanes) to afford **DQ** (1.6 g, 70%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.86 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.56-7.54 (m, 1H), 6.84 (s, 1H), 4.31-4.29 (m, 2H), 1.39 (s, 9H), 1.30 (s, 12H).

To a stirred solution of methylamine hydrochloride (3 g, 44.43 mmol) in CH_2Cl_2 (100 mL) under inert atmosphere were added diisopropylethylamine (24.56 mL, 132.55 mmol) and 4-nitrophenylchloroformate (**DR**; 10.74 g, 53.28 mmol) at 0 °C. The reaction was then warmed to RT and stirred for 16 h. After complete consumption of the starting material, the reaction mass was diluted with ice cold water (40 mL) and the compound was extracted with CH_2Cl_2 (2x40 mL). The combined organic extracts were washed with water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (15% EtOAc/hexanes) to afford **DS** (1.6 g, 18%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 6.8 Hz, 1H), 7.31 (d, J = 6.8 Hz, 2H), 5.06 (br s, 1H), 2.93 (d, J = 4.8 Hz, 3H).

To stirred solution of **N** (1 g, 2.92 mmol) in THF:toluene (1:1, 30 mL) under inert atmosphere were added **DQ** (1.2 g, 3.21 mmol) and cesium fluoride (1.3 g, 8.77 mmol) at RT. After the reaction was purged with argon for 20 min, $Pd(dppf)_2Cl_2$ (213 mg, 0.29 mmol) was added. The reaction was heated to 90°C and stirred for 12 h. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (2-5% MeOH/CH_2Cl_2) to afford **DT** (520 mg, 33%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H), 8.84 (d, J = 5.5 Hz, 1H), 8.68 (s, 1H), 8.48 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 5.5 Hz, 1H), 8.01-8.00 (m, 4H), 7.94 (d, J = 8.0 Hz, 2H), 7.59-7.57 (m, 1H), 6.91 (s, 1H), 4.33-4.32 (m, 2H), 4.08 (s, 3H), 1.41 (s, 9H).

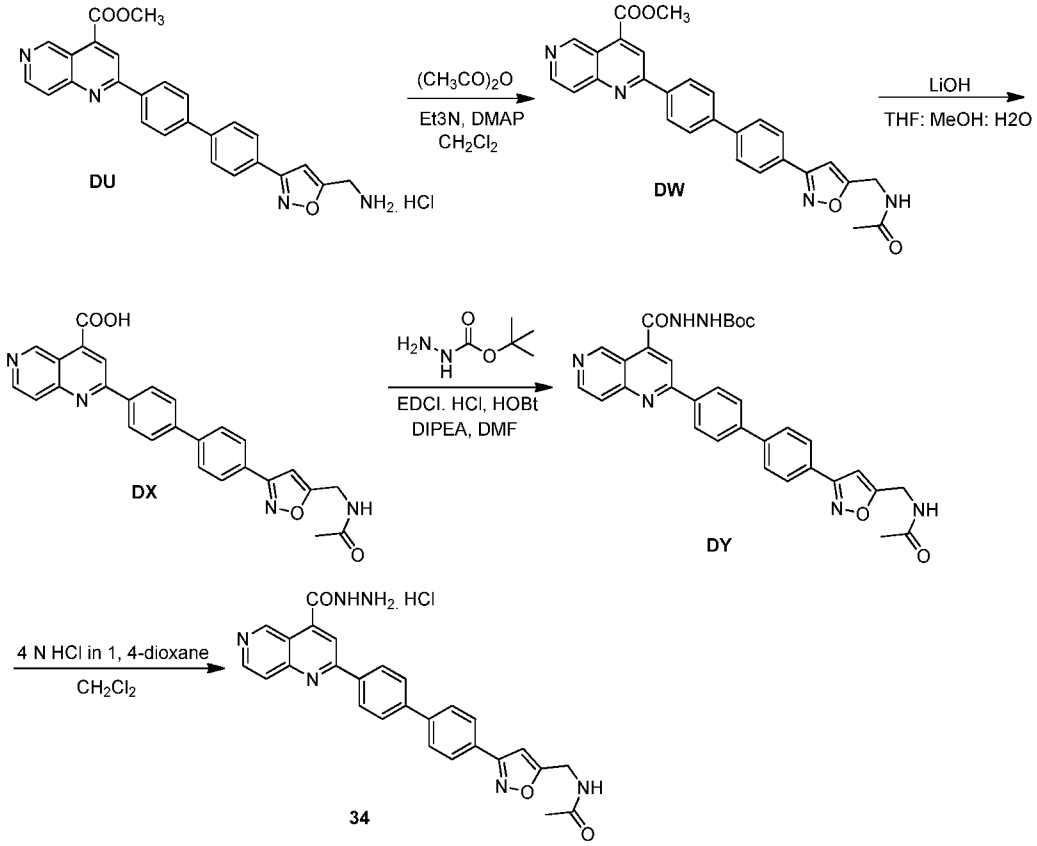
To a stirred solution of **DT** (1.6 g, 2.98 mmol) in CH_2Cl_2 (15 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (3 mL) at 0 °C. The reaction was then warmed to RT and stirred for 3 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude **DU** (1.2 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 8.89 (d, J = 6.0 Hz, 1H), 8.75-8.73 (m, 3H), 8.53 (d, J = 8.4 Hz, 2H), 8.20 (d, J = 6.0 Hz, 1H), 8.04-7.98 (m, 6H), 7.24 (s, 1H), 4.37-4.36 (m, 2H), 4.18 (s, 3H).

To a stirred solution of **DU** (100 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere were added triethylamine (69 mg, 0.68 mmol), **DS** (54 mg, 0.68 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was then warmed to RT and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was diluted with water (10 mL) and the compound was extracted with EtOAc (2x15 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (2-5% MeOH/CH_2Cl_2) to afford **DV** (45 mg, 40%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.85 (d, J = 6.0 Hz, 1H), 8.69 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 5.6 Hz, 1H), 8.02-7.93 (m, 6H), 6.87 (s, 1H), 6.06 (t, J = 6.0 Hz, 1H), 5.99-5.97 (m, 1H), 4.40 (d, J = 5.6 Hz, 2H), 4.08 (s, 3H), 2.58 (d, J = 4.8 Hz, 3H).

A mixture of **DV** (45 mg, 0.09 mmol) in hydrazine hydrate (2 mL) under inert atmosphere was heated to 100 °C and stirred for 1 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with water (10 mL) and dried under vacuum to afford the **33** (15 mg, 33%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H),

9.05 (s, 1H), 8.80 (d, *J* = 6.0 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 2H), 8.36 (s, 1H), 8.03-7.94 (m, 6H), 6.87 (s, 1H), 6.60 (t, *J* = 5.6 Hz, 1H), 5.99-5.98 (m, 1H), 4.41-4.39 (m, 2H), 2.58 (d, *J* = 4.8 Hz, 3H). MS (ESI): *m/z* 494.3 $[M+1]^+$. HPLC Purity: 85.01%

Scheme 31



Example 34

***N*-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl) methyl)acetamide hydrochloride (34)**

To a stirred solution of **DU** (300 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere were added triethylamine (0.29 mL, 2.06 mmol), dimethylaminopyridine (3 mg, catalytic) and acetic anhydride (84 mg, 0.82 mmol) at 0 °C. The reaction was warmed to RT and stirred for 2 h. After complete consumption of the starting material, the reaction mass was diluted with water (20 mL) and the compound was extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (2-5% MeOH/CH_2Cl_2) to afford **DW** (90 mg, 26%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H), 8.84 (d, *J* = 5.5 Hz, 1H), 8.67 (s, 1H),

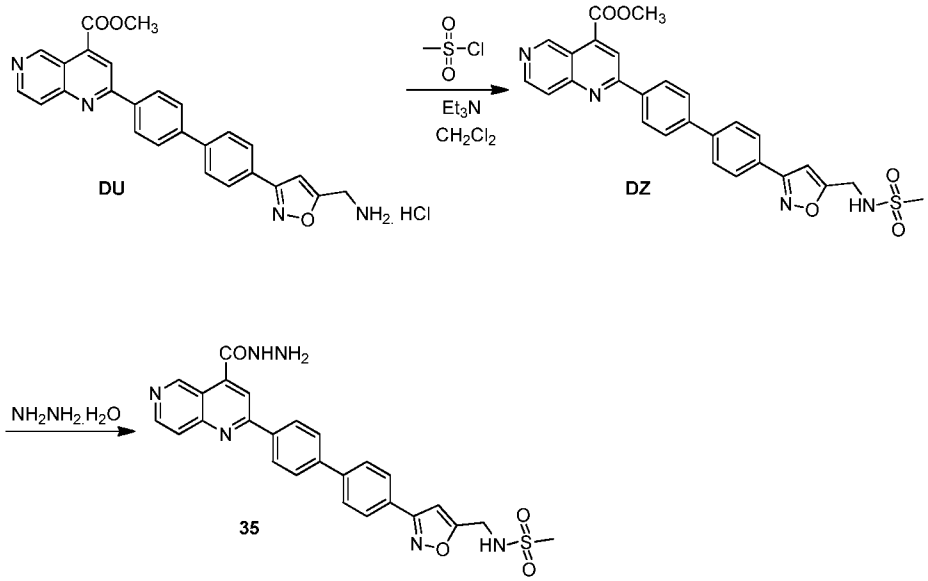
8.57 (t, J = 5.5 Hz, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 5.5 Hz, 1H), 8.01-7.99 (m, 4H), 7.95-7.93 (m, 3H), 6.95 (s, 1H), 4.45-4.44 (m, 2H), 4.07 (s, 3H), 1.90 (s, 3H).

To a stirred solution **DW** (120 mg, 0.25 mmol) in THF:MeOH:H_2O (2:2:1, 10 mL) was added lithium hydroxide (32 mg, 0.75 mmol) at 0 °C. The reaction was subsequently warmed to RT and stirred for 6 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was diluted with water (10 mL) and acidified with 2N HCl solution to obtain the solid. The solid was filtered and dried under vacuum to afford **DX** (52 mg, 87%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.50 (br s, 1H), 10.06 (br s, 1H), 8.85 (br s, 1H), 8.67 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.01-8.09 (m, 1H), 8.01-7.94 (m, 6H), 6.96 (s, 1H), 4.46-4.45 (m, 2H), 1.91 (s, 3H).

To a stirred solution of **DX** (50 mg, 0.11 mmol) in DMF (2 mL) under inert atmosphere were added EDCI·HCl (41 mg, 0.21 mmol), HOBt (29 mg, 0.21 mmol) and diisopropylethylamine (42 mg, 0.32 mmol) at 0 °C and stirred for 5 min. Then tert-butylcarbazate was added to the reaction mixture and stirred for 12 h at RT. After complete consumption of the starting material, the reaction mass was diluted with water (10 mL) and the compound was extracted with EtOAc (2x10 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (2-5% MeOH/CH_2Cl_2) to afford **DY** (90 mg, 26%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (br s, 1H), 9.71 (br s, 1H), 9.30 (br s, 1H), 8.84-8.80 (m, 2H), 8.58 (t, J = 5.6 Hz, 1H), 8.52-8.48 (m, 1H), 8.38 (s, 1H), 8.06-7.94 (m, 7H), 4.46-4.45 (m, 2H), 1.91 (s, 3H), 1.50 (s, 9H).

To a stirred solution of **DY** (30 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (0.2 mL) at 0 °C. The reaction was warmed to RT and stirred for 3 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with methanol (2x5 mL) and ether (2x5 mL) to afford **34** (20 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (br s, 1H), 9.69 (br s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.57 (t, J = 4.0 Hz, 1H), 8.52-8.48 (m, 3H), 8.11 (d, J = 6.0 Hz, 1H), 8.04-7.95 (m, 6H), 6.96 (s, 1H), 4.46-4.45 (m, 2H), 1.91 (s, 3H). MS (ESI): m/z 479.3 $[M+1]^+$. HPLC Purity: 87.08%

Scheme 32



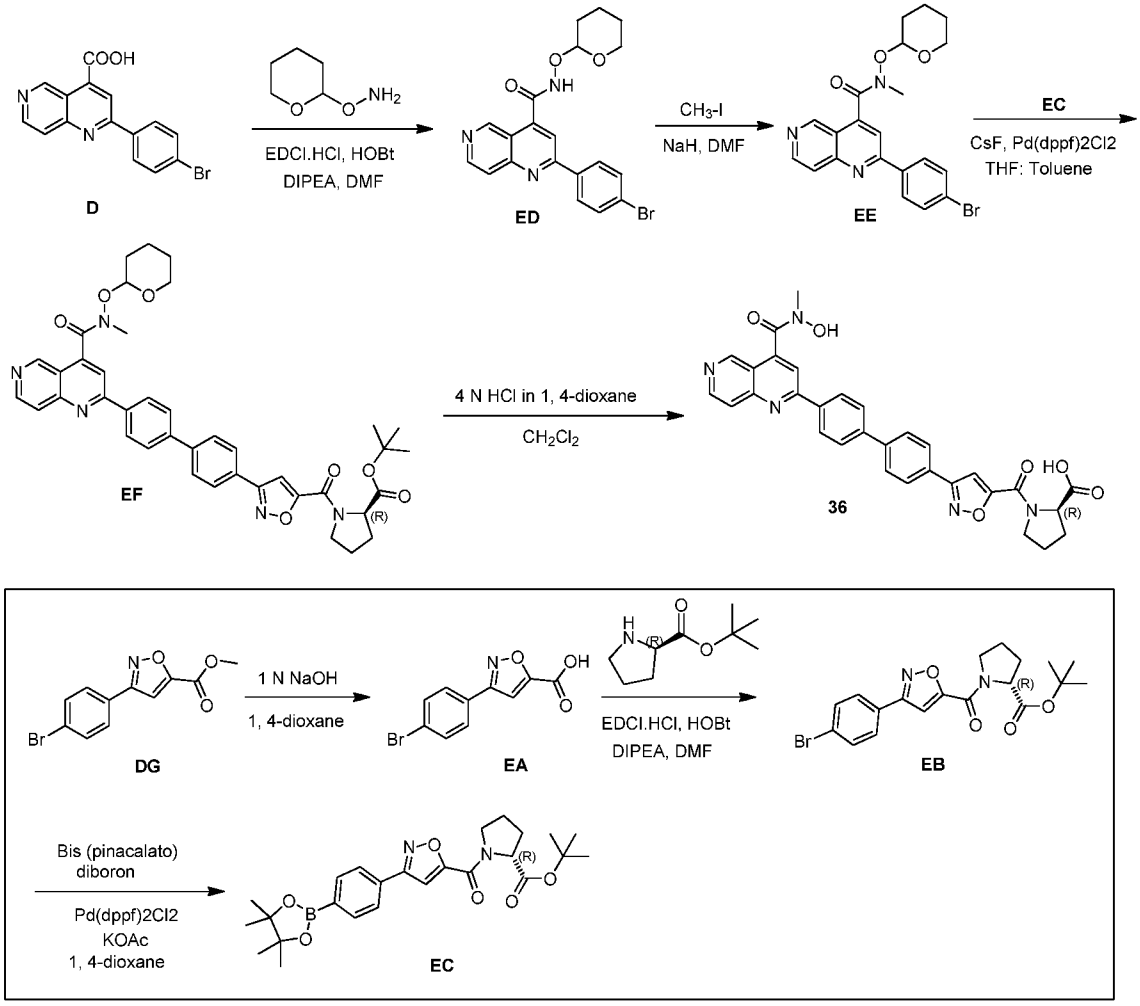
Example 35:

***N*-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)methanesulfonamide (35)**

To a stirred solution of **DU** (200 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere were added triethylamine (0.1 mL, 1.37 mmol) and methanesulfonylchloride (52mg, 0.45 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (20 mL) and extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography (50-60% EtOAc/hexanes) to afford **DZ** (20 mg, 17%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 8.68 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 5.6 Hz, 2H), 8.02 (t, J = 8.4 Hz, 2H), 7.96 (d, J = 6.4 Hz, 3H), 7.90 (t, J = 6.0 Hz, 2H), 7.07 (s, 1H), 4.42 (d, J = 6.4 Hz, 2H), 4.08 (s, 3H), 3.30 (s, 3H).

A mixture of **DZ** (45 mg, 0.08 mmol) in hydrazine hydrate (1 mL) under inert atmosphere was heated to 100 °C and stirred for 1 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was triturated with water (10 mL) and dried under vacuum to afford **35** (15 mg, 33%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 9.65 (s, 1H), 8.80 (d, J = 6.0 Hz, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.37 (s, 1H), 8.04-7.94 (m, 7H), 7.90 (t, J = 6.4 Hz, 1H), 7.07 (s, 1H), 4.82 (br s, 2H), 4.42 (d, J = 6.0 Hz, 2H), 2.99 (s, 3H). MS (ESI): m/z 515.4 $[M+1]^+$. HPLC Purity: 92.98%

Scheme 33



Example 36:

(*R*)-1-(3-(4'-(4-(hydroxy(methyl)carbamoyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)pyrrolidine-2-carboxylic acid (36)

To a stirred solution of **DG** (800 mg, 2.83 mmol) in DMF (25 mL) under inert atmosphere was added 1N NaOH solution (170 mg in 0.45 mL water, 4.25 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with water (40 mL) and acidified with 1N HCl to pH~2 and filtered. The obtained solid was triturated with toluene (2x5 mL) and ether (2x5 mL) to afford **EA** (600 mg, 63%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.70 (s, 1H).

To a stirred solution of **EA** (100 mg, 0.37 mmol) in DMF (10 mL) under inert atmosphere were added EDCI·HCl (178 mg, 093 mmol), HOBt (90 mg, 0.66 mmol),

diisopropylethylamine (0.2 mL, 1.16 mmol) and *D*-proline tertbutyl ester (154 mg, 0.74 mmol) at RT. The reaction was stirred for 14 h. After complete consumption of the starting material, the reaction mass was diluted with water (10 mL) and extracted with EtOAc (2x10 mL). The combined organic extracts were washed with water (10 mL), a brine solution (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes to afford **EB** (124 mg, 77%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.62 (m, 2H), 7.61-7.59 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 4.58-4.55 (m, 1H), 4.14-4.00 (m, 1H), 3.89-3.71 (m, 1H), 2.28-2.20 (m, 1H), 2.18-2.10 (m, 1H), 2.09-2.02 (m, 1H), 2.00-1.90 (m, 1H), 1.49-1.41 (m, 9H).

To a stirred solution of **EB** (120 mg, 0.28 mmol) in 1,4-dioxane (20 mL) under inert atmosphere were added bis(pinacalato)diboron (87 mg, 0.34 mmol) and fused potassium acetate (83 mg, 0.84 mmol) at RT. After the reaction mixture was purged with argon for 30 min, $Pd(dppf)_2Cl_2$ (20 mg, 0.02 mmol) was added. The reaction was then heated to reflux and stirred for 5 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 10-20% EtOAc/hexanes to afford **EC** (58 mg, 44%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.88 (m, 2H), 7.83-7.79 (m, 2H), 7.26-7.23 (m, 1H), 4.58-4.55 (m, 1H), 4.14-4.00 (m, 1H), 3.89-3.83 (m, 1H), 2.39-2.27 (m, 1H), 2.25-2.19 (m, 1H), 2.08-2.00 (m, 1H), 1.99-1.90 (m, 1H), 1.54 (s, 9H), 1.36 (s, 12H).

To a stirred solution of **D** (1 g, 3.03 mmol) in DMF (10 mL) under inert atmosphere were added EDCI·HCl (1.45 g, 7.56 mmol), HOBt (730 mg, 5.40 mmol), diisopropylethylamine (1.67 mL, 9.06 mmol) and *o*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (712 mg, 6.07 mmol) at RT. The reaction was stirred for 14 h. After complete consumption of the starting material, the reaction mass was diluted with water (40 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (30 mL), a brine solution (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-4% MeOH/CH_2Cl_2 to afford **ED** (1.1 g, 84%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s, 1H), 9.54 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.35 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 2H), 8.02 (d, *J* = 5.6 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 5.22 (s, 1H), 4.10-4.05 (m, 1H), 3.63-3.60 (m, 1H), 1.80-1.77 (m, 3H), 1.62-1.59 (m, 3H).

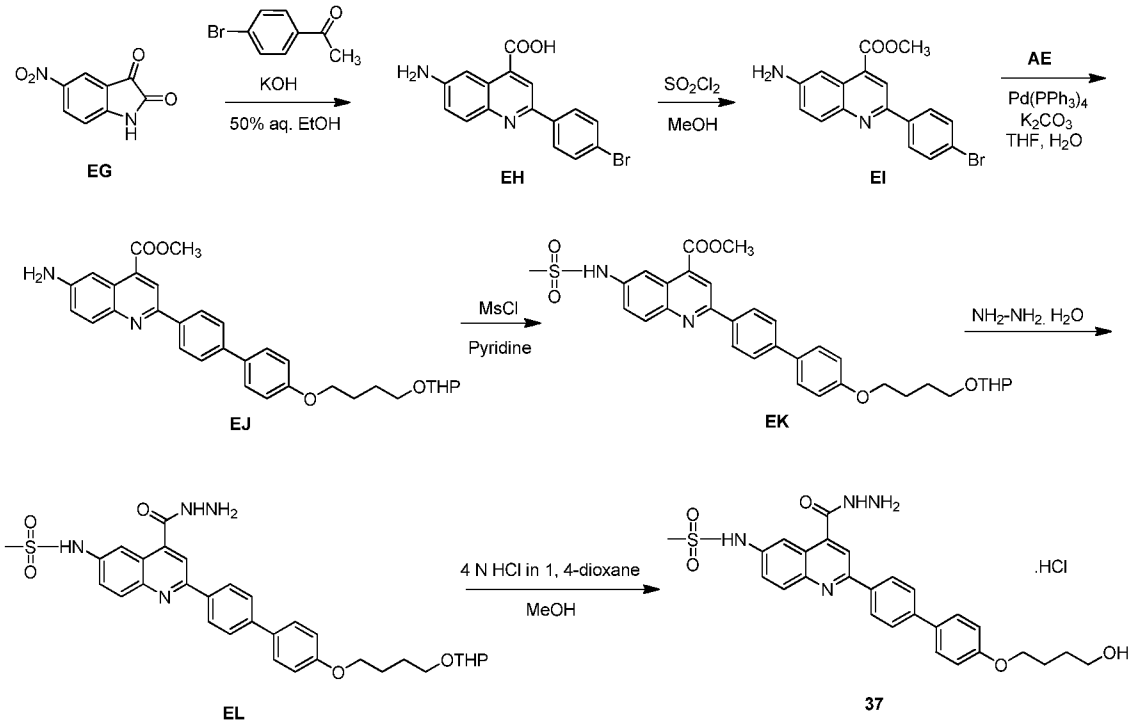
To a stirred solution of **ED** (1 g, 2.33 mmol) in DMF (15 mL) under inert atmosphere was added 50% sodium hydride (224 mg, 9.33 mmol) at 0 °C. After being stirred for 15 min at 0

°C, methyl iodide (0.03 mL, 0.46 mmol) was added and the reaction mixture was stirred for 30 min at RT. The reaction was monitored by TLC. After complete consumption of the starting material; the reaction mixture was cooled to 0 °C, diluted with water (30 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-3% MeOH/CH_2Cl_2 to afford **EE** (250 mg, 24%) as a thick brown syrup. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.82-8.79 (m, 1H), 8.43 (s, 1H), 8.33-8.30 (m, 2H), 8.03-7.94 (m, 1H), 7.81-7.79 (m, 2H), 3.93-3.87 (m, 1H), 3.58-3.56 (m, 3H), 1.82-1.74 (m, 2H), 1.61-1.55 (m, 2H), 1.35-1.17 (m, 4H). MS (ESI): *m/z* 442 $[M-2]^+$. Rotameric isomers were observed by ^{1}H NMR in the ratio of 4: 1.

To a stirred solution of **EE** (100 mg, 0.22 mmol) in THF:toluene (1:1, 30 mL) under inert atmosphere were added **EC** (127 mg, 0.34 mmol) and cesium fluoride (102 mg, 0.67 mmol) at RT. After the reaction was purged with argon for 30 min, $Pd(dppf)_2Cl_2$ (16 mg, 0.02 mmol) was added. The reaction was heated to reflux and stirred for 5 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 4-6% MeOH/CH_2Cl_2 to obtain **EF** (60 mg, mixture of rotamers). The compound was further purified through preparative HPLC to afford (27 mg, 18%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.81 (d, J = 5.6 Hz, 1H), 8.51-8.50 (m, 3H), 8.14-7.97 (m, 7H), 7.81 (s, 1H), 4.98-4.95 (m, 0.5H), 4.45-4.42 (m, 0.5H), 3.91 (t, J = 7.2 Hz, 2H), 3.59-3.50 (m, 4H), 2.31-2.29 (m, 1H), 2.03-1.98 (m, 4H), 1.43 (s, 6H), 1.33 (s, 9H).

To a stirred solution of **EF** (27 mg, 0.03 mmol) in CH_2Cl_2 (0.4 mL) under inert atmosphere was added a 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. The reaction was then warmed to RT and stirred for 5 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with isopropyl ether (2x5 mL) to afford **36** (15 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (br s, 1H), 9.29 (s, 1H), 8.81 (d, J = 6.0 Hz, 1H), 8.51 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H), 8.14-8.08 (m, 4H), 8.03-7.98 (m, 4H), 7.80 (s, 1H), 5.05-5.02 (m, 0.4H), 4.51-4.47 (m, 0.6H), 3.93 (t, J = 6.4 Hz, 1H), 3.47 (s, 3H), 2.03-1.94 (m, 4H). MS (ESI): *m/z* 562.4 $[M-1]^+$. HPLC Purity: 93.28%

Scheme 34



Example 37

_N_-(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)quinolin-6-yl)methanesulfonamide (37)

To a stirred solution of 5-nitroindoline-2,3-dione (**EG**; 1 g, 5.20 mmol) in aqueous ethanol (10 mL) under inert atmosphere were added 1-(4-bromophenyl)ethanone (1 g, 5.20 mmol) and potassium hydroxide (2.9 g, 52.04 mmol) at RT. The reaction mixture was heated to reflux and stirred for 2 h. After complete consumption of the starting material, the reaction mixture was cooled to RT and acidified with acetic acid. The obtained solid was filtered and the filtrate was concentrated under reduced pressure to obtain the crude **EH** (5 g) as an off-white solid. LCMS (ESI): 53%, *m/z* 343 $[M+1]^+$

To a stirred solution of **EH** (5 g, 14.61 mmol) in methanol (15 mL) under inert atmosphere was added sulfurylchloride (17.39 g, 146.17 mmol) at 0 °C. The reaction mixture was then heated to reflux and stirred for 12 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with a saturated sodium bicarbonate solution (40 mL) and the compound was extracted with EtOAc (3x40 mL). The combined organic extracts were washed with water (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes to afford **EI** (300 mg, 7%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.27 (s, 1H), 8.12 (d, *J*

= 8.5 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 6.04 (br s, 2H), 3.96 (s, 3H).

To a stirred solution of **EI** (200 mg, 56.17 mmol) in THF (15 mL) under inert atmosphere were added 4,4,5,5-tetramethyl-2-(4-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)phenyl)-1,3,2-dioxaborolane **AE** (252 mg, 67.20 mmol) , potassium carbonate (232 mg, 1.60 mmol) and water (2 mL) at RT. After the reaction mixture was purged under argon for 15 min, $Pd(PPh_3)_4$ (32 mg, 0.028 mol) was added. The reaction as then heated to reflux and stirred for 4 h. After complete consumption of the starting material, the volatiles were evaporated under vacuum to obtain the crude, which was purified by silica gel column chromatography eluting with 30% EtOAc/hexanes to afford **EJ** (100 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.22-7.20 (m, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.64-4.62 (m, 1H), 4.12-4.10 (m, 2H), 4.08-4.03 (m, 4H), 3.90-3.80 (m, 3H), 3.56-3.48 (m, 2H), 1.94-1.90 (m, 1H), 1.88-1.82 (m, 2H), 1.78-1.72 (m, 2H), 1.70-1.68 (m, 2H), 1.60-1.54 (m, 2H), 1.50-1.46 (m, 1H).

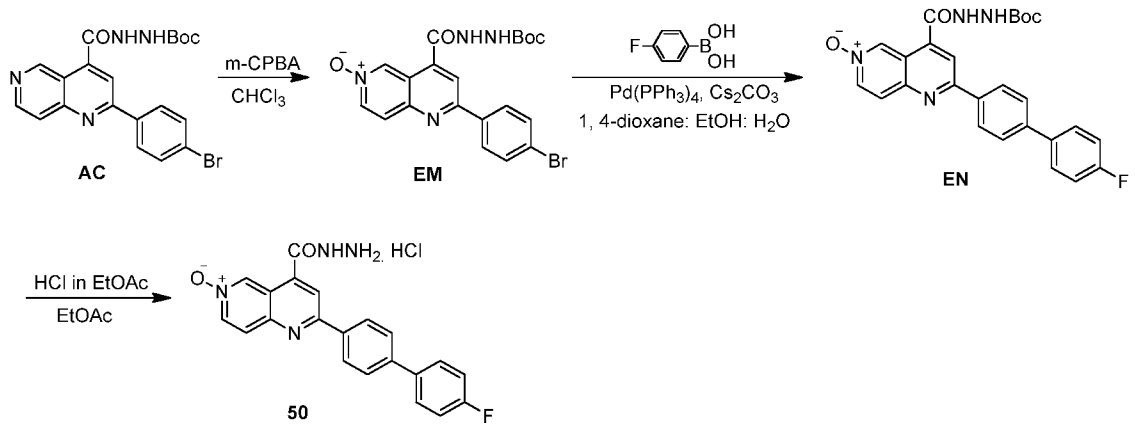
To a stirred solution of **EJ** (60 mg, 0.11 mmol) in pyridine (0.3 mL) under inert atmosphere was added methanesulfonylchloride (111 mg, 0.96 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (5 mL) and extracted with EtOAc (2x10 mL). The combined organic layers were washed with water (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes to afford **EK** (10 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.66 (br s, 1H), 8.52 (br s, 1H), 8.28-8.22 (m, 3H), 7.76-7.72 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 4.62-4.60 (m, 1H), 4.12-4.06 (m, 5H), 3.94-3.82 (m, 2H), 3.54-3.44 (m, 3H), 3.18 (s, 3H), 1.98-1.66 (m, 7H).

A stirred solution of **EK** (60 mg) in hydrazine hydrate (1 mL) under inert atmosphere was heated to 100 °C and stirred for 1 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was diluted with water (5 mL) and extracted with 10% MeOH/CH_2Cl_2 (2x7 mL). The combined organic extracts were washed with water (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 10% MeOH/CH_2Cl_2 to afford **EL** (20 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.20 (br s, 1H), 10.06 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 2H), 8.13-8.09 (m, 3H), 7.82

(d, J = 8.5 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.69 (s, 1H), 7.06 (d, J = 8.5 Hz, 2H), 4.71 (br s, 1H), 4.57 (s, 1H), 4.06 (t, J = 6.5 Hz, 2H), 3.75-3.68 (m, 2H), 3.44-3.41 (m, 2H), 3.09 (s, 3H), 1.82-1.79 (m, 2H), 1.72-1.68 (m, 4H), 1.47-1.45 (m, 4H), 1.33 (s, 1H).

To a stirred solution of **EL** (20 mg) in methanol (5 mL) under inert atmosphere was addeda 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. The reaction was then warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with isopropyl alcohol (2x5 mL) and pentane (2x5 mL) to afford **37** (35 mg as an HCl salt) as a brick red solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 10.34 (s, 1H), 8.34 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H), 8.17-8.14 (m, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.72-7.69 (m, 3H), 7.05 (d, J = 8.5 Hz, 2H), 4.04 (t, J = 7.0 Hz, 3H), 3.46 (t, J = 7.0 Hz, 3H), 3.11 (s, 3H), 1.78-1.74 (m, 2H), 1.60-1.56 (m, 2H). Mass: m/z 521 $[M+1]^+$. HPLC Purity: 99.69%

Scheme 35



Example 50

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-4-(hydrazinecarbonyl)-1,6-naphthyridine 6-oxide hydrochloride (50)

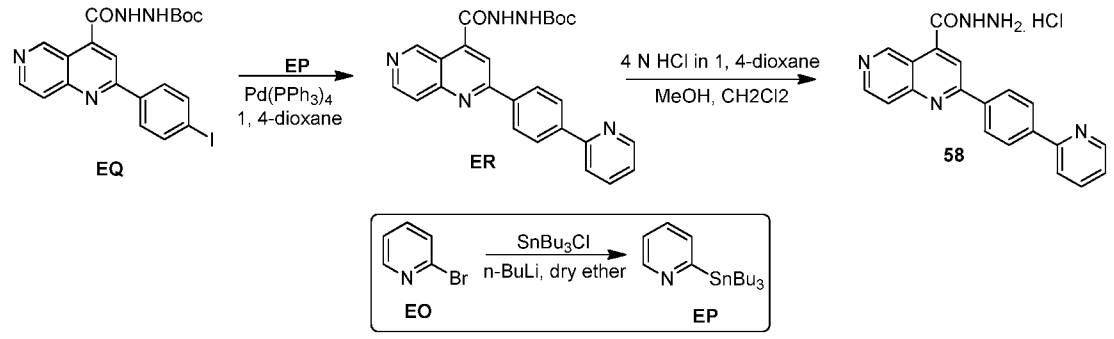
To a stirred solution of tert-butyl 2-(2-(4-bromophenyl)-1,6-naphthyridine-4-carbonyl) hydrazinecarboxylate (**AC**; 120 mg, 0.27 mmol) in chloroform (10 mL) under inert atmosphere was added *m*-chloroperbenzoic acid (116 mg, 0.67 mmol) at 0 °C. The reaction was warmed to RT and stirred for 2 h. After complete consumption of the starting material, the reaction mixture was diluted with a saturated sodium bicarbonate solution (15 mL) and extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-5%

$MeOH/CH_2Cl_2$ to afford **EM** (90 mg, 75%) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.26 (br s, 1H), 9.13 (br s, 1H), 8.45-8.43 (m, 1H), 8.30 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 1.27 (s, 9H).

To a stirred solution of **EM** (110 mg, 0.23 mmol) in 1,4-dioxane:EtOH:H_2O (4:2:1, 20 mL) under inert atmosphere were added (4-fluorophenyl)boronic acid (40 mg, 0.28 mmol) and cesium carbonate (230 mg, 0.71 mmol) at RT. After the reaction was purged with argon for 20 min, $Pd(PPh_3)_4$ (27 mg, 0.02 mmol) was added. The reaction was heated to reflux and stirred for 4 h. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure. The residue was diluted with water (15 mL) and was extracted with CH_2Cl_2 (2x20 ml). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude was purified by silica gel column chromatography eluting with 2-4% $MeOH/CH_2Cl_2$ to afford **EN** (80 mg, 70%) as an off-white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 10.69 (br s, 1H), 9.28 (s, 1H), 9.16 (s, 1H), 8.46-8.31 (m, 4H), 8.09 (d, J = 7.5 Hz, 1H), 7.91-7.84 (m, 4H), 7.35 (t, J = 8.5 Hz, 2H), 1.48 (s, 9H).

To a stirred solution of **EN** (40 mg, 0.08 mmol) in ethyl acetate (2 mL) under inert atmosphere was added 2N HCl in ethyl acetate (5 mL) at 0 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with diisopropyl ether (2x5 mL) and pentane (2x5 mL) to afford **50** (26 mg of an HCl salt) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 9.15 (s, 1H), 8.50-8.42 (m, 4H), 8.11 (d, J = 7.0 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.87-7.84 (m, 2H), 7.35 (t, J = 9.0 Hz, 2H). MS (ESI): m/z 375 $[M+1]^+$. HPLC Purity: 94.93%

Scheme 36



Example 58

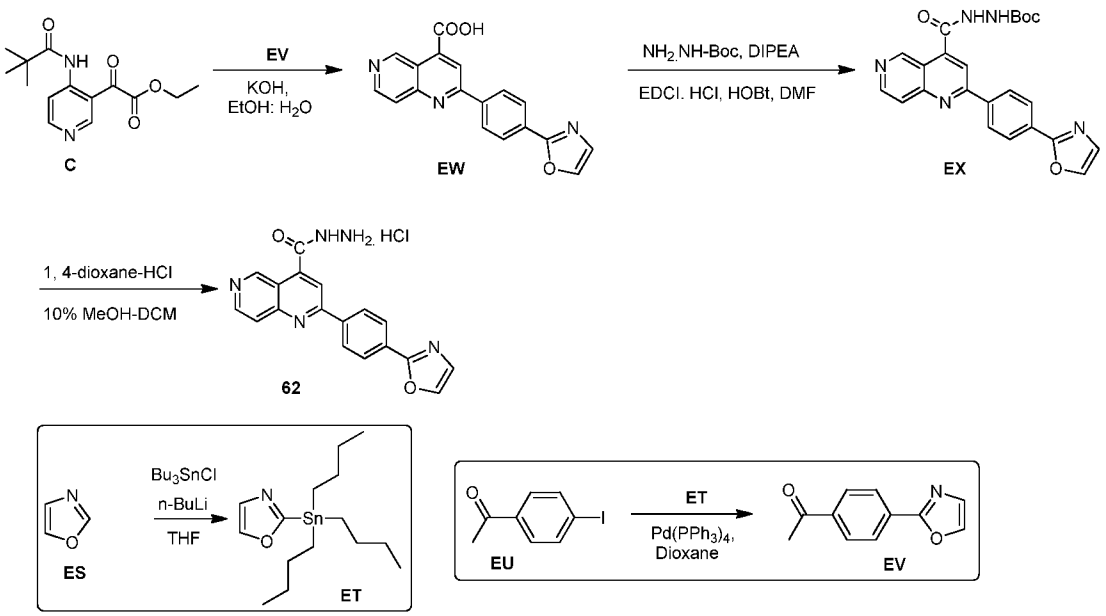
2-(4-(pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (58)

To a stirred solution of 2-bromopyridine (**EO**; 1 g, 6.32 mmol) in dry ether (20 mL) under inert atmosphere was added n-butyl lithium (4.12 mL, 9.49 mmol) at -78 °C. The reaction was stirred for 45 min at -78 °C. After a solution of tributyltin chloride (2.57 mL, 9.49 mmol) was added, the reaction was heated to 50 °C and stirred for 30 min. The reaction was monitored by TLC. After complete consumption of the starting material, the crude was diluted with a saturated ammonium chloride solution (40 mL) and was extracted with EtOAc (2x40 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude **EP** (3.2 g) as a sticky solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 6.0 Hz, 1H), 1.71-1.37 (m, 12H), 1.35-1.23 (m, 6H), 1.19-1.05 (m, 9H). MS (ESI): *m/z* 370 $[M+1]^+$

A stirred solution of tert-butyl 2-(3-(4-iodophenyl)-1-naphthoyl)hydrazinecarboxylate (**EQ**; 150 mg, 0.30 mmol) in 1,4-dioxane (8 mL) was purged under argon for 15 min at RT. To this reaction mixture was added $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and purged with argon for 15 min. After the addition of **EP** (225 mg, 0.61 mmol), the reaction was heated to reflux and stirred for 12 h. The reaction was monitored by TLC. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with water (15 mL) and was extracted with EtOAc (2x15 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain **ER** (40 mg, 29%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.69 (br s, 1H), 9.28 (br s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.72 (d, *J* = 6.5 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 2H), 8.33 (d, *J* = 8.5 Hz, 3H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.94 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 1.35 (s, 9H). MS (ESI): *m/z* 442 $[M+1]^+$

To a stirred solution of **ER** (35 mg, 0.07 mmol) in 10% methanol:CH_2Cl_2 (2 mL) under inert atmosphere was added a 4N HCl solution in 1,4-dioxane (2 mL) at 0 °C. The reaction was then warmed to RT and stirred for 3 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with *n*-pentane (2x2 mL) to afford **58** (30 mg as an HCl salt) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.28 (br s, 1H), 9.78 (s, 1H), 8.90 (d, *J* = 6.0 Hz, 1H), 8.77 (d, *J* = 6.0 Hz, 1H), 8.68 (d, *J* = 7.0 Hz, 1H), 8.58 (d, *J* = 8.5 Hz, 2H), 8.37 (d, *J* = 8.5 Hz, 2H), 8.26-8.20 (m, 2H), 8.08 (d, *J* = 6.0 Hz, 1H), 7.56-7.55 (m, 1H). MS (ESI): *m/z* 342 $[M+1]^+$. HPLC Purity: 96.95%

Scheme 37



Example 62

2-(4-(oxazol-2-yl) phenyl)-1, 6-naphthyridine-4-carbohydrazide hydrochloride (62)

To a stirred solution of oxazole (**ES**; 1 g, 14.71 mmol) in THF (25 mL) under inert atmosphere was added *n*-butyl lithium (7.3 mL, 14.71 mmol) dropwise for 10 min at -78 °C. After stirring for 10 min at -78 °C, tributyltin chloride (3.93 mL, 14.71 mmol) was added to the reaction mass and the reaction was stirred for 1 h at -78 °C. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was quenched with hexane (40 mL) and the volatiles were evaporated under reduced pressure to obtain crude **ET** (5.2 g) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.17 (s, 1H), 1.62-1.38 (m, 6H), 1.27-1.05 (m, 9H), 0.96-0.85 (m, 12H).

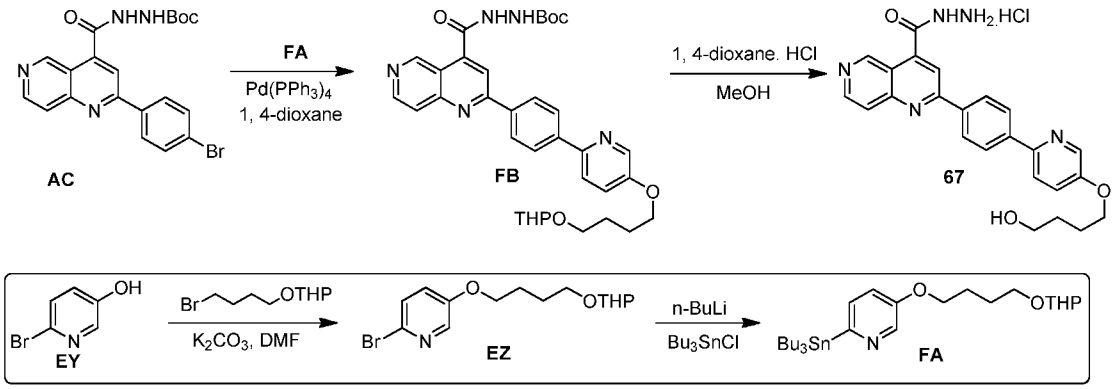
To a stirred solution of 1-(4-iodophenyl)ethanone (**EU**; 500 mg, 2.03 mmol) in 1,4-dioxane (5 mL) under inert atmosphere was added **ET** (1.1 g, 3.04 mmol) at RT in a sealed tube. After the reaction was purged under argon for 10 min, $Pd(PPh_3)_4$ (234 mg, 0.20 mmol) was added to the reaction mass. The reaction was then heated to 100 °C and stirred for 6 h. After complete consumption of the starting material, the reaction mass was filtered through Celite. The filtrate was diluted with water (20 mL) and was extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain crude **EV** (200 mg, 53%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 9.0 Hz, 2H), 7.77 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.30 (s, 1H), 2.65 (s, 3H).

To a stirred solution of ethyl 2-oxo-2-(4-pivalamidopyridin-3-yl)acetate (**C**; 200 mg, 0.71 mmol) in ethanol:water (10:1, 11 mL) under inert atmosphere was added potassium hydroxide (201 mg, 3.59 mmol). The reaction was heated to reflux and stirred for 2 h. After the reaction mass was cooled to RT, **EV** (201 mg, 1.07 mmol) was added. The reaction was then heated to reflux and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (15 mL) and was extracted with CH_2Cl_2 (2x20 mL). The aqueous layer was acidified with acetic acid to pH~4. The obtained solid was filtered and co-distilled with toluene (2x5 mL) to obtain crude **EW** (250 mg) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.00 (br s, 1H), 10.05 (d, J = 10.0 Hz, 1H), 8.72 (d, J = 6.0 H, 1H), 8.49-8.41 (m, 3H), 8.30 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.04-7.95 (m, 2H), 7.46 (s, 1H).

To a stirred solution of **EW** (250 mg, 0.78 mmol) in DMF (5 mL) under inert atmosphere were added EDCI·HCl (226 mg, 1.18 mmol), HOBt (160 mg, 1.18 mmol), diisopropylethylamine (0.5 mL, 2.36 mmol) and Boc-hydrazine (310 mg, 2.36 mmol) at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (25 mL) and the compound was extracted with EtOAc (3x20 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The residue was purified via column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **EX** (50 mg, 14%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.72 (s, 1H), 9.30 (s, 1H), 8.85 (d, J = 6.0 Hz, 1H), 8.53 (d, J = 8.0 Hz, 2H), 8.33 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 6.0 Hz, 1H), 7.47 (s, 1H), 1.49 (s, 9H).

To a stirred solution of **EX** (50 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was warmed to RT and stirred for 3 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with diethyl ether (2x5 mL) and pentane (2x5 mL) to afford **62** (45 mg as an HCl salt) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.75 (s, 1H), 8.90 (d, J = 6.0 Hz, 1H), 8.62 (s, 1H), 8.59 (d, J = 8.5 Hz, 2H), 8.33 (s, 1H), 8.25-8.21 (m, 3H), 7.49 (s, 1H). MS (ESI): m/z 332 $[M+1]^+$. HPLC Purity: 96.37%

Scheme 38



Example 67

2-(4-(5-(4-hydroxybutoxy)pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (67)

To a stirred solution of 6-bromopyridin-3-ol (**EY**; 430 mg, 2.47 mmol) in DMF (5 mL) under inert atmosphere were added 2-(4-bromobutoxy)tetrahydro-2H-pyran (762 mg, 3.21 mmol) and potassium carbonate at 0 °C. The reaction was warmed to RT and stirred for 12 h. After complete consumption of the starting material, the reaction mixture was quenched with ice cold water (30 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude. The crude material was purified via column chromatography eluting with 20% EtOAc/hexanes to afford **EZ** (660 mg, 80%) as a colorless liquid. MS (ESI): *m/z* 331 $[M+1]^+$

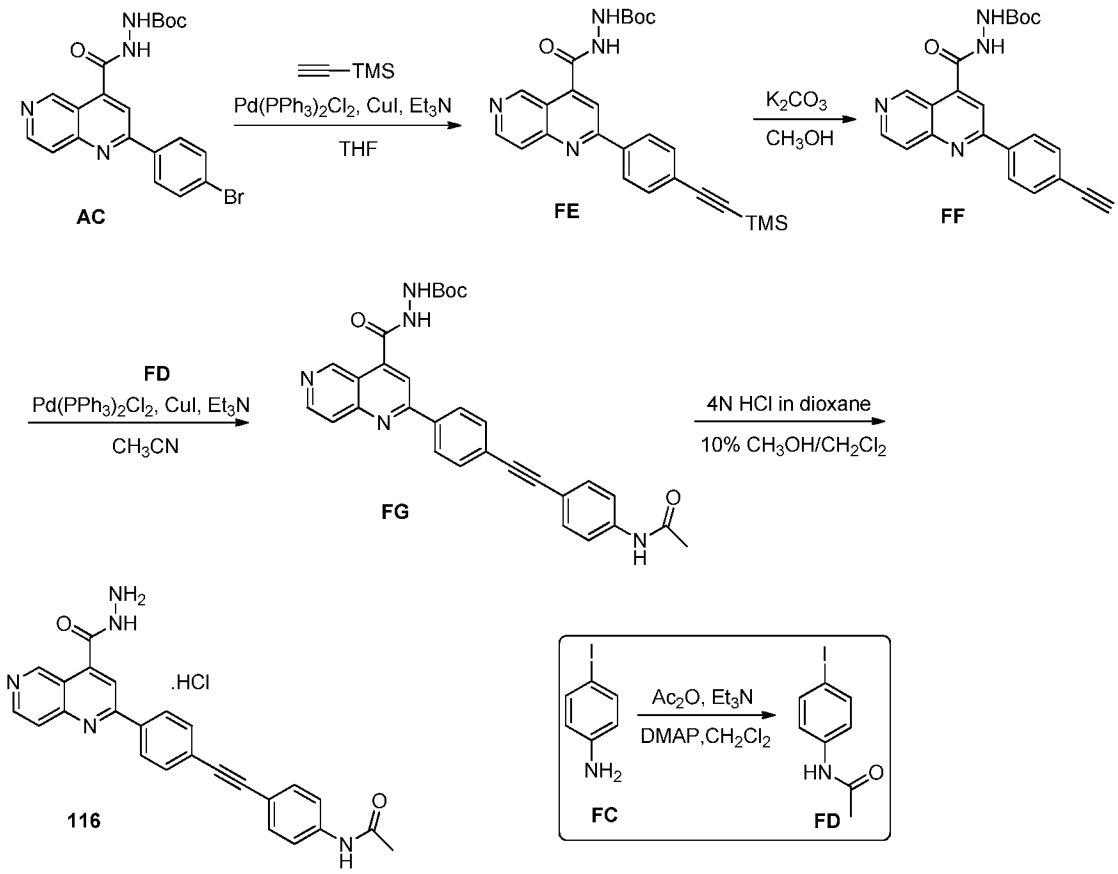
To a stirred solution of **EZ** (660 mg, 2.00 mmol) in dry ether (10 mL) under inert atmosphere was added n-butyl lithium (1.87 mL, 3.00 mmol) dropwise for 5 min at -78 °C. After stirring for 1 h at -78 °C, tributylchlorostannane (0.81 mL, 3.00 mmol) was added to the reaction mass and the reaction was stirred at -78 °C for 30 min. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was quenched with an aqueous ammonium chloride solution (30 mL) and was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain crude **FA** (1.4 g) as a colorless liquid. MS (ESI): *m/z* 541 $[M+1]^+$

To a stirred solution of **FA** (1 g, 1.85 mmol) in 1,4-dioxane (10 mL) under inert atmosphere was added **AC** (704 mg, 1.85 mmol) at RT. After the reaction was purged under argon for 15 min, $Pd(PPh_3)_4$ (214 mg, 0.18 mmol) was added. The reaction was then heated to reflux and stirred for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was purified via column

chromatography eluting with 10% MeOH/CH_2Cl_2 to afford compound **FB** (200 mg, 18%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.69 (br s, 1H), 9.29 (br s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.46-8.43 (m, 2H), 8.32 (s, 1H), 8.27 (d, J = 8.5 Hz, 2H), 8.05 (t, J = 9.0 Hz, 2H), 7.52 (d, J = 6.0 Hz, 1H), 4.57 (d, J = 4.0 Hz, 1H), 4.32 (d, J = 4.0 Hz, 1H), 4.16 (t, J = 6.0 Hz, 2H), 3.78-3.68 (m, 2H), 3.45-3.40 (m, 2H), 1.86-1.80 (m, 2H), 1.73-1.59 (m, 4H), 1.49-1.45 (m, 10H), 1.04-1.03 (m, 3H).

To a stirred solution of **FB** (100 mg, 0.16 mmol) in methanol (2 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (2 mL) at 0 °C. The reaction was warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with diethyl ether (2x5 mL) and CH_2Cl_2 (2x5 mL) to afford **67** (56 mg as an HCl salt) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.08 (br s, 1H), 9.73 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.59 (s, 1H), 8.52 (d, J = 8.5 Hz, 2H), 8.44 (s, 1H), 8.30 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.57-7.55 (m, 1H), 4.15 (t, J = 7.0 Hz, 2H), 3.48 (t, J = 7.0 hz, 2H), 1.80 (t, J = 8.0 Hz, 2H), 1.61 (t, J = 8.0 Hz, 2H). Mass: m/z 430 $[M+1]^+$. HPLC Purity: 97.41%

Scheme 39



EXAMPLE 116

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)acetamide HCl Salt (116)

To a stirred solution of 4-iodoaniline (**FC**; 5.0 g, 22.83 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (8.0 mL, 57.06 mmol) followed by Ac_2O (3.41 mL, 34.24 mmol) and DMAP (catalytic amount) at 0 °C under inert atmosphere. The reaction mixture was stirred for 2 h at 0 °C and then for 2 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 15% EtOAc/hexane as eluent to afford **FD** (3.5 g, 13.4 mmol, 59%) as a brownish solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.16 (bs, NH), 2.17 (s, 3H).

To a stirred solution of **AC** (2.0 g, 4.52 mmol) in THF (40 mL) were added TMS-acetylene (2.2 g, 22.6 mmol) and Et_3N (6.34 mL, 45.2 mmol) at RT. After the reaction mixture was degassed by purging with argon for 20 min, CuI (86.15 mg, 0.45 mmol) and $Pd(PPh_3)_2Cl_2$

(317 mg, 0.45 mmol) were added at RT. The reaction was degassed for an additional 10 min. After stirring for 18 h at RT, the reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford **FE** (1.75 g, 3.8 mmol, 84%) as a brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (bs, 1H), 9.70 (bs, 1H), 9.29 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 2H), 8.30 (s, 1H), 8.03 (d, J = 5.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 1.49 (s, 9H), 0.27 (s, 9H). MS (ESI): m/z 461 $[M+1]^+$.

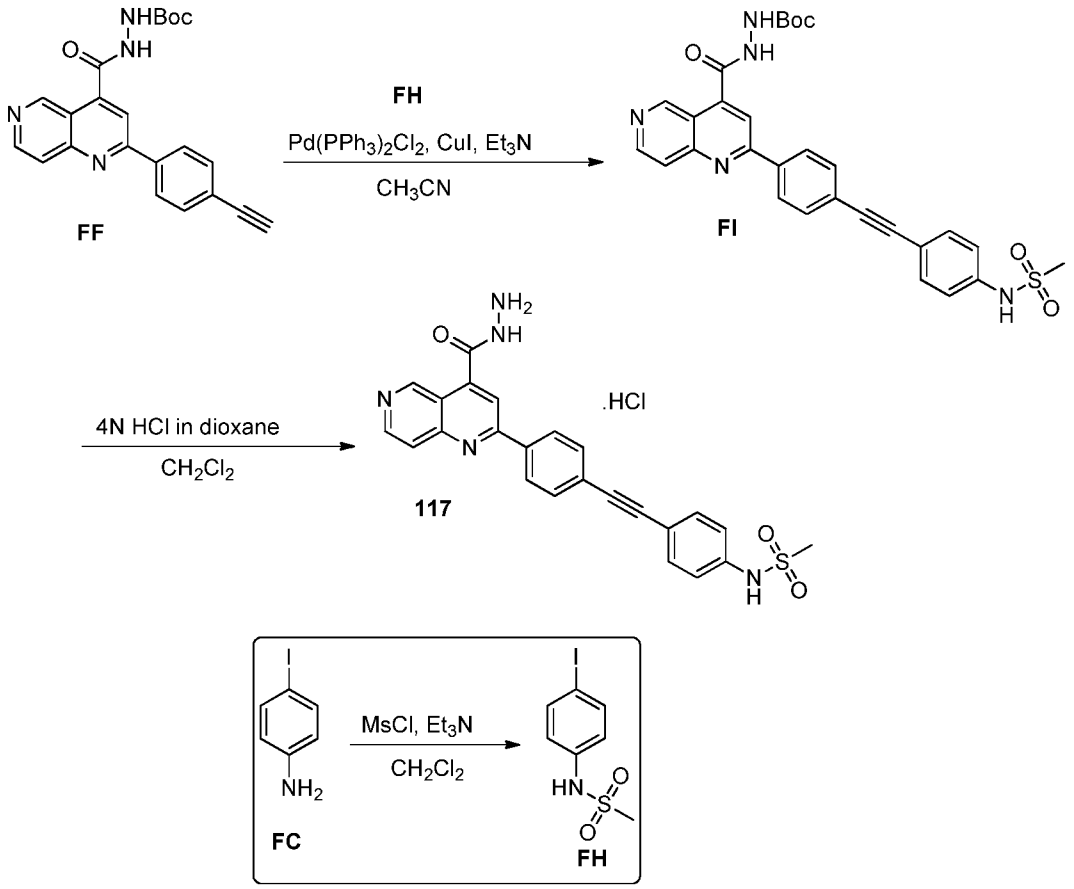
To a stirred solution of **FE** (1.0 g, 2.17 mmol) in CH_3OH (20 mL) was added K_2CO_3 (899 mg, 6.52 mmol) at RT. After stirring for 3 h, the reaction mixture was filtered and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 3% CH_3OH/CH_2Cl_2 as eluent to afford **FF** (250 mg, 0.64 mmol, 29%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (bs, 1H), 9.70 (bs, 1H), 9.29 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 2H), 8.30 (s, 1H), 8.03 (d, J = 6.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 4.43 (s, 1H), 1.49 (s, 9H). MS (ESI): m/z 389 $[M+1]^+$.

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (15 mL) were added **FD** (151 mg, 0.58 mmol) and Et_3N (0.54 mL, 3.86 mmol) at RT. After the reaction was degassed by purging with argon for 20 min, CuI (7.36 mg, 0.038 mmol) and $Pd(PPh_3)_2Cl_2$ (27.0 mg, 0.038 mmol) were added at RT. The reaction mixture was degassed for an additional 10 min. After stirring for 3 h at reflux temperature, the reaction mixture was cooled to RT, filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with water and extracted with 10% MeOH/EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **FG** (100 mg, 0.19 mmol, 49%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (bs, 1H), 10.15 (bs, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.41 (d, J = 8.0 Hz, 2H), 8.32 (s, 1H), 8.04 (d, J = 6.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 2.07 (s, 3H), 1.49 (s, 9H). MS (ESI): m/z 522 $[M+1]^+$

To a stirred solution of **FG** (50 mg, 0.09 mmol) in 10% CH_3OH/CH_2Cl_2 (5 mL) was added 4N HCl in 1,4-dioxane (1.0 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 5 h at RT. After consumption of the starting material (by TLC), the volatiles

were evaporated under reduced pressure to obtain the crude, which was triturated with 5% CH_3OH/CH_2Cl_2 to afford an HCl salt of **116** (12 mg) as a brownish solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.94 (bs, 1H), 10.21 (bs, 1H), 9.82 (s, 1H), 8.98-8.96 (m, 1H), 8.56 (s, 1H), 8.46 (d, J = 8.4 Hz, 2H), 8.21-8.19 (m, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 4.19 (bs, 2H), 2.08 (s, 3H). MS (ESI): m/z 422 $[M+1]^+$. HPLC: 93.6%.

Scheme 40



EXAMPLE 117

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)methanesulfonamide HCl salt (117)

To a stirred solution of 4-iodoaniline (**FC**; 2.0 g, 9.13 mmol) in CH_2Cl_2 (20 mL) was added pyridine (1.47 mL, 18.26 mmol) at RT. After the reaction was cooled to 0 °C, methanesulfonyl chloride (1.06 mL, 13.69 mmol) was added under an inert atmosphere. The resulting solution was stirred for 1 h at RT. Progress of the reaction was monitored by TLC. The reaction was then quenched with 1N HCl and extracted with EtOAc (2×50 mL). The

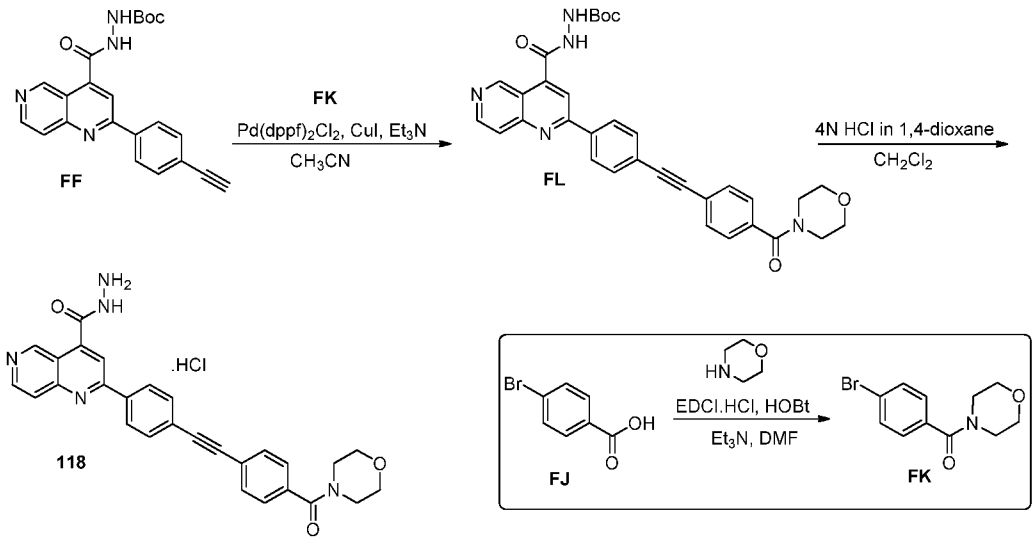
combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes as eluent to afford **FH** (2.2 g, 7.40 mmol, 81%) as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.42 (bs, 1H), 3.01 (s, 3H).

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (15 mL) were added **FH** (172 mg, 0.58 mmol) and Et_3N (0.54 mL, 3.86 mmol) at RT. The reaction was degassed by purging with argon for 20 min. To the resulting reaction mixture were added CuI (7.36 mg, 0.038 mmol) and $Pd(PPh_3)_2Cl_2$ (27.13 mg, 0.038 mmol) at RT and the reaction was degassed for an additional 10 min. The reaction mixture was then stirred for 3 h at reflux temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to RT, filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **FI** (40 mg, 0.07 mmol, 18%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (bs, 1H), 10.16 (bs, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.42 (d, *J* = 8.5 Hz, 2H), 8.32 (s, 1H), 8.04 (d, *J* = 6.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 3.07 (s, 3H), 1.49 (s, 9H). LC-MS: *m/z* 558 $[M+1]^+$ at 3.12 min (85.2% purity).

To a stirred solution of **FI** (40 mg, 0.07 mmol) in CH_2Cl_2 (4 mL) was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 2 h at 0 °C and 1 h at RT. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to obtain the crude, which was triturated with 5% CH_3OH/CH_2Cl_2 to afford an HCl salt of **117** (15 mg) as a red color solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (bs, 1H), 10.13 (s, 1H), 9.69 (s, 1H), 8.86 (d, *J* = 6.0 Hz, 1H), 8.54 (s, 1H), 8.51-8.44 (m, 2H), 8.12 (d, *J* = 6.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 3.07 (s, 3H). MS (ESI): *m/z* 458 $[M+1]^+$. HPLC: 93.02%.

Scheme 41



EXAMPLE 118

2-(4-((4-(Morpholine-4-carbonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide HCl salt (118)

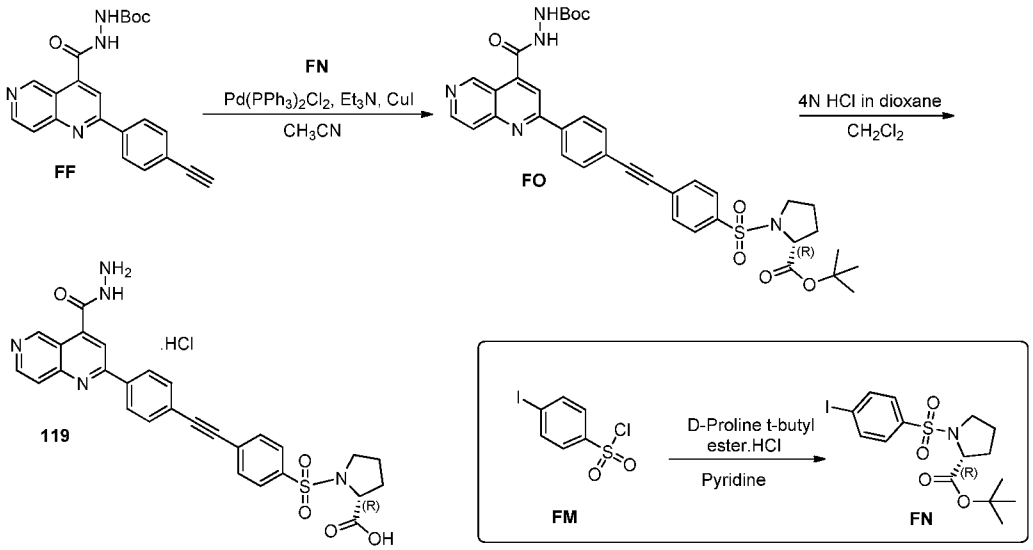
To a stirred solution of 4-bromobenzoic acid (**FJ**; 0.5 g, 2.5 mmol) in DMF (15 mL) were added EDCI·HCl (718.8 mg, 3.75 mmol), HOBt (506.6 mg, 3.75 mmol) and Et_3N (1.05 mL, 7.5 mmol) at RT under inert atmosphere. After being stirred for 10 min, morpholine (0.326 mL, 3.75 mmol) was added to the reaction mixture and stirring was continued for an additional 16 h at RT. Progress of the reaction was monitored (by TLC). The reaction mixture was then diluted with ice-cold water and extracted with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude, which was purified by silica gel column chromatography eluting with 2% CH_3OH/CH_2Cl_2 as eluent to afford **FK** (0.6 g, 2.22 mmol, 89%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 3.80-3.60 (m, 8H). MS (ESI): *m/z* 270 $[M+1]^+$.

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (10 mL) were added **FK** (156 mg, 0.58 mmol) and Et_3N (0.54 mL, 3.86 mmol) at RT. After the reaction was degassed by purging with argon for 20 min, CuI (7.36mg, 0.038 mmol) and $Pd(PPh_3)_2Cl_2$ (27.1mg, 0.038 mmol) were added at RT and the reaction was degassed for an additional 10 min. The reaction mixture was then stirred for 3 h at reflux temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to RT, filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 7% $MeOH/CH_2Cl_2$ to afford **FL** (40 mg, 0.069 mmol, 17.9%) as an off-white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 10.65

(bs, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 3.65-3.61 (m, 8H), 1.49 (s, 9H). LC-MS: m/z 578 $[M+1]^+$ at 3.89 min (89.3% purity).

To a stirred solution of **FL** (40 mg, 0.069 mmol) in CH_2Cl_2 (3 mL) was added 4N HCl in dioxane (0.3 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 3 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was then concentrated under reduced pressure to obtain the crude residue, which was purified *via* re-crystallization using CH_3OH/Et_2O to afford an HCl salt of **118** (20 mg) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.98 (bs, 1H), 9.71 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.55 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.34 (s, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 3.65-3.56 (m, 8H). MS (ESI): m/z 478 $[M+1]^+$. HPLC: 95.1%.

Scheme 42



EXAMPLE 119

(R)-1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl) pyrrolidine-2-carboxylic acid HCl salt (119)

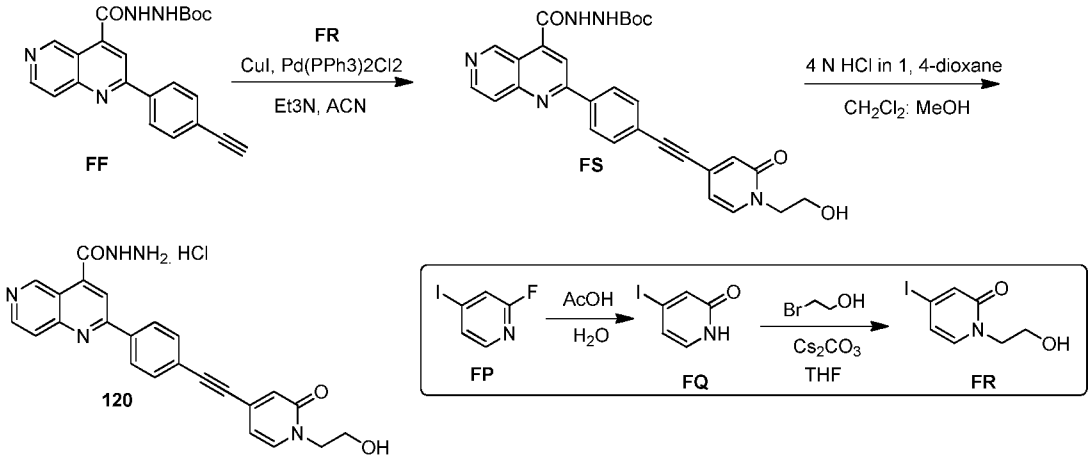
To a stirred solution of the HCl salt of D-proline-tert-butyl ester (343 mg, 1.65 mmol) in pyridine (10 mL) was added 4-iodobenzene-1-sulfonyl chloride (**FM**; 500 mg, 1.65 mmol) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 16 h at RT. Progress of the reaction was monitored by TLC. The reaction mixture was then diluted with water and extracted with EtOAc (3×30 mL). The combined organic extracts were dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 15% EtOAc/hexane as eluent to afford **FN** (550 mg, 1.25 mmol, 76%) as an orange color solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 4.22 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.46-3.42 (m, 1H), 3.36-3.32 (m, 1H), 2.09-2.04 (m, 1H), 1.99-1.93 (m, 2H), 1.84-1.80 (m, 1H), 1.44 (s, 9H).

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (10 mL) were added **FN** (253 mg, 0.58 mmol) and Et_3N (0.54 mL, 3.86 mmol) at RT. After the reaction was degassed by purging with argon for 20 min, CuI (7.36 mg, 0.038 mmol) and $Pd(PPh_3)_2Cl_2$ (27.1 mg, 0.038 mmol) were added at RT and the reaction mixture was degassed for an additional 10 min. The reaction mixture was then stirred for 4 h at reflux temperature with progress of the reaction being monitored by TLC. The reaction mixture was then cooled to RT, filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain the crude. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **FO** (75 mg, 0.107 mmol, 27.8%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.72 (bs, 1H), 9.31 (s, 1H), 8.85 (d, *J* = 4.8 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 2H), 8.34 (s, 1H), 8.05 (d, *J* = 4.8 Hz, 1H), 7.90-7.83 (m, 6H), 4.13 (dd, *J* = 8.4, 3.2 Hz, 1H), 3.41-3.35 (m, 1H), 3.26-3.22 (m, 1H), 2.02-1.97 (m, 1H), 1.87-1.80 (m, 2H), 1.71-1.66 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H). LC-MS: *m/z* 696 $[M-1]^-$ at 4.42 min (95.3% purity).

To a stirred solution of **FO** (40 mg, 0.078 mmol) in CH_2Cl_2 (3 mL) was added 4N HCl in dioxane (0.5 mL) at 0 °C under inert atmosphere. The resulting reaction mixture was stirred for 12 h at RT with progress of the reaction being monitored by TLC. The reaction mixture was then concentrated under reduced pressure to obtain the crude material, which was purified by trituration using CH_3CN to afford an HCl salt of **119** (20 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (bs, 1H), 9.85 (bs, 1H), 8.98 (bs, 1H), 8.62 (s, 1H), 8.52 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H), 7.91-7.82 (m, 6H), 4.17 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.42-3.36 (m, 1H), 3.28-3.17 (m, 1H), 2.05-1.81 (m, 3H), 1.68-1.58 (m, 1H). MS (ESI): *m/z* 542 $[M+1]^+$. HPLC: 93.07%.

Scheme 43



Example 120

2-(4-((1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide hydrochloride (120)

To a stirred solution of 2-fluoro-4-iodopyridine (**FP**; 1 g, 4.42 mmol) in water (1.6 mL) was added acetic acid (3.3 mL) at RT. The reaction mixture was heated to 110-120 °C and stirred for 12 h. After complete consumption of the starting material (as monitored by TLC), the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was co-distilled with toluene (5 mL) and was triturated with ether (2x10 mL) to afford **FQ** (970 mg, 98%) as an off-white sold. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.78 (br s, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.86 (s, 1H), 6.49 (d, J = 6.8 Hz, 1H).

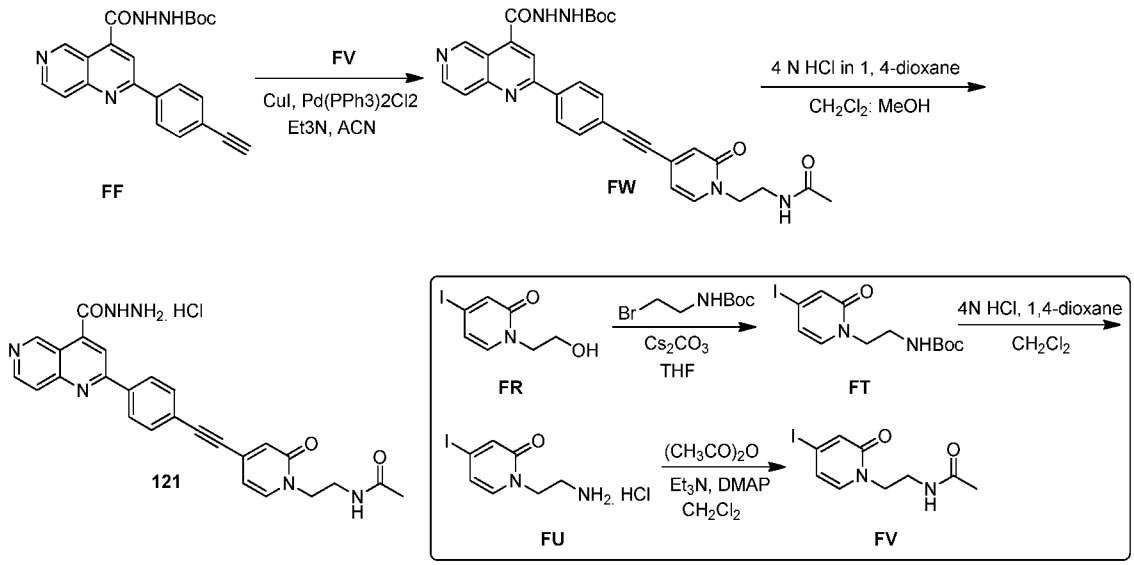
To a stirred solution of **FQ** (500 mg, 2.26 mmol) in THF (20 mL) under inert atmosphere was added cesium carbonate (1.65 g, 5.06 mmol) at RT. After the reaction was stirred for 15 min, 2-bromoethanol was added to the reaction mixture. The reaction mixture was heated to reflux and stirred for 12 h. After complete consumption of the starting material, the reaction mixture was filtered under vaccum and the filtrate was concentrated under reduced pressure to obtain the crude material, which was purified by silica gel column chromatography eluting with 40-50% EtOAc/hexanes to afford **FR** (510 mg, 71%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 (d, J = 7.2 Hz, 1H), 6.90 (s, 1H), 6.53 (d, J = 7.2 Hz, 1H), 4.86 (t, J = 5.2 Hz, 1H), 3.87 (t, J = 5.6 Hz, 2H), 3.57 (t, J = 5.6 Hz, 2H).

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (20 mL) under inert atmosphere were added triethylamine (0.5 mL, 3.85 mmol) and **FR** (122 mg, 0.46 mmol) at 0 °C. After the reaction was purged with argon for 30 min, copper iodide (7.3 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (27 mg, 0.03 mmol) were added. The reaction was then heated to reflux and stirred for 3 h. After complete consumption of the starting material, the reaction mass was

cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude residue. The residue was purified by silica gel column chromatography eluting with 8-10% MeOH/CH_2Cl_2 to afford **FS** (90 mg, 35%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.71 (br s, 1H), 9.30 (br s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.45 (d, J = 7.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 7.0 Hz, 1H), 6.62 (s, 1H), 6.34 (d, J = 7.2 Hz, 1H), 4.90 (t, J = 5.6 Hz, 1H), 3.95 (t, J = 5.6 Hz, 2H), 3.64 (t, J = 5.6 Hz 2H), 1.49 (s, 9H).

To a stirred solution of **FS** (45 mg, 0.08 mmol) in CH_2Cl_2 (1:1, 1 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was then warmed to RT and stirred for 1 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude material, which was triturated with CH_3CN (2x4 mL), diisopropyl ether (2x4 mL) and pentane (2x4 mL) to afford **120** (30 mg as an HCl salt) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (br s, 1H), 9.71 (br s, 1H), 8.88-8.87 (m, 1H), 8.53 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.0 Hz, 1H), 6.62 (s, 1H), 6.34 (d, J = 7.0 Hz, 1H), 3.97-3.90 (m, 2H), 3.65-3.56 (m, 2H). Mass: m/z 426 $[M+1]^+$. HPLC Purity: 95.82%

Scheme 44



Example 121

***N*-(2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2*H*)-yl)ethyl)acetamide hydrochloride (121)**

To a stirred solution of **FR** (1 g, 4.52 mmol) in THF (30 mL) under inert atmosphere was added cesium carbonate (1.27 g, 10.16 mmol) at RT. After stirring at RT for 15 min, tert-butyl (2-bromoethyl)carbamate was added to the reaction mixture and the reaction was heated to reflux and stirred for 12 h. After complete consumption of the starting material, the reaction mixture was filtered under vaccum and the filtrate was concentrated under reduced pressure to obtain the crude material. The crude material was purified by silica gel column chromatography eluting with 2-5% MeOH/CH_2Cl_2 to afford **FT** (750 mg, 45%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.22 (d, J = 7.0 Hz, 1H), 6.89 (s, 1H), 6.86-6.84 (m, 1H), 6.54 (d, J = 7.0 Hz, 1H), 3.84-3.82 (m, 2H), 3.19-3.17 (m, 2H), 1.33 (s, 9H).

To a stirred solution of **FT** (300 mg, 0.82 mmol) in CH_2Cl_2 (1 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (2 mL) at 0 °C. After stirring for 2 h at RT, the volatiles were evaporated under reduced pressure to obtain the crude material, which was triturated with CH_2Cl_2 (2x7 mL) to afford **FU** (240 mg as an HCl salt) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (d, J = 7.2 Hz, 1H), 7.07 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.64-6.62 (m, 2H), 3.84-3.82 (m, 2H), 3.19-3.08 (m, 2H).

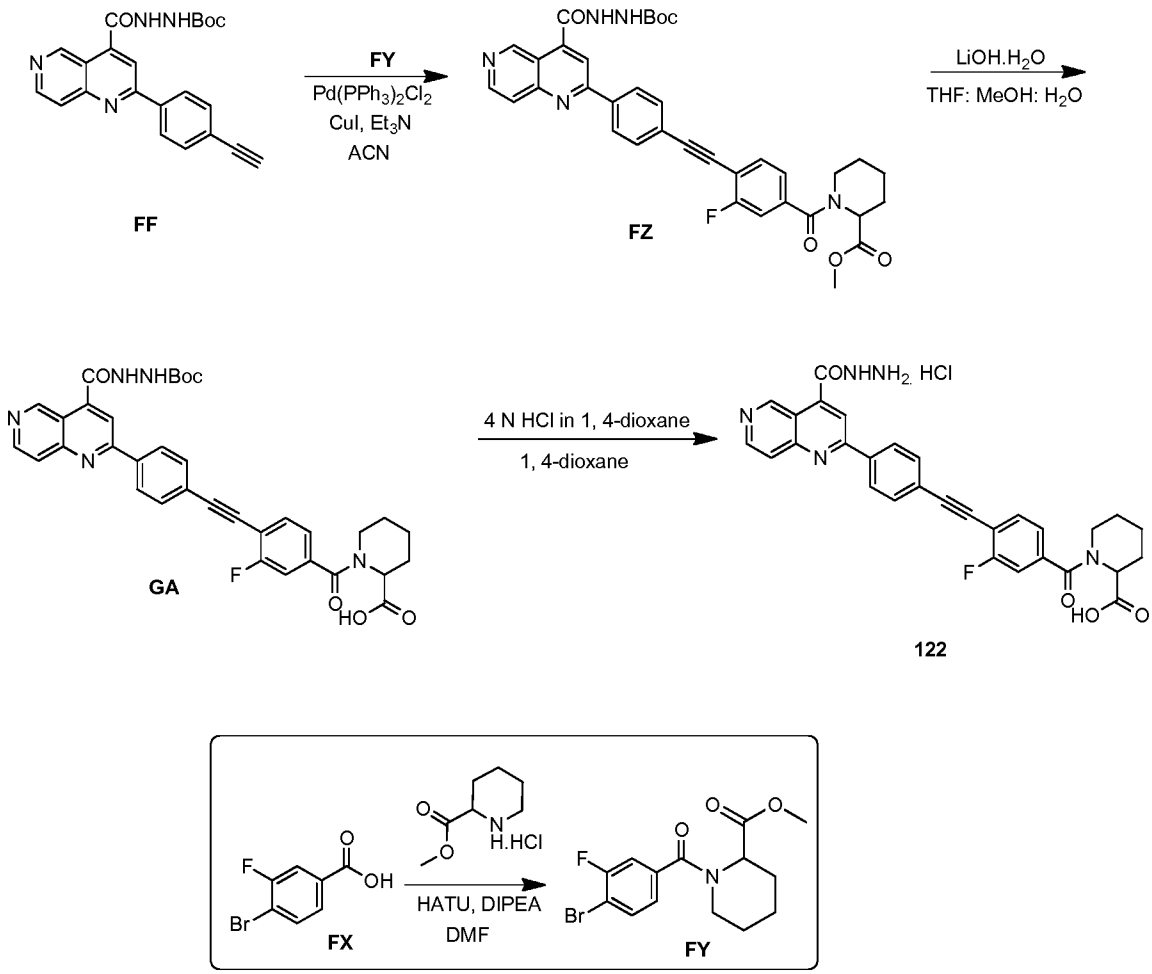
To a stirred solution of **FU** (300 mg, 1.13 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere were added triethylamine (286 mg, 2.83 mmol), *p*-dimethylaminopyridine (13.8 mg, 0.11 mmol) and acetic anhydride (138 mg, 1.35 mmol) at 0 °C. After stirring for 2 h at RT, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2x10 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude residue was purified by silica gel column chromatography eluting with 3-5% MeOH/CH_2Cl_2 to afford **FV** (150 mg, 43%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.91 (br s, 1H), 7.26 (d, J = 7.0 Hz, 1H), 6.91 (s, 1H), 6.54 (d, J = 7.0 Hz, 1H), 3.86-3.84 (m, 2H), 3.30 (s, 2H), 1.76 (s, 3H).

To a stirred solution of **FF** (150 mg, 0.38 mmol) in CH_3CN (30 mL) under inert atmosphere were added triethylamine (0.5 mL, 3.85 mmol) and **FV** (142 mg, 0.46 mmol) at 0 °C. After the reaction was purged with argon for 30 min, copper iodide (7.3 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (27 mg, 0.03 mmol) were added. The reaction was then heated to reflux and stirred for 3 h. After complete consumption of the starting material, the reaction mass was cooled to RT and the volatiles were evaporated under reduced pressure to obtain the crude material, which was purified by silica gel column chromatography eluting with 8-10% MeOH/CH_2Cl_2 to afford **FW** (101 mg, 46%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.71 (br s, 1H), 9.21 (br s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.45

(d, J = 8.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.94 (t, J = 5.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 6.8 Hz, 1H), 6.61 (s, 1H), 6.35 (d, J = 6.8 Hz, 1H), 3.91 (t, J = 4.0 Hz, 2H), 3.31-3.30 (m, 2H), 1.78 (s, 3H), 1.49 (s, 9H).

To a stirred solution of **FW** (101 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. After stirring for 4 h at RT, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was triturated with CH_2Cl_2 (2x5 mL), CH_3CN (2x5 mL) and pentane (2x5 mL) to afford **121** (12 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (br s, 1H), 9.74 (br s, 1H), 8.90 (br s, 1H), 8.55 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.17-8.15 (m, 1H), 7.99-7.97 (m, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 6.8 Hz, 1H), 6.61 (s, 1H), 6.34 (d, J = 6.8 Hz, 1H), 3.94-3.91 (m, 2H), 3.34-3.33 (m, 2H), 1.78 (s, 3H). Mass: *m/z* 467.4 $[M+1]^+$. HPLC Purity: 97.84%

Scheme 45



Example 122

2-(3-fluoro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)cyclohexanecarboxylic acid hydrochloride (122)

To a stirred solution of 4-bromo-3-fluorobenzoic acid (**FX**; 500 mg, 2.28 mmol) in DMF (20 mL) under inert atmosphere were added methyl piperidine-2-carboxylate hydrochloride (282 mg, 3.24 mmol), HATU (1.3 g, 3.47 mmol) and diisopropylethylamine (1.68 mL, 9.12 mmol) at 0 °C. The reaction was then warmed to RT and stirred for 14 h. After complete consumption of the starting material, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The residue was purified by silica gel column chromatography (70-80% EtOAc/hexanes) to afford **FY** (500 mg, 77%) as a thick brown syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (m, 1H), 7.22 (d, J = 6.0 Hz, 1H), 7.10 (d, J =

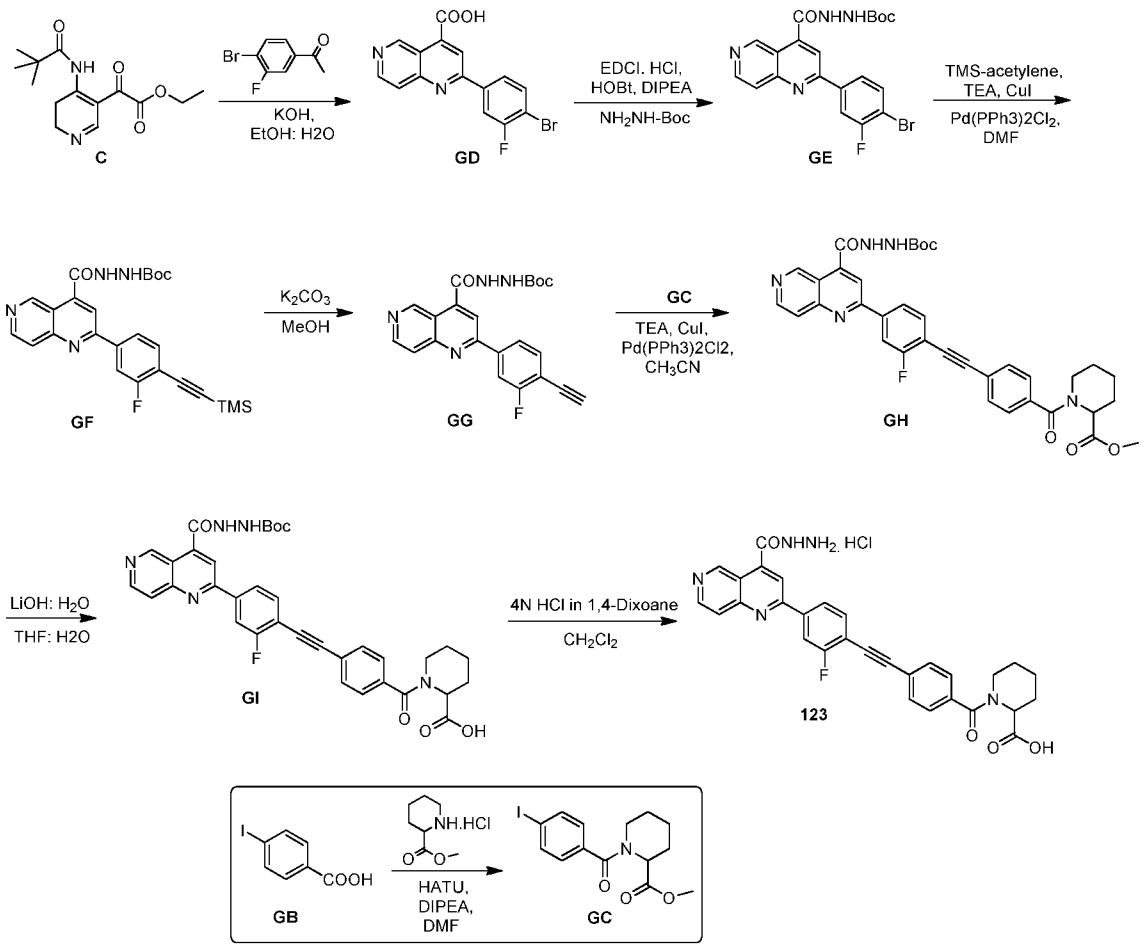
6.0 Hz, 1H), 3.80 (s, 3H), 3.60 (d, *J* = 9.0 Hz, 1H), 3.29 (t, *J* = 6.0 Hz, 1H), 2.38 (d, *J* = 9.0 Hz, 1H), 1.80-1.72 (m, 2H), 1.66-1.60 (m, 2H), 1.48-1.38 (m, 2H).

To a stirred solution of **FF** (300 mg, 0.77 mmol) in CH_3CN (30 mL) under inert atmosphere were added triethylamine (1.1 mL, 7.70 mmol) and **FY** (2.2 g, 21.6 mmol) at 0 °C. The reaction mixture was purged with argon for 30 min followed by the addition of copper iodide (14 mg, 0.07 mmol) and $Pd(PPh_3)_2Cl_2$ (54 mg, 0.07 mmol). After stirring at reflux for 3 h, the reaction was cooled to RT and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to obtain the crude material, which was purified by silica gel column chromatography eluting with 2-4% MeOH/CH_2Cl_2 to afford **FZ** (59 mg, 11%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.71 (br s, 1H), 9.29 (br s, 1H), 8.84 (d, *J* = 5.2 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 2H), 8.33 (br s, 1H), 8.05 (d, *J* = 5.6 Hz, 1H), 7.84-7.79 (m, 3H), 7.40-7.29 (m, 2H), 5.27-5.25 (m, 1H), 4.46-4.44 (m, 1H), 3.75-3.73 (m, 4H), 3.51-3.48 (m, 1H), 3.17-3.15 (m, 1H), 1.72-1.69 (m, 2H), 1.49 (s, 12H).

To a stirred solution of **FZ** (60 mg, 0.09 mmol) in THF:MeOH:H_2O (4:1:1; 12 mL) was added lithium hydroxide monohydrate (9.6 mg, 230.4 mmol) at 0 °C. The reaction was warmed to RT and stirred for 4 h. After consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude residue, which was diluted with water (10 mL) and acidified with glacial acetic acid (pH~4) (10 mL) to obtain a solid. The solid was filtered, dried and triturated with isopropyl alcohol:pentane (1:4, 2x5 mL) to afford crude **GA** (45 mg) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.11 (br s, 1H), 10.66 (br s, 1H), 9.71 (br s, 1H), 9.29 (br s, 1H), 8.86-8.84 (m, 1H), 8.46-8.44 (m, 2H), 8.33 (s, 1H), 8.06-8.05 (m, 1H), 7.84-7.82 (m, 3H), 7.38-7.36 (m, 2H), 5.17-5.14 (m, 1H), 4.32-4.31 (m, 1H), 3.79-3.76 (m, 1H), 2.25-2.24 (m, 2H), 1.69-1.66 (m, 3H), 1.69 (s, 9H), 1.50-1.48 (m, 2H).

To a stirred solution of **GA** (45 mg, 0.07 mmol) in 1,4-dioxane (10 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. After stirring for 2 h at RT, the volatiles were evaporated under reduced pressure to obtain the crude residue. The crude residue was triturated with isopropyl alcohol:CH_3CN (1:1, 2x5 mL) to afford **122** (30 mg as HCl salt) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.59 (br s, 1H), 9.69 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.48 (d, *J* = 10.0 Hz, 3H), 8.10 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.78-7.77 (m, 1H), 7.39-7.37 (m, 1H), 7.29-7.28 (m, 1H), 5.18-5.16 (m, 1H), 4.32-4.30 (m, 2H), 3.22-3.19 (m, 1H), 2.22-2.20 (m, 1H), 1.68-1.67 (m, 2H), 1.56-1.54 (m, 1H), 1.47-1.45 (m, 1H), 1.31-1.29 (m, 1H). MS (ESI): *m/z* 538.4 $[M+1]^+$. HPLC Purity: 90.87%

Scheme 46



Example 123

1-(4-((2-fluoro-4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl) piperidine-2-carboxylic acid hydrochloride (123)

To a stirred solution of 4-iodobenzoic acid (**GB**; 500 mg, 2.01 mmol) in DMF (30 mL) under inert atmosphere were added HATU (1.57 g, 4.03 mmol), diisopropylethylamine (1.1 mL, 6.04 mmol) and methyl piperidine-2-carboxylate hydrochloride (434 mg, 2.41 mmol) at 0 °C. After stirring for 16 h at RT, the reaction mass was diluted with water (25 mL) and extracted with EtOAc (2x25 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude residue was purified by silica gel column chromatography eluting with 30-50% EtOAc/exanes to afford **GC** (650 mg, 86%) as a pale yellow sticky solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.18-7.12 (m, 2H), 5.47 (br s, 1H), 3.78-3.75 (m, 3H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.24 (t, *J* = 13.0 Hz, 1H), 2.34 (d, *J* = 12.5 Hz, 1H), 1.76 (d, *J* = 11.0 Hz, 2H), 1.40-1.30 (m, 3H). MS (ESI): *m/z* 374 $[M+1]^+$

To a stirred solution of ethyl 2-oxo-2-(4-pivalamido-5,6-dihydropyridin-3-yl)acetate (**C**; 2 g, 7.19 mmol) in ethanol:water (1:1, 40 mL) was added potassium hydroxide (1.44 g, 28.70 mmol) at RT. After the reaction was heated at90°C for 2 h, the reaction mixture was cooled to RT at which point 1-(4-bromo-3-fluorophenyl)ethanone (1.9 g, 8.63 mmol) was added. The resulting reaction mixture was heated at reflux for 16 h. After complete consumption of the starting material, the reaction mass was cooled to RT, diluted with water (40 mL), and washed with CH_2Cl_2 (2x30 mL). The pH of the aqueous layer was adjusted to 4 with glacial acetic acid. The precipitate was filtered, washed with water, dried, and co distilled with toluene (2x15 mL) to afford **GD** (1.9 g, 83 %) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.01 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.61 (s, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 6.0 Hz, 1H), 7.94 (t, J = 9.0 Hz, 1H). MS : m/z 346 $[M+1]^+$

To a stirred solution of **GD** (2 g, 5.78 mmol) in DMF (30 mL) under inert atmosphere were added EDCI·HCl (2.2 g, 11.56 mmol), HOBt (1.56 g, 11.56 mmol), diisopropylethylamine (3.2 mL, 17.34 mmol) and Boc-hydrazine (2.3 g, 17.34 mmol) at 0 °C. The reaction was warmed to RT and stirred for 16 h. After complete consumption of the starting material, the reaction mass was diluted with water (30 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (30 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The residue was purified by silica gel column chromatography eluting with 2-5% MeOH/CH_2Cl_2 to afford **GE** (1.8 g, 67%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.73 (br s, 1H), 9.31 (br s, 1H), 8.84 (d, J = 5.5 Hz, 1H), 8.36 (br s, 2H), 8.18 (d, J = 7.0 Hz, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.96 (t, J = 8.5 Hz, 1H), 1.49 (s, 9H). MS (ESI): m/z 462 $[M+1]^+$

To a stirred solution of **GE** (1 g, 2.16 mmol) in DMF (15 mL) under inert atmosphere were added triethylamine (3.2 mL, 21.60 mmol) and TMS-acetylene (2.2 g, 21.6 mmol) at RT. The reaction mixture was cooled to 0 °C and purged with argon for 30 min. Then copper iodide (41 mg, 0.21 mmol) and $Pd(PPh_3)_2Cl_2$ (152 mg, 0.21 mmol) were added to the reaction mass and the reaction was heated to 80 °C for 16 h. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was diluted with water (25 mL), extracted with EtOAc (2x30 mL), and the combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified by silica gel column chromatography eluting with 2-5% MeOH/CH_2Cl_2 to afford **GF** (980 mg, with a minor impurity) as a brown solid. ^{1}H NMR

(500 MHz, DMSO-d_6): δ 10.63 (br s, 1H), 9.74 (br s, 1H), 9.31 (br s, 1H), 8.85 (br s, 1H), 8.36 (br s, 1H), 8.31-8.23 (m, 1H), 8.06 (br s, 1H), 7.78-7.77 (m, 1H), 7.62-7.55 (m, 1H), 1.49 (s, 9H), 0.28 (s, 9H). MS (ESI): *m/z* 479 $[M+1]^+$

To a stirred solution of **GF** (1 g, 2.09 mmol) in methanol (20 mL) under inert atmosphere was added potassium carbonate (1.4 g, 10.46 mmol) at 0 °C. The reaction was warmed to RT and stirred for 2 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure. The residue was diluted with water (30 mL), extracted with EtOAc (2x30 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified by silica gel column chromatography eluting with 5-10% MeOH/CH_2Cl_2 to afford **GG** (812 mg, 88%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.62 (br s, 1H), 9.72 (br s, 1H), 9.30 (br s, 1H), 8.84 (d, *J* = 6.0 Hz, 1H), 8.40-8.23 (m, 3H), 8.04 (d, *J* = 5.5 Hz, 1H), 7.78 (t, *J* = 8.5 Hz, 1H), 4.72 (s, 1H), 1.48 (s, 9H). MS (ESI): *m/z* 407 $[M+1]^+$

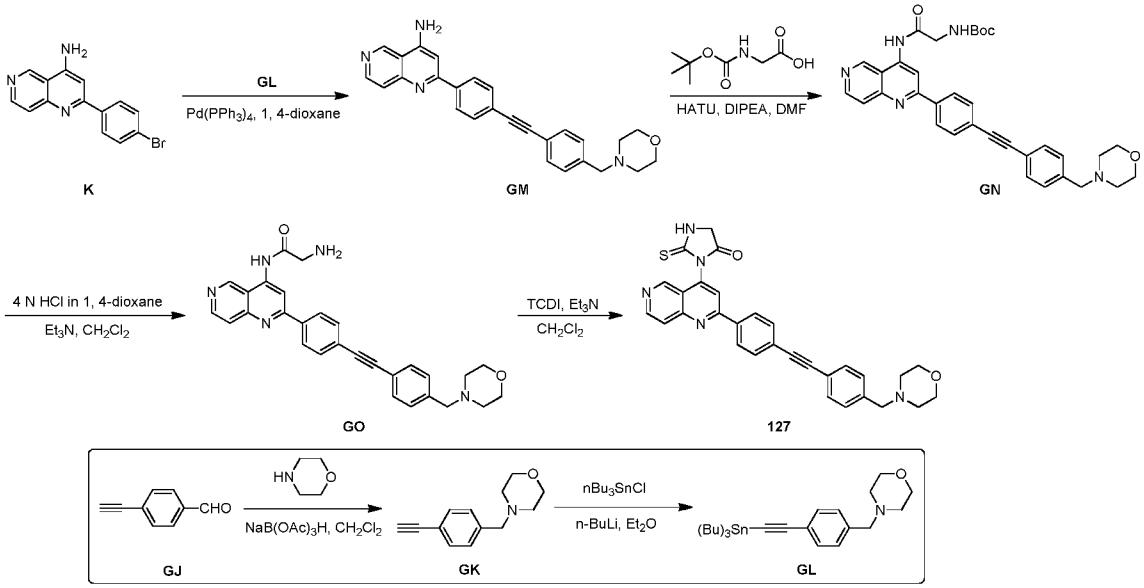
To a stirred solution of **GG** (300 mg, 0.73 mmol) in CH_3CN (20 mL) under inert atmosphere were added triethylamine (1.07 mL, 7.30 mmol) and **GC** (330 mg, 0.88 mmol) at RT. After the reaction was purged with argon for 30 min, copper iodide (14.1 mg, 0.07 mmol) and $Pd(PPh_3)_2Cl_2$ (54.3 mg, 0.07 mmol) were added. The reaction mixture was then heated at 80 °C for 4 h. After complete consumption of the starting material, the reaction mass was cooled to RT and filtered through a Celite pad. The filtrate was diluted with water (20 mL), extracted with EtOAc (2x20 mL), and the combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude material was purified by silica gel column chromatography eluting with 2-4% MeOH/CH_2Cl_2 to afford **GH** (17 0mg, 35%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (br s, 1H), 9.74 (br s, 1H), 9.31 (br s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 8.39-8.30 (m, 3H), 8.06 (d, J = 6.0 Hz, 1H), 7.97-7.87 (m, 2H), 7.48-7.42 (m, 2H), 5.28 (br s, 1H), 3.74-3.66 (m, 3H), 2.22-2.18 (m, 2H), 1.72-1.68 (m, 4H), 1.60-1.56 (m, 2H), 1.48 (s, 9H), 1.43-1.40 (m, 1H). MS (ESI): *m/z* 650 $[M-1]^+$

To a stirred solution of **GH** (100 mg, 0.15 mmol) in THF:H_2O (1:1, 5 mL) was added lithium hydroxide monohydrate (69 mg, 1.50 mmol) at 0 °C. After stirring at RT for 4 h, the volatiles were evaporated under reduced pressure. The resulting residue was diluted with water (15 mL) and extracted with diethyl ether (2x20 mL). The pH of the aqueous layer was adjusted with glacial acetic acid to ~4. The precipitate was filtered, dried and co-distilled with toluene (2x5 mL) to afford **GI** (60 mg, 61%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ

13.00 (br s, 1H), 10.64 (br s, 1H), 9.74 (br s, 1H), 9.32 (br s, 1H), 8.86 (br s, 1H), 8.39-8.30 (m, 3H), 8.08-8.06 (m, 1H), 7.91-7.89 (m, 1H), 7.72-7.62 (m, 2H), 7.55-7.45 (m, 2H), 5.18-5.17 (m, 1H), 4.39-4.27 (m, 1H), 3.45-3.41 (m, 1H), 3.21-3.16 (m, 1H), 2.20-2.17 (m, 1H), 1.77-1.75 (m, 2H), 1.68-1.57 (m, 2H), 1.41 (s, 9H). MS (ESI): *m/z* 636 $[M-1]^+$

To a stirred solution of **GI** (40 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. After stirring for 2 hr at RT, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was triturated with isopropyl alcohol:CH_3CN (2x5 mL) to afford **123** (30 mg as an HCl salt) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.10 (br s, 1H), 9.91-9.86 (m, 1H), 9.06-9.04 (m, 1H), 8.61 (s, 1H), 8.40-8.33 (m, 2H), 8.21 (br s, 1H), 7.91 (t, *J* = 7.0 Hz, 1H), 7.70-7.68 (m, 2H), 7.46-7.41 (m, 3H), 5.18-5.16 (m, 1H), 4.37-4.26 (m, 1H), 3.43-3.41 (m, 1H), 3.20-3.13 (m, 1H), 2.80-2.72 (m, 1H), 2.21-2.18 (m, 1H), 1.70-1.68 (m, 3H), 1.36-1.29 (m, 2H). MS (ESI): *m/z* 575 $[M+1]^+$. HPLC Purity: 95.51%.

Scheme 47



Example 127

3-(2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (127)

To a stirred solution of 4-ethynylbenzaldehyde (**GJ**; 1 g, 7.69 mmol) in CH_2Cl_2 (50 mL) under inert atmosphere were added morpholine (1.47 g, 16.90 mmol) and sodium triacetoxyborohydride (1.95 g, 9.20 mmol) at 0 °C. After stirring at RT for 48 h, the reaction mixture was neutralized with a saturated $NaHCO_3$ solution (25 mL) and the compound was

extracted with CH_2Cl_2 (2x30 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified via flash column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **GK** (600 mg, 39%) as a sticky solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.71-3.66 (m, 4H), 3.48 (s, 2H), 3.05 (s, 1H), 2.44-2.42 (m, 4H).

To a stirred solution of **GK** (200 mg, 0.99 mmol) in dry ether (20 mL) under inert atmosphere was added *n*-butyl lithium (1.6M in hexane) (76.4 mg, 1.19 mmol) at 0 °C. The reaction was stirred at RT for 1 h at which point tributyl tin chlorde (485 mg, 1.49 mmol) was added and the reaction was stirred for 16 h. After complete consumption of the starting material; the reaction mixture was quenched with an ammonium chloride solution (20 mL) and was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain crude **GL** (600 mg) as a pale brown liquid. LCMS: 19.37%, MS (ESI): 491.8 $[M+1]^+$

To a stirred solution of 2-(4-bromophenyl)-1,6-naphthyridin-4-amine **K** (2.5 g, 8.36 mmol) in 1,4-dioxane (100 mL) under inert atmosphere was added **GL** (10.26 g, 20.89 mmol). After the reaction was purged under argon for 10 min, $Pd(PPh_3)_4$ (965 mg, 0.83 mmol) was added and the reaction was purged under argon for an additional 10 min. The reaction was then heated to reflux and stirred for 4 h. After complete consumption of the starting material, the volatiles were removed under reduced pressure to obtain the crude residue, which was purified through silica gel column chromatography eluting with 10% MeOH/CH_2Cl_2 to afford **GM** (2.9 g, 83%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H), 8.56-8.55 (m, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 5.0 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 4H), 7.22 (s, 1H), 3.58 (s, 3H), 3.50 (s, 3H), 2.36 (s, 4H).

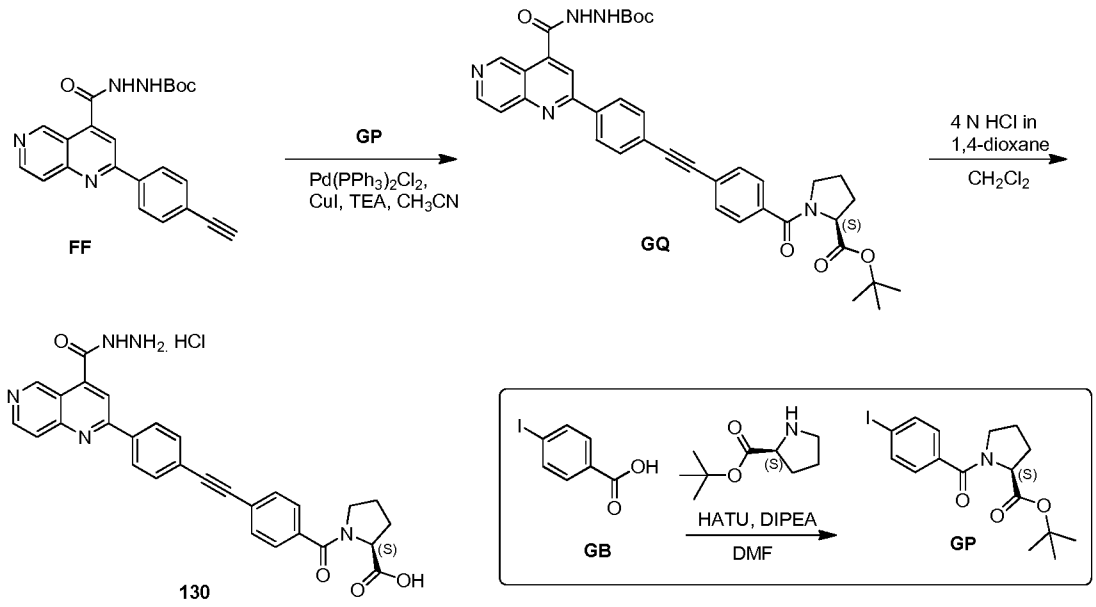
To a stirred solution of **GM** (120 mg, 0.28 mmol) in DMF (2 mL) under inert atmosphere were added 2-((tert-butoxycarbonyl)amino)acetic acid (100 mg, 0.57 mmol), diisopropylethy amine (224 mg, 1.72 mmol) and HATU (440 mg, 1.12 mmol) at RT and the reaction was stirred for 12 h. After complete consumption of the starting material, the reaction mass was diluted with water (15 mL) and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through 5% MeOH/CH_2Cl_2 to afford **GN** (60 mg, 36%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 9.76 (s, 1H), 8.84 (s, 1H), 8.77-8.76 (m, 1H), 8.25 (d,

J = 7.5 Hz, 2H), 7.92 (d, *J* = 5.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 3H), 7.24-7.22 (m, 1H), 4.06-4.03 (m, 2H), 3.61-3.58 (m, 4H), 3.51 (s, 2H), 2.38-2.36 (m, 4H), 1.38 (s, 9H).

To a stirred solution of **GN** (400 mg, 0.69 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere was added a 4N HCl solution in 1,4-dioxane (1 mL) at 0 °C. After stirring at RT for 3 h, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was triturated with diisopropyl ether (2x10 mL) to obtain 350 mg of material. The material was dissolved in CH_2Cl_2 followed by the addition of triethyl amine (0.5 mL). The obtained solid was filtered and dried under reduced pressure to afford **GO** (100 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.74 (br s, 1H), 11.40 (br s, 1H), 10.24 (br s, 1H), 8.94 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.41 (br s, 2H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.19 (br s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.70 (s, 3H), 4.37 (s, 3H), 4.20-4.19 (m, 2H), 3.94 (d, *J* = 12.0 Hz, 2H), 3.81 (t, *J* = 11.5 Hz, 2H), 3.56 (s, 1H), 3.23 (d, *J* = 12.0 Hz, 2H).

To a stirred solution of **GO** (100 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere were added triethylamine (63.5 mg, 0.62 mmol) and TCDI (56 mg, 0.31 mmol) at 0 °C and the reaction mixture was stirred for 30 min. After stirring for 1 h at RT, the reaction mass was diluted with water (10 mL) and the product was extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 and was further purified through preparative HPLC to afford **127** (5.4 mg, 5%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.80 (br s, 1H), 11.40 (s, 1H), 8.82 (d, *J* = 8.0 Hz, 1H), 8.42 (s, 1H), 8.38 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.62-3.58 (m, 4H), 3.52 (s, 2H), 2.38-2.32 (m, 4H). MS (ESI): *m/z* 520 $[M+1]^+$. HPLC Purity: 96.48%

Scheme 48



Example 130

(*S*)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid hydrochloride (130)

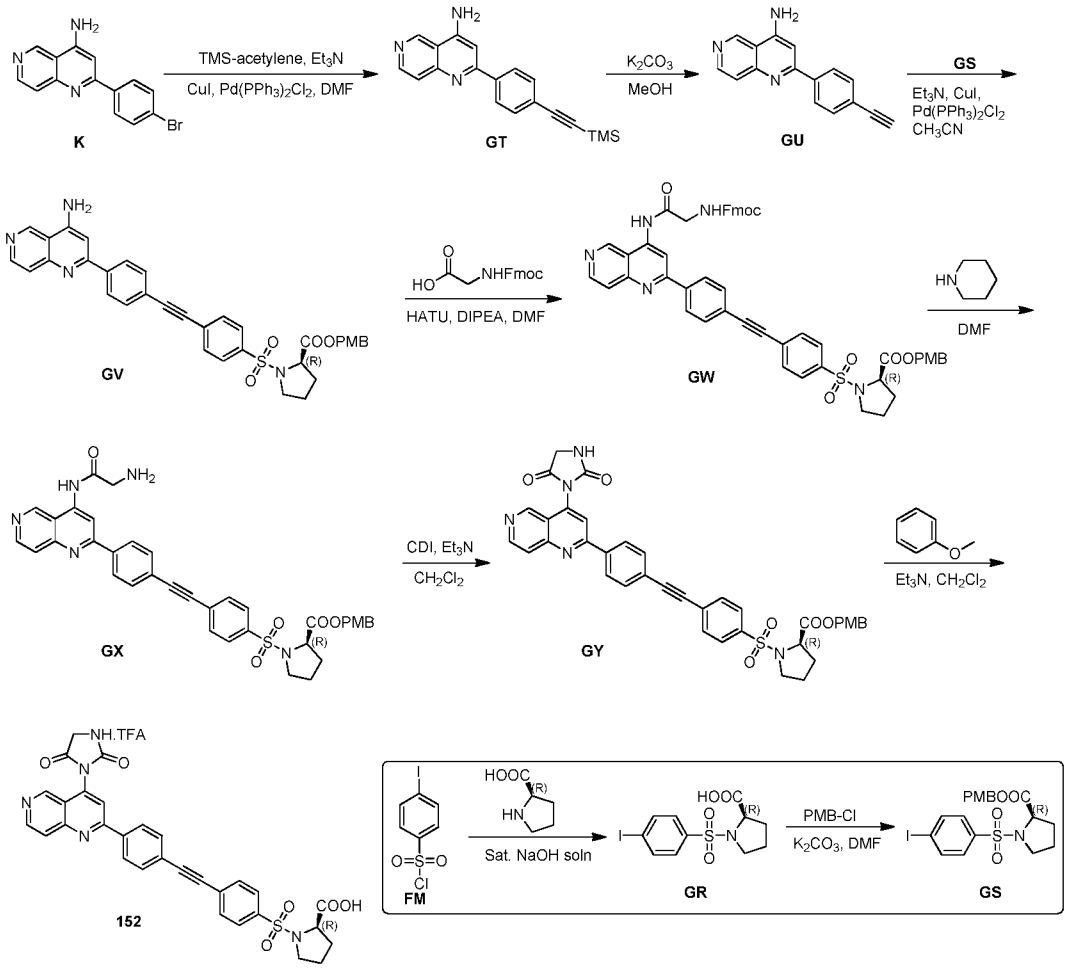
To a stirred solution of 4-iodobenzoic acid (**GB**; 500 mg, 2.01 mmol) in DMF (10 mL) under inert atmosphere were added HATU (1.17 g, 3.02 mmol) and diisopropylethylamine (1.08 mL, 6.04 mmol) at RT and the resulting reaction mixture was stirred for 15 min. After cooling to 0 °C, (S)-tert-butyl pyrrolidine-2-carboxylate (379.6 mg, 2.21 mmol) was added to the reaction mass The reaction was stirred at RT for 24 h. After complete consumption of the starting material, the reaction mixture was diluted with ice cold water (25 mL) and the compound was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **GP** (700 mg, 87%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.70 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.54-4.51 (m, 1H), 2.80 (s, 1H), 2.33-2.21 (m, 1H), 2.04-1.94 (m, 3H), 1.90-1.84 (m, 1H), 1.49 (s, 9H).

To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl)hydrazine carboxylate **FF** (150 mg, 0.38 mmol) in CH_3CN (10 mL) under inert atmosphere were added **GP** (232 mg, 0.57 mmol), triethylamine (0.54 mL, 3.86 mmol), copper iodide (7.3 mg, 0.038 mmol) and $Pd(PPh_3)_2Cl_2$ (27.1 mg, 0.038 mmol) at RT. After stirring at reflux for 4 h, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 3-5% MeOH/CH_2Cl_2 to afford **GQ** (50 mg, 20%) as a yellow solid. ^{1}H NMR (400

MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.80 (br s, 1H), 9.30 (s, 1H), 8.86 (br s, 1H), 8.45-8.34 (m, 3H), 8.26-7.79 (m, 2H), 7.78-7.41 (m, 5H), 4.40-4.36 (m, 1H), 3.65-3.49 (m, 2H), 3.10-3.07 (m, 1H), 2.30-2.26 (m, 1H), 1.90-1.83 (m, 2H), 1.49 (s, 9H), 1.43 (s, 9H).

To a stirred solution of **GQ** (50 mg, 0.07 mmol) in CH_2Cl_2 (4 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (0.5 mL) at 0 °C. After stirring at RT for 4 h, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was triturated with CH_3CN (2x5 mL) and was further purified through preparative chiral HPLC to afford **130** (10 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 9.80 (br s, 1H), 8.95 (br s, 1H), 8.62 (s, 1H), 8.50 (d, J = 8.4 Hz, 2H), 8.22 (br s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 4.44-4.41 (m, 1H), 3.65-3.51 (m, 3H), 2.30-2.19 (m, 2H), 1.91-1.87 (m, 3H), 1.03 (d, J = 6.0 Hz, 2H). MS (ESI): m/z 506.4 $[M+1]^+$. HPLC Purity: 90.68%

Scheme 49



Example 152

(*R*)-1-((4-((4-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl) sulfonyl) pyrrolidine-2-carboxylic acid (152)

To a stirred solution of (R)-pyrrolidine-2-carboxylic acid (5 g, 43.43 mmol) in aq. sodium hydroxide (20 mL) was added 4-iodobenzene-1-sulfonyl chloride (**FM**; 13.2 g, 43.43 mmol) at 0 °C. After stirring at RT for 12 h, the volatiles were removed under reduced pressure. The residue was diluted with 2N HCl solution to pH~2 and the obtained solids were filtered and dried under reduced pressure to afford **GR** (13.5 g, 82%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.75 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 4.12-4.10 (m, 1H), 3.37-3.31 (m, 1H), 3.18-3.14 (m, 1H), 1.97-1.93 (m, 1H), 1.87-1.78 (m, 2H), 1.63-1.60 (m, 1H).

To a stirred solution of **GR** (8.5 g, 22.37 mmol) in DMF (50 mL) under inert atmosphere were added potassium carbonate (15.4 g, 111.85 mmol) and *p*-methoxybenzyl chloride (4.2 g, 26.84 mmol) at 0 °C. After stirring at 70-80 °C for 8 h, the reaction mixture was diluted with water (50 mL) and was extracted with EtOAc (3x50 mL). The combined organic extracts were washed with water (40 mL), brine (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude material was purified through silica gel column chromatography eluting with 5% EtOAc/hexanes to afford **GS** (10 g, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 5.07-5.03 (m, 2H), 4.39-4.37 (m, 1H), 3.87 (s, 3H), 3.42-3.33 (m, 2H), 2.07-2.05 (m, 1H), 1.99-1.92 (m, 2H), 1.82-1.80 (m, 1H).

To a stirred solution of 2-(4-bromophenyl)-1,6-naphthyridin-4-amine (**K**; 200 mg, 0.66 mmol) in DMF (10 mL) under inert atmosphere were added TMS-acetylene (55 mg, 6.68 mmol) and triethylamine (1 mL, 6.68 mmol) at 0 °C. After the reaction mixture was purged under argon for 15 min, copper iodide (12.7 mg, 0.06 mmol) and $Pd(PPh_3)_2Cl_2$ (46.9 mg, 0.06 mmol) were added at RT. The reaction was heated to 50 °C and stirred for 12 h. After complete consumption of the starting material, the volatiles were removed under reduced pressure to obtain the crude material, which was purified through silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **GT** (100 mg, 49%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (br s, 2H), 8.10 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.40-7.38 (m, 2H), 7.22 (s, 1H), 0.26 (s, 9H).

To a stirred solution of **GT** (4 g, 12.62 mmol) in MeOH (100 mL) under inert atmosphere was added potassium carbonate (8.7 g, 63.09 mmol) at 0 °C and the resulting reaction mixture was stirred at RT for 4 h. After complete consumption of the starting material, the volatiles

were removed under reduced pressure to obtain the crude material, which was purified through silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **GU** (1.5 g, 48%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.52 (s, 1H), 8.55 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.63-7.62 (m, 3H), 7.39 (s, 2H), 7.19 (s, 1H), 4.32 (s, 1H).

To a stirred solution of **GU** (650 mg, 2.66 mmol) in CH_3CN (50 mL) under inert atmosphere were added **GS** (1.6 g, 3.19 mmol) and triethyl amine (3.9 mL, 26.62 mmol) at 0 °C. After purging under argon for 30 min, copper iodide (51 mg, 0.26 mmol) and $Pd(PPh_3)_2Cl_2$ (187 mg, 0.26 mmol) were added to the reaction mass at RT. The reaction mixture was then heated to reflux and stirred for 8 h. After complete consumption of the starting material, the volatiles were removed under reduced pressure to obtain crude **GV** (1 g) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.61 (br s, 1H), 8.66 (br s, 1H), 8.13 (d, J = 7.5 Hz, 2H), 7.89-7.73 (m, 7H), 7.32 (d, J = 8.5 Hz, 2H), 7.21 (s, 1H), 6.95 (d, J = 9.0 Hz, 2H), 5.11-5.05 (m, 2H), 4.34-4.31 (m, 1H), 3.76 (s, 3H), 3.40-3.38 (m, 1H), 3.24-3.20 (m, 1H), 3.11-3.07 (m, 2H), 1.20-1.97 (m, 1H), 1.87-1.80 (m, 2H), 1.66-1.64 (m, 1H).

To a stirred solution of 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)acetic acid (2.4 g, 8.08 mmol) in DMF (100 mL) under inert atmosphere were added HATU (9.4 g, 24.26 mmol), diisopropylethyl amine (6 mL, 32.36 mmol) and **GV** (1 g, 1.60 mmol) at 0 °C. After stirring at RT for 12 h, the reaction mixture was diluted with water (30 mL) and was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **GW** (500 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 9.78 (s, 1H), 8.87 (s, 1H), 8.77 (d, J = 5.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 2H), 7.94-7.87 (m, 5H), 7.83-7.75 (m, 5H), 7.74-7.71 (m, 1H), 7.45-7.41 (m, 2H), 7.37-7.30 (m, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.11-5.04 (m, 2H), 4.38-4.25 (m, 5H), 4.14 (d, J = 6.0 Hz, 2H), 3.78 (s, 3H), 3.39-3.36 (m, 1H), 3.25-3.20 (m, 1H), 3.02-1.97 (m, 1H), 1.90-1.78 (m, 2H), 1.67-1.64 (m, 1H), 1.03 (d, J = 6.0 Hz, 3H).

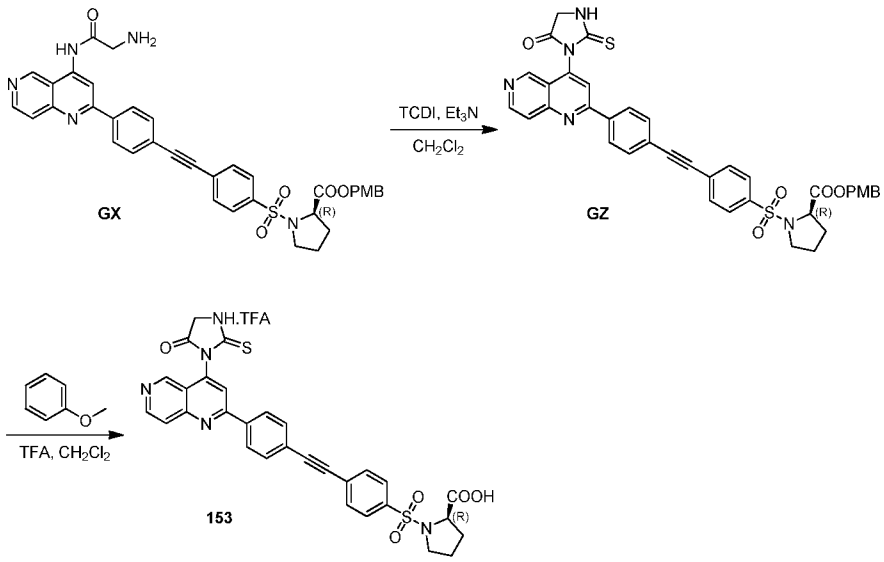
To a stirred solution of **GW** (500 mg, 5.55 mmol) in DMF (15 mL) under inert atmosphere was added piperidine (0.3 mL, 2.78 mmol) at 0 °C. Upon stirring at RT for 4 h,. the reaction mixture was diluted with water (20 mL) and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford **GX** (170 mg, 45%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-

d$_6$): δ 9.64 (s, 1H), 8.93 (s, 1H), 8.77 (d, *J* = 6.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 2H), 7.94-7.80 (m, 7H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.90-5.64 (m, 2H), 5.07 (d, *J* = 6.0 Hz, 2H), 4.33-4.31 (m, 1H), 3.76-3.73 (m, 3H), 3.55 (s, 2H), 3.42-3.38 (m, 1H), 3.12-3.08 (m, 2H), 2.02-1.99 (m, 1H), 1.84-1.78 (m, 2H), 1.66-1.62 (m, 1H).

To a stirred solution of **GX** (200 mg, 0.29 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere were added triethylamine (0.13 mL, 0.88 mmol) and CDI (57.6 mg, 0.35 mmol) at 0 °C. Upon stirring at RT for 6 h, the reaction mixture was diluted with water (15 mL) and was extracted with CH_2Cl_2 (2x15 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **GY** (100 mg, 48%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.39 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.67 (s, 1H), 8.38 (d, *J* = 8.4 Hz, 3H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.88-7.79 (m, 6H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.10-5.03 (m, 2H), 4.40-4.30 (m, 2H), 4.02-4.16 (m, 1H), 3.74 (s, 3H), 3.40-3.35 (m, 1H), 3.23-3.19 (m, 1H), 2.01-1.96 (m, 1H), 1.87-1.77 (m, 2H), 1.65-1.62 (m, 1H).

To a stirred solution of **GY** (20 mg, 0.02 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere were added anisole (9.2 mg, 0.08 mmol) and trifluoroacetic acid (0.1 mL) at 0 °C. After stirring at RT for 4 h, the volatiles were removed under reduced pressure to obtain the crude material, which was triturated with isopropyl alcohol (2x3 mL), diethyl ether (2x3 mL) and n-pentane (2x3 mL) to afford **152** (18 mg as a TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.43 (br s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.69 (s, 1H), 8.42-9=8.39 (m, 3H), 8.08 (d, *J* = 6.0 Hz, 1H), 7.91-7.83 (m, 6H), 4.41-4.37 (m, 1H), 4.22-4.15 (m, 2H), 3.42-3.36 (m, 1H), 3.25-3.19 (m, 1H), 2.02-1.95 (m, 1H), 1.92-1.77 (m, 2H), 1.64-1.58 (m, 1H). MS (ESI): *m/z* 581 $[M-1]^+$. HPLC Purity: 97.44%

Scheme 50



Example 153

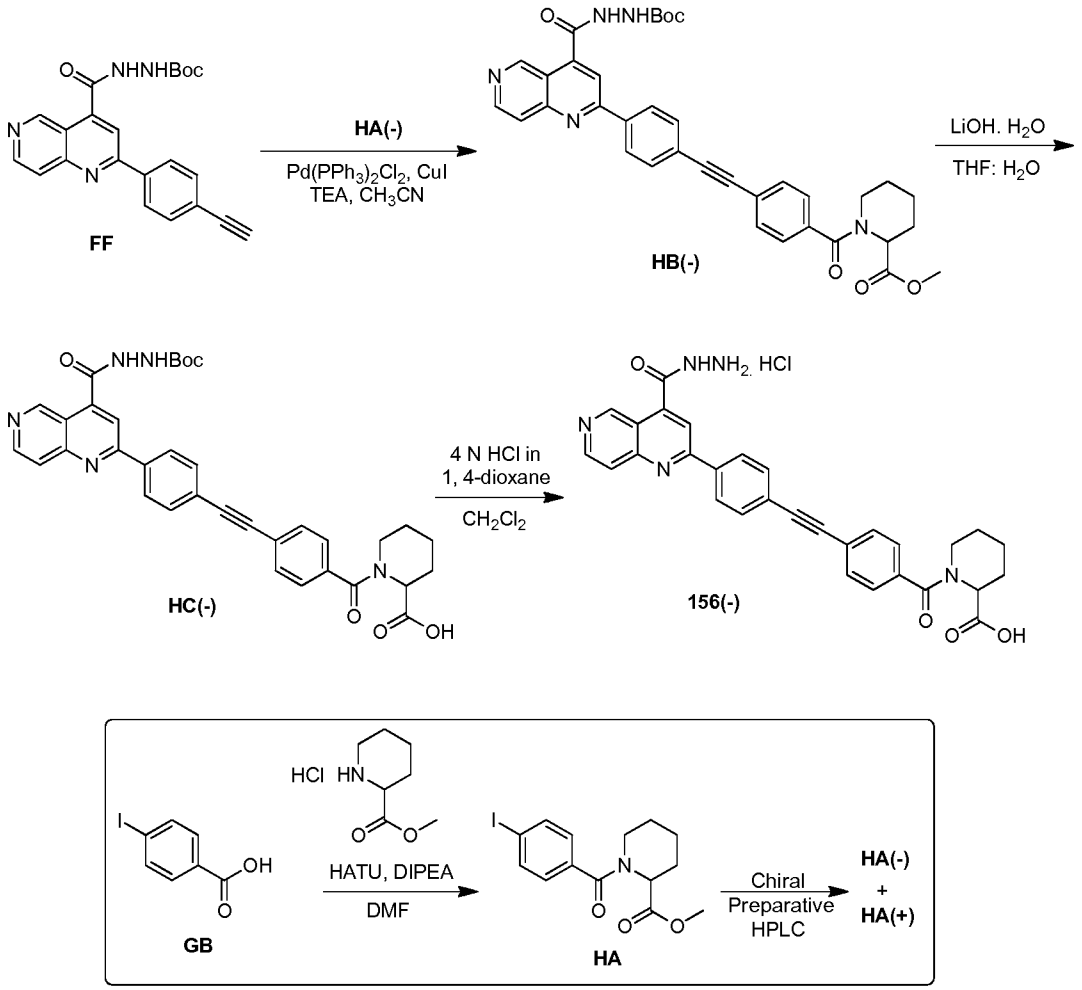
(*R*)-1-((4-((4-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) phenyl) sulfonyl) pyrrolidine-2-carboxylic acid (153)

To a stirred solution of **GX** (320 mg, 0.46 mmol) in CH_2Cl_2 (20 mL) under inert atmosphere were added triethylamine (0.11 mL, 1.42 mmol) and TCDI (101.4 mg, 0.56 mmol) at 0 °C. After stirring at RT for 6 h, the reaction mixture was diluted with water (20 mL) and was extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude residue was purified through silica gel column chromatography eluting with 3% MeOH/CH_2Cl_2 to afford **GZ** (35 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.79 (br s, 1H), 9.42 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.46 (s, 1H), 8.39 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 6.8 Hz, 1H), 7.89-7.80 (m, 6H), 7.31 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 5.11-5.04 (m, 2H), 4.63-4.58 (m, 1H), 4.45-4.40 (m, 1H), 4.34-4.31 (m, 1H), 3.76 (s, 3H), 3.42-3.38 (m, 1H), 3.28-3.24 (m, 1H), 2.02-1.60 (m, 4H).

To a stirred solution of **GZ** (10 mg, 0.01 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere were added anisole (4.5 mg, 0.04 mmol) and trifluoroacetic acid (0.1 mL) at 0 °C. After stirring at RT for 4 h, the volatiles were removed under reduced pressure to obtain the crude material. The crude material was triturated with isopropyl alcohol (2x2 mL), diethyl ether (2x2 mL) and n-pentane (2x2 mL) to afford **153** (11 mg as a TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 10.79 (s, 1H), 9.42 (s, 1H), 8.82 (s, 1H), 8.45 (s, 1H), 8.38 (d, J = 7.6 Hz, 2H), 8.08-8.07 (m, 1H), 7.87-7.83 (m, 6H), 4.61-4.56 (m, 1H), 4.43-

4.38 (m, 1H), 4.16-4.10 (m, 1H), 3.36 (s, 1H), 3.21-3.12 (m, 1H), 1.95-1.84 (m, 3H), 1.62-1.61 (m, 1H). MS (ESI): *m/z* 598.4 $[M+1]^+$. HPLC Purity: 99.55%

Scheme 51



Examples 156(-)

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid hydrochloride (156(-))

To a stirred solution of 4-iodobenzoic acid (**GB**; 750 mg, 3.02 mmol) in DMF (10 mL) under inert atmosphere were added HATU (1.77 g, 4.53 mmol) and diisopropylethylamine (2.70 mL, 15.12 mmol) at RT. After stirring for 15 min at RT, methyl piperidine-2-carboxylate hydrochloride (651 mg, 3.62 mmol) was added to the reaction mass at 0 °C. The reaction mixture was then stirred at RT for 16 h. After complete consumption of the starting material, the reaction mixture was diluted with ice cold water (30 mL) and was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (30 mL), dried over

sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford **HA** (500 mg, racemic). ^{1}H NMR (400 MHz, $CDCl_3$): 7.79-7.75 (m, 2H), 7.21-7.17 (m, 2H), 5.48 (br s, 1H), 3.80 (s, 3H), 3.60 (d, *J* = 12.4 Hz, 1H), 3.25 (t, *J* = 12.0 Hz, 1H), 2.37 (d, *J* = 12.4 Hz, 1H), 1.80-1.72 (m, 3H), 1.48-1.34 (m, 2H).

The racemic **HA** was further purified through chiral preparative HPLC (with R_t at 17.28 min, 19.98 min) (Chiralpak IC, 250x4.6 mm, 5 µ); mobile phase (A) *n*-Hexane (B) Ethanol (A: B: 90: 10); flow Rate: 1.0 mL/min) to afford **HA(-)** (220mg) and **HA(+)** (250mg) as off-white solids.

HA(-) analytical data:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.49 (br s, 1H), 3.80 (s, 3H), 3.62 (d, *J* = 12.8 Hz, 1H), 3.26 (t, *J* = 12.0 Hz, 1H), 2.36 (d, *J* = 12.0 Hz, 1H), 1.79-1.74 (m, 2H), 1.64-1.58 (m, 1H), 1.45-1.40 (m, 2H); LC-MS: 98.16%; 374 (M^++NH_4); (column; X-bridge C-18, 50 × 3.0 mm, 3.5 µm); R_t 3.75 min. 5 mM NH_4OAc (Aq): ACN; 0.8 mL/min; Chiral HPLC: 99.31%, R_t = 17.39 min (Chiralpak IC, 250x4.6 mm, 5 µ); mobile phase (A) *n*-Hexane (B) Ethanol (A : B : 90: 10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20}$: -50.01° (c = 0.25, CH_2Cl_2).

HA(+) analytical data:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.48 (br s, 1H), 3.78 (s, 3H), 3.59 (d, *J* = 12.8 Hz, 1H), 3.24 (t, *J* = 12.0 Hz, 1H), 2.34 (d, *J* = 12.0 Hz, 1H), 1.77-1.75 (m, 2H), 1.61-1.58 (m, 1H), 1.42-1.38 (m, 2H); LC-MS: 99.69%; 374 (M^++NH_4); (column; X-bridge C-18, 50 × 3.0 mm, 3.5 µm); R_t 3.73 min. 5 mM NH_4OAc (Aq): ACN; 0.8 mL/min; Chiral HPLC: 99.92%, R_t = 20.17 min (Chiralpak IC, 250x4.6 mm, 5 µ); mobile phase (A) *n*-Hexane (B) Ethanol (A : B : 90: 10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20}$: +58.19° (c = 0.25, CH_2Cl_2).

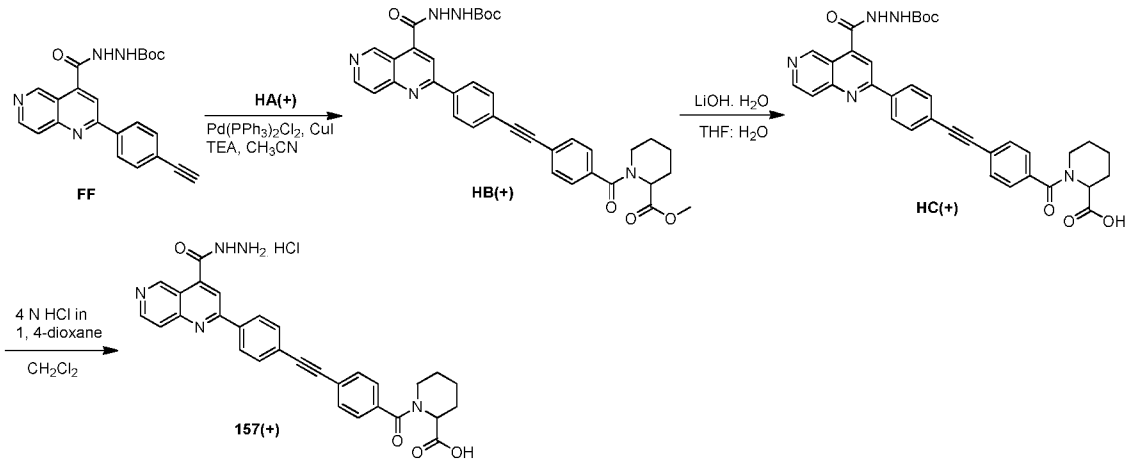
To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl)hydrazine carboxylate (**FF**; 135 mg, 0.34 mmol) in CH_3CN (10 mL) under inert atmosphere were added **HA(-)** (168.7 mg, 0.45 mmol) and triethylamine (0.48 mL, 3.47 mmol). After the reaction was purged under argon for 20 min, copper iodide (6.62 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (24.4 mg, 0.03 mmol) were added at RT. The reaction was heated at reflux for 4 h, at which point the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to obtain the crude material, which was purified through silica gel column chromatography eluting with 3-5% MeOH/CH_2Cl_2 to afford **HB(-)** (100 mg with TEA impurity) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (br s, 1H),

9.71 (br s, 1H), 9.30 (br s, 1H), 8.84 (br s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.71-7.70 (m, 2H), 7.47-7.41 (m, 2H), 5.29-5.27 (m, 0.5H), 4.43-4.41 (m, 0.5H), 3.74 (s, 3H), 3.52-3.49 (m, 1H), 3.10-3.08 (m, 1H), 2.21-2.18 (m, 1H), 1.76-1.69 (m, 2H), 1.49 (s, 9H), 1.19-1.16 (m, 3H).

To a stirred solution of **HB(-)** (100 mg, 0.15 mmol) in THF:H_2O (4:1, 10 mL) was added lithium hydroxide monohydrate (33 mg, 0.78 mmol) at 0 °C and the resulting reaction mixture was stirred for 5 h at RT. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure, the residue was neutralized with an acetic acid solution (1 mL), and was dried under reduced pressure to afford **HC(-)** (60 mg, 61%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.70 (br s, 1H), 9.28 (br s, 1H), 8.83-8.81 (m, 1H), 8.42 (d, J = 7.5 Hz, 2H), 8.32 (s, 1H), 8.04-8.02 (m, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 4.93-4.91 (m, 0.5H), 4.32-4.30 (m, 0.5H), 3.81-3.79 (m, 1H), 2.95-2.93 (m, 1H), 2.16-2.14 (m, 1H), 1.60-1.58 (m, 1H), 1.48 (s, 9H), 1.34-1.32 (m, 2H), 1.26-1.23 (m, 2H).

To a stirred solution of **HC(-)** (60 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (0.6 mL) at 0 °C and the resulting mixture was stirred for 3 h at RT. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude material, which was washed with CH_3CN (2x5 mL) to afford **156(-)** (15 mg as HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 9.77 (s, 1H), 8.91-8.89 (m, 1H), 8.65 (s, 1H), 8.52 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.46-7.40 (m, 2H), 5.20-5.18 (m, 1H), 4.45-4.40 (m, 0.5H), 4.38-4.29 (m, 0.5H), 3.49-3.47 (m, 1H), 3.22-3.17 (m, 1H), 2.82-2.75 (m, 0.5H), 2.23-2.21 (m, 0.5H), 1.72-1.69 (m, 3H), 1.58-1.55 (m, 1H). MS (ESI): m/z 520.4 $[M+1]^+$. HPLC Purity: 95.11%

Scheme 52



Example 157(+)

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid hydrochloride (157(+))

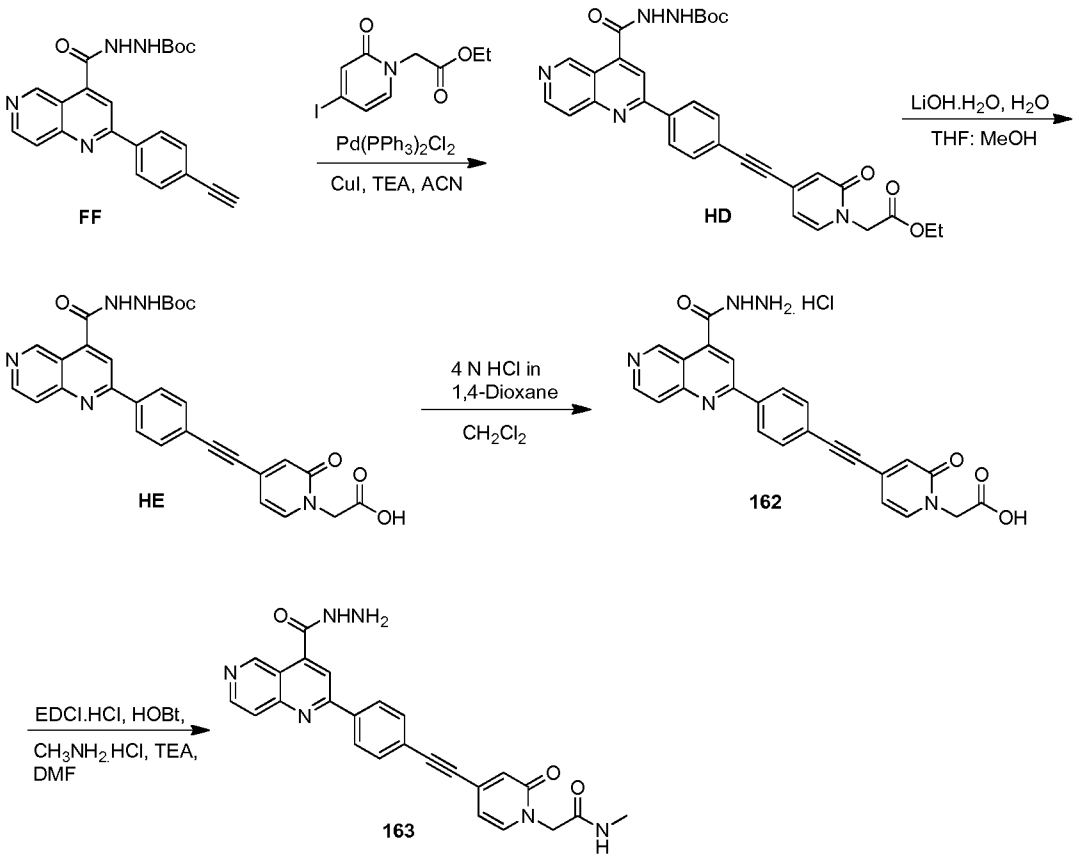
To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl)hydrazine carboxylate (**FF**; 150 mg, 0.38 mmol) in CH_3CN (10 mL) under inert atmosphere were added **HA(+)** (187 mg, 0.50 mmol) and triethylamine (0.54 mL, 3.86 mmol). After the reaction was purged under argon for 20 min, copper iodide (7.36 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (27.1 mg, 0.03 mmol) were added at RT. The reaction was heated at reflux for 4 h, at which point, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to obtain the crude material, which was purified through silica gel column chromatography eluting with 3-5% MeOH/CH_2Cl_2 to afford **HB(+)** (80 mg, 32%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.72 (br s, 1H), 9.30 (br s, 1H), 8.84 (br s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.71-7.70 (m, 2H), 7.47-7.41 (m, 2H), 5.29-5.27 (m, 0.5H), 4.44-4.43 (m, 0.5H), 3.74 (s, 3H), 3.52-3.49 (m, 1H), 3.10-3.08 (m, 1H), 2.21-2.18 (m, 1H), 1.76-1.69 (m, 2H), 1.53 (s, 9H), 1.19-1.16 (m, 3H).

To a stirred solution of **HB(+)** (80 mg, 0.12 mmol) in THF:H_2O (4:1, 10 mL) was added lithium hydroxide monohydrate (26.5 mg, 0.63 mmol) at 0 °C and the resulting reaction mixture was stirred for 5 h at RT. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure, the residue was neutralized with an acetic acid solution (1 mL), and was filtered and dried under reduced pressure to afford crude **HC(+)** (65 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.89 (br s, 1H), 9.24 (br s, 1H), 8.81-8.80 (m, 1H), 8.42 (d, J = 8.0 Hz, 2H), 8.38 (s, 1H), 8.02-8.01 (m, 1H), 7.80 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 4.80-4.79 (m,

0.5H). 4.34-4.31 (m, 0.5H), 3.79-3.77 (m, 1H), 2.97-2.94 (m, 1H), 2.16-2.14 (m, 1H), 1.60-1.59 (m, 1H), 1.49 (s, 9H), 1.34-1.32 (m, 2H), 1.26-1.23 (m, 2H).

To a stirred solution of **HC(+)** (30 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) under inert atmosphere was added 4N HCl in 1,4-dioxane (0.4 mL) at 0 °C and the reaction mixture was stirred for 3 h at RT. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude material, which was washed with CH_3CN (2x3 mL) to afford **157(+)** (15 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (br s, 1H), 9.73 (br s, 1H), 8.89-8.87 (m, 1H), 8.56 (s, 1H), 8.49 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.46-7.41 (m, 2H), 5.20-5.18 (m, 1H), 4.45-4.40 (m, 0.5H), 4.38-4.29 (m, 0.5H), 3.49-3.47 (m, 1H), 3.22-3.16 (m, 1H), 2.81-2.69 (m, 0.5H), 2.23-2.20 (m, 0.5H), 1.72-1.69 (m, 3H), 1.58-1.55 (m, 1H). MS: *m/z* 518.4 $[M-1]^+$. HPLC Purity: 94.48%

Scheme 53



Examples 162 and 163

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)acetic acid hydrochloride (162)

To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl) hydrazine carboxylate (**FF**; 400 mg, 1.02 mmol) in CH_3CN (30 mL) under inert atmosphere were added ethyl 2-(4-iodo-2-oxopyridin-1(2H)-yl) acetate (379 mg, 1.23 mmol) and triethylamine (1.48 mL, 10.29 mmol) at RT. After the reaction was purged under argon for 15 min, copper iodide (19 mg, 0.10 mmol) and $Pd(PPh_3)_2Cl_2$ (72 mg, 0.10 mmol) were added. The reaction was heated at reflux for 3 h, at which point, the volatiles were evaporated under reduced pressure to obtain the crude material. The crude material was purified through silica gel column chromatography eluting with 4-5% MeOH/CH_2Cl_2 to afford **HD** (211 mg, 36%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.71 (br s, 1H), 9.30 (br s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 8.0 Hz, 2H), 8.34 (br s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 7.2 Hz, 1H), 6.67 (s, 1H), 6.42 (d, J = 7.2 Hz, 1H), 4.72 (s, 2H), 4.18-4.13 (q, 2H), 1.49 (s, 9H), 1.23-1.21 (m, 3H).

To a stirred solution of **HD** (211 mg, 0.37 mmol) in THF/MeOH (4:1, 10 mL) under inert atmosphere were added lithium hydroxide monohydrate (311 mg, 7.41 mmol) and water (1.5 mL) at 0 °C. After stirring at RT for 3 h, the volatiles were evaporated under reduced pressure, the residue was diluted with water (25 mL), and acidified with acetic acid to pH~4. The obtained solid was filtered, co-distilled with toluene (2x5 mL) and dried under reduced pressure to obtain crude **HE** (170 mg) as a yellow solid.

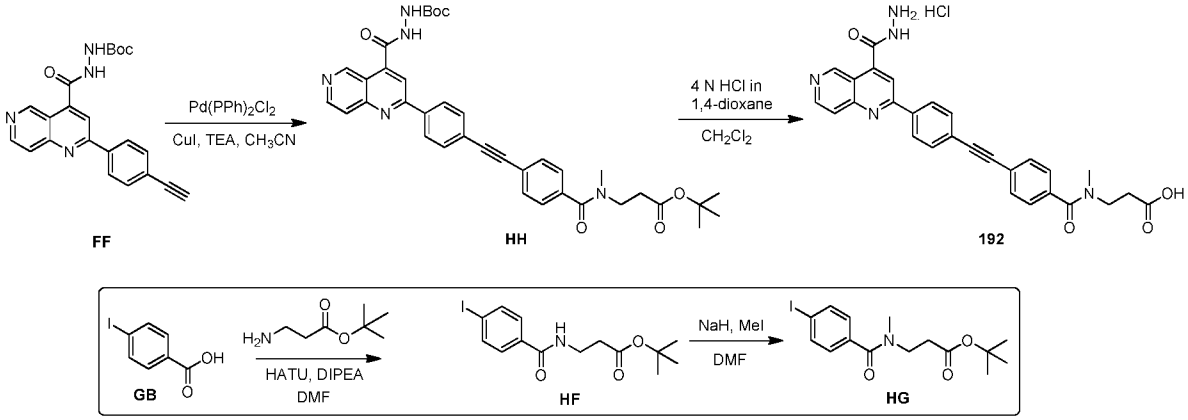
To a stirred solution of **HE** (30 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (0.5 mL) at 0 °C. After stirring for 30 min at RT, the volatiles were evaporated under reduced pressure to obtain the crude material, which was triturated with isopropyl alcohol:*n*-pentane (1:4, 5 mL) to afford **162** (20 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.64 (br s, 1H), 9.69 (s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.51-8.46 (m, 3H), 8.11 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 6.8 Hz, 1H), 6.65 (s, 1H), 6.41-6.38 (m, 1H), 4.64 (s, 2H). MS (ESI): *m/z* 453.2 $[M+1]^+$. HPLC Purity: 94.24%

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)-N-methylacetamide (163)

To a stirred solution of **162** (30 mg, 0.06 mmol) in DMF (10 mL) under inert atmosphere were added EDCI·HCl (32 mg, 0.16 mol), HOBt (16 mg, 0.12 mol), triethylamine (0.03 mL, 0.27 mmol) and methylamine hydrochloride (9 mg, 0.13 mol) at 0 °C. After stirring at RT for 12 h, the reaction mixture was diluted with ice cold water (20 mL) and was extracted with 20% MeOH/CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude

material. The crude material was purified through silica gel column chromatography containing neutral alumina using 4-8% MeOH/CH_2Cl_2 to afford **163** (16 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.62 (s, 1H), 8.99-8.98 (m, 1H), 8.80 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H), 8.10-8.09 (m, 1H), 8.02 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 6.8 Hz, 1H), 6.61 (s, 1H), 6.38-6.35 (m, 1H), 4.52 (s, 2H), 2.94 (d, J = 4.8 Hz, 3H), 2.62 (d, J = 4.8 Hz, 2H). MS (ESI): m/z 440.3 $[M+1]^+$

Scheme 54



Example 192

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-*N*-methylbenzamido)propanoic acid hydrochloride (192)

To a stirred solution of 4-iodobenzoic acid (**GB**; 500 mg, 2.01 mmol) in DMF (10 mL) under inert atmosphere were added HATU (1.14 g, 3.02 mmol), diisopropylethylamine (1.10 mL, 6.04 mmol) at 0 °C. After stirring for 15 min, tert-butyl 3-aminopropanoate (439 mg, 2.41 mmol) was added to the reaction at 0 °C. The reaction mixture was stirred for 12 h at RT, at which point, the reaction mixture was diluted with water (25 mL) and was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with water (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude residue. The crude residue was purified through flash column chromatography eluting with 15% EtOAc/hexanes to afford **HF** (550 mg, 73%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57-8.55 (m, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 3.45-3.41 (m, 2H), 2.50-2.46 (m, 2H), 1.38 (s, 9H).

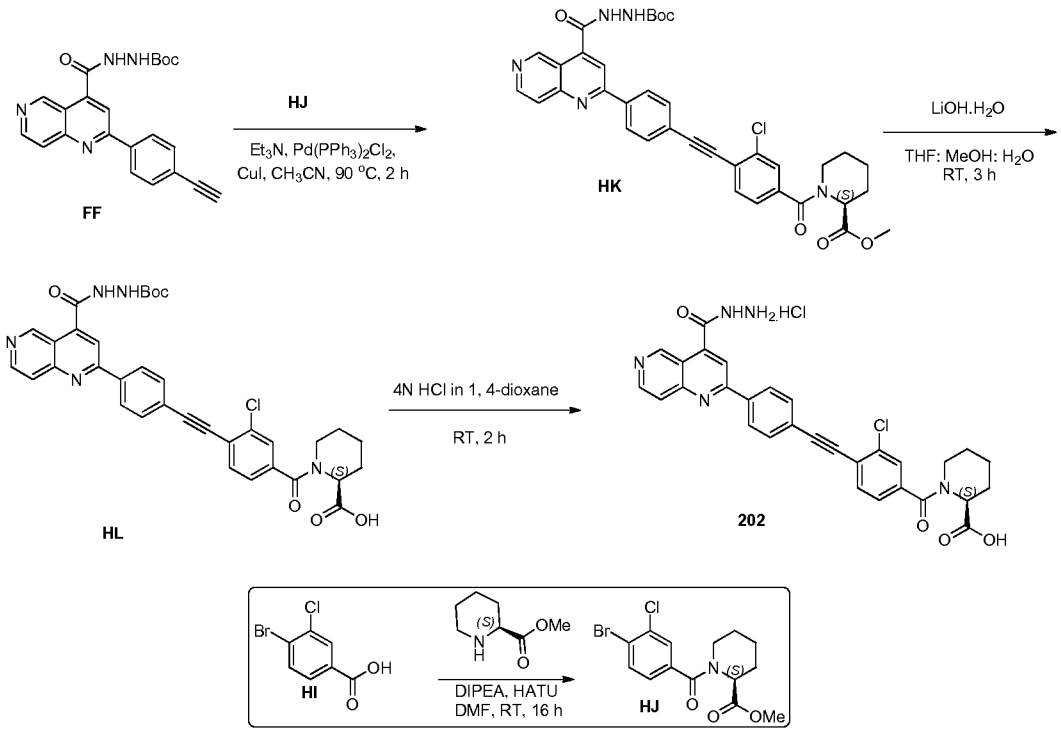
To a stirred solution of **HF** (300 mg, 0.80 mmol) in DMF (10 mL) under inert atmosphere was added sodium hydride (38.4 mg, 1.60 mmol) at 0 °C. After stirring at RT for 15 min, methyl iodide (170 mg, 1.20 mmol) was added at 0 °C. The reaction was then stirred for 2 h at RT, at

which point, the reaction mixture was diluted with ice cold water (20 mL) and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude material. The crude material was purified through flash column chromatography eluting with 20% EtOAc/hexanes to afford **HG** (250 mg, 64%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.80 (d, J = 7.0 Hz, 2H), 7.16 (d, J = 7.0 Hz, 2H), 3.66-3.58 (m, 1H), 3.44-3.38 (m, 1H), 2.95-2.86 (m, 5H), 1.40 (s, 9H).

To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl) hydrazinecarboxylate (**FF**; 200 mg, 0.51 mmol) in CH_3CN (20 mL) under inert atmosphere were added **HG** (240 mg, 0.61 mmol), triethylamine (0.74 mL, 5.15 mmol), and copper iodide (9.9 mg, 0.051 mmol) at RT. After the reaction was purged under argon for 15 min, $Pd(PPh_3)_2Cl_2$ (36 mg, 0.051 mmol) was added and the reaction was heated at reflux for 4 h. After complete consumption of the starting material, the volatiles were evaporated under reduced pressure to obtain the crude material, which was purified through flash column chromatography eluting with 3-5% MeOH/CH_2Cl_2 to afford **HH** (20 mg, 6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.30 (br s, 1H), 8.90-8.76 (m, 1H), 8.45 (d, 2H), 8.33-8.31 (m, 1H), 8.08-8.06 (m, 1H), 7.98-7.96 (m, 1H), 7.82-7.80 (m, 2H), 7.78-7.73 (m, 2H), 7.64-7.61 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.44 (m, 2H), 3.66-3.64 (m, 1H), 3.17-3.16 (m, 1H), 3.10-2.91 (m, 4H), 2.55-2.52 (m, 1H), 1.49 (s, 9H), 1.41-1.37 (m, 9H).

To a stirred solution of **HH** (20 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) under inert atmosphere was added 4N HCl solution in 1,4-dioxane (0.5 mL) at 0 °C. After stirring at RT for 6 h, the volatiles were evaporated under reduced pressure to obtain the crude material, which. was triturated with 20% MeOH/CH_3CN (2x2 mL) to afford **192** (14 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H), 8.88-8.87 (m, 1H), 8.53 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 3.71-3.66 (m, 2H), 3.51-3.46 (m, 2H), 2.92 (br s, 3H). MS (ESI): m/z 494.6 $[M+1]^+$. HPLC Purity: 97.03%.

Scheme 55



Example 202

(S)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid hydrochloride (202)

To a stirred solution of 4-bromo-3-chlorobenzoic acid (**HI**; 6.5 g, 27.60 mmol) in DMF (50 mL) under nitrogen atmosphere were added HATU (15.74 g, 41.40 mmol), DIPEA (14.4 mL, 82.81 mmol) and (S)-methyl piperidine-2-carboxylate hydrochloride (5.34 g, 29.74 mmol) at RT and the reaction mixture was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and the compound was extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water (2x100 mL), brine (2x75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to afford compound **HJ** (8.9 g, 90%) as a yellow thick syrup. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.89-7.84 (m, 1H), 7.61-7.56 (m, 1H), 7.28 (d, J = 7.5 Hz, 1H), 5.24 (br s, 1H), 4.44-4.37 (m, 1H), 3.73 (s, 3H), 3.45 (d, J = 12.5 Hz, 1H), 3.12 (t, J = 12.5 Hz, 1H), 2.67-2.64 (m, 1H), 1.70-1.67 (m, 2H), 1.53-1.40 (m, 2H). MS (ESI): m/z 360.63 $[M+1]^+$

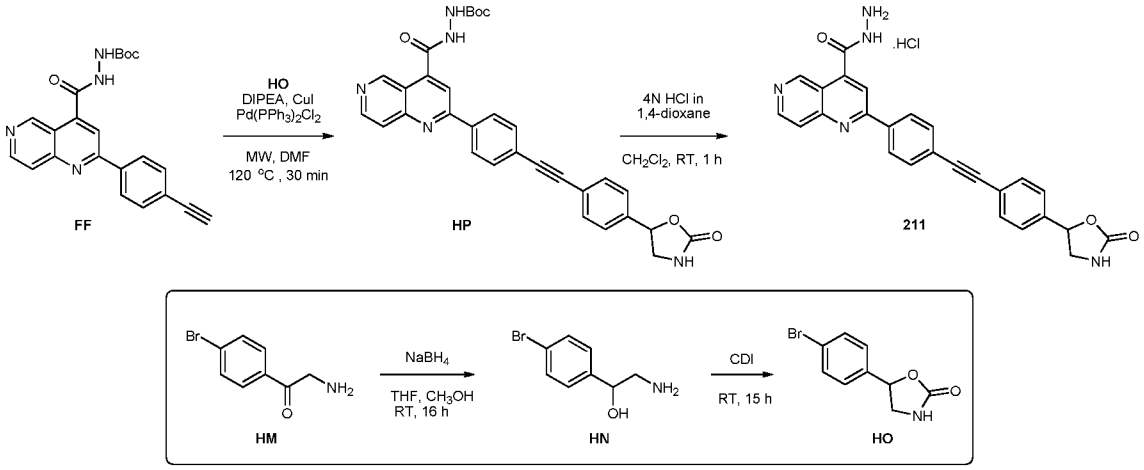
To a stirred solution of compound **FF** (250 mg, 0.64 mmol) in CH_3CN (20 mL) under argon atmosphere were added compound **HJ** (311 mg, 0.64 mmol) and TEA (1 mL, 6.44 mmol). The reaction was purged with argon for 10 min followed by the addition of copper iodide (12 mg, 0.06 mmol) and $Pd(PPh_3)_2Cl_2$ (45 mg, 0.06 mmol). The reaction was heated to 90 °C and

stirred for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2-5% MeOH/DCM to afford compound **HK** (120 mg, 28%) as a pale brown solid. The compound was carried forward into the next step without further purification. MS (ESI): *m/z* 668.15 $[M+1]^+$

To a stirred solution of compound **HK** (120 mg, 0.17 mmol) in THF:H_2O (5 mL:5 mL) was added lithium hydroxide monohydrate (75 mg, 1.79 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The reaction residue was diluted with water (5 mL), washed with DCM (5 mL) and the pH was adjusted to ~3 using an acetic acid solution (0.2 mL). The solid precipitate was filtered, dried under reduced pressure, and washed with CH_3CN (2 mL) to afford compound **HL** (61 mg, 52%) as a pale yellow solid. The compound was carried forward without further purification. MS (ESI): *m/z* 655$[M+1]^+$

To a stirred solution of compound **HL** (60 mg, 0.09 mmol) in DCM (4 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude product was triturated with CH_3CN (2 mL) to afford **202** (38 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.1 (brs, 1H), 9.71 (brs, 1H), 8.86 (brs, 1H), 8.55 (s, 1H), 8.48 (d, J = 8.0 Hz, 2H), 8.18-8.14 (m, 1H), 7.84-7.78 (m, 3H), 7.56-7.52 (m, 2H), 7.41-7.31 (m, 1H), 5.14 (brs, 0.6H), 4.41-4.32 (m, 0.4H), 3.48-3.41 (m, 0.4H), 3.17 (t, J = 10 Hz, 0.6H), 2.76-2.68 (m, 0.5H), 2.24-2.14 (m, 1H), 2.09-2.01 (m, 0.5 H), 1.72-1.62 (m, 3H), 1.44-1.22 (m,2H). MS (ESI): *m/z* 554.5 and 555.3 $[M+1]^+$ (Chloro pattern is observed in the mass spectrum). HPLC Purity: 93.36%

Scheme 56



Example 211

2-(4-((4-(2-oxooxazolidin-5-yl) phenyl) ethynyl) phenyl)-1, 6-naphthyridine-4-carbohydrazide hydrochloride (211)

To a stirred solution of 2-amino-1-(4-bromophenyl)ethan-1-one (**HM**; 2.5 g, 11.68 mmol) in MeOH:THF (20 mL:20 mL) under nitrogen atmosphere was added $NaBH_4$ (1.33 g, 35.04 mmol) portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction was diluted with cold water (15 mL) and concentrated under reduced pressure. The crude was diluted with water (30 mL) and extracted with 10% MeOH:DCM (2x100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **HN** (1.1 g, 43.6) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.16-5.08 (m, 1H), 4.44-4.41 (m, 1H), 3.60 (m, 1H), 2.67-2.63 (m, 2H). MS (ESI): m/z 217.08 $[M+1]^+$

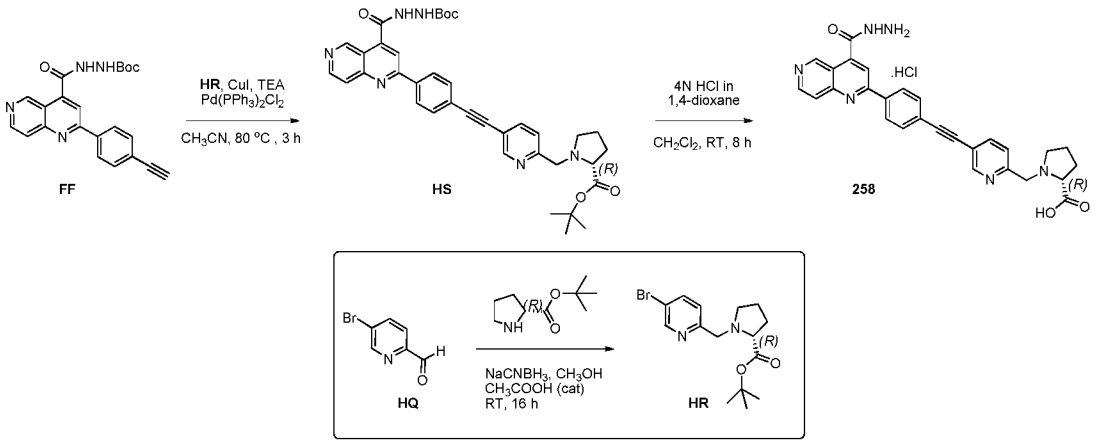
To a stirred solution of compound **HN** (1 g, 4.62 mmol) in DCM (20 mL) under nitrogen atmosphere was added CDI (825 mg, 5.09 mmol) portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 15h. After complete consumption of the starting material (by TLC), the reaction was diluted with cold water (20 mL) and extracted with DCM (2x50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **HO** (750 mg, 67%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H), 7.27-7.24 (m, 2H), 5.58 (t, J = 8.0 Hz, 1H), 5.34 (br s, 1H), 4.00-3.96 (m, 1H), 3.51-3.47 (m, 1H). MS (ESI): m/z 243.07 $[M+1]^+$

To a stirred solution of compound **FF** (200 mg, 0.51 mmol) in DMF (5 mL) under argon atmosphere were added compound **HO** (133 mg, 0.51 mmol) and DIPEA (0.93 mL, 5.15 mmol) at RT. The reaction was purged under argon for 20 min followed by addition of copper

iodide (9.8 mg, 0.05 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol). The reaction was heated in the MW to 120 °C and stirred for 30 min. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite pad was washed with ethyl acetate (15 mL). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **HP** (70 mg, 25%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (br s, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.43 (d, J = 8.0 Hz, 2H), 8.32 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.73 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 5.67 (t, J = 7.2 Hz, 1H), 3.92 (t, J = 8.8 Hz, 1H), 3.35 (t, J = 9.2 Hz, 1H), 1.49 (s, 9H). MS (ESI): m/z 550.59 $[M+1]^+$

To a stirred solution of compound **HP** (25 mg, 0.04 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with diethylether (2 mL) to afford **211** (13 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 12.04 (s, 1H), 9.72 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.56 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.74 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 5.67 (t, J = 7.2 Hz, 1H), 3.92 (t, J = 8.8 Hz, 1H), 3.38-3.33 (m, 1H). MS (ESI): m/z 450.47 $[M+1]^+$. UPLC Purity: 93.22%.

Scheme 57



Example 258

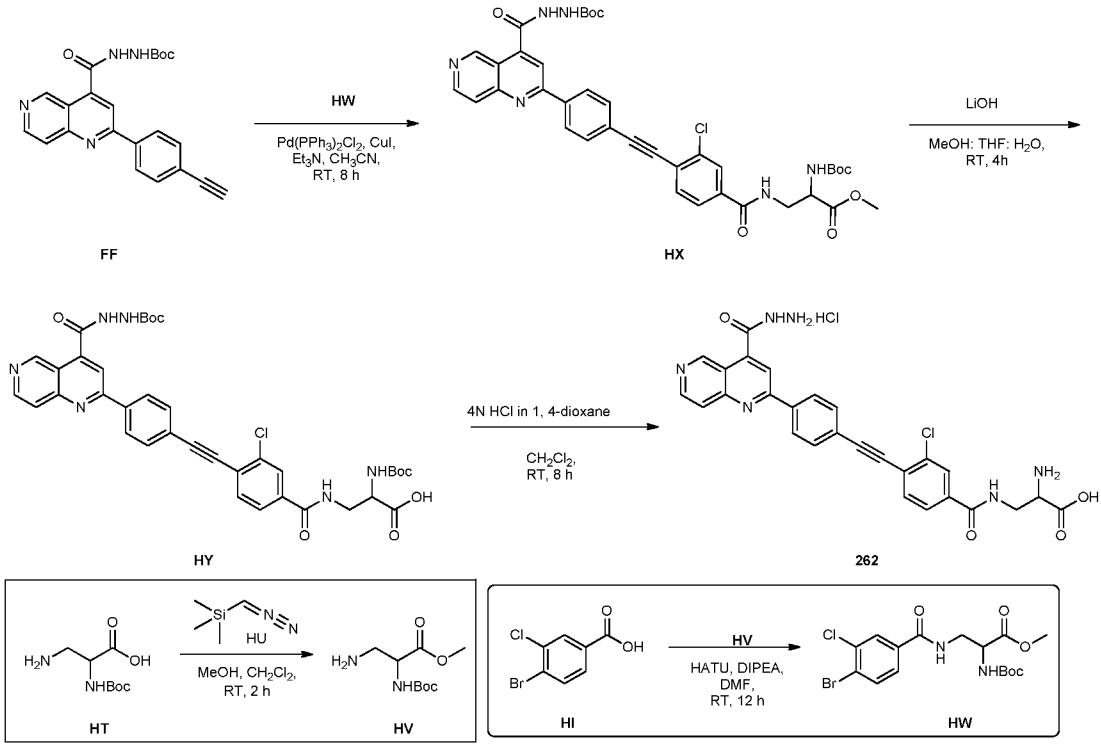
((5-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) pyridin-2-yl) methyl)-D-proline hydrochloride (258)

To a stirred solution of 5-bromo-2-formylpyridine (**HQ**; 760 mg, 4.09 mmol) in MeOH (15 mL) under nitrogen atmosphere was added D-proline tert-butylester (700 mg, 4.09 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. Then $NaCNBH_3$ (1.28 g, 20.46 mmol) and acetic acid (0.2 mL) were added at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude was diluted with water (30 mL) and extracted with EtOAc (2x50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **HR** (600 mg, crude) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.01-7.98 (m, 1H), 7.43 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 14.0 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.27-3.24 (m, 1H), 2.91-2.86 (m, 1H), 2.44 (t, J = 8.0 Hz, 1H), 2.08-1.98 (m, 1H), 1.82-1.70 (m, 3H), 1.36 (s, 9H). MS (ESI): *m/z* 342.25 $[M+1]^+$

To a stirred solution of compound **FF** (300 mg, 0.77 mmol) in CH_3CN (25 mL) under argon atmosphere were added compound **HR** (263 mg, 0.77 mmol) and TEA (1.09 mL, 7.73 mmol) at RT. The reaction was purged under argon for 20 min followed by addition of copper iodide (14.7 mg, 0.07 mmol) and $Pd(PPh_3)_2Cl_2$ (54 mg, 0.07 mmol). The reaction was heated to 80 °C and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate (15 mL). The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **HS** (140 mg, 28%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 9.01 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.70 (s, 2H), 8.45 (d, J = 7.6 Hz, 1H), 8.05-7.99 (m, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.56-7.35 (m, 2H), 4.14-4.00 (m, 1H), 3.77 (m, 1H), 2.91-2.86 (m, 1H), 2.08-1.97 (m, 2H), 1.68-1.59 (m, 1H), 1.84-1.75 (m, 3H), 1.49 (s, 9H), 1.39 (s, 9H). MS (ESI): *m/z* 649.76$[M+1]^+$

To a stirred solution of compound **HS** (30 mg, 0.04 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 8h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (2 mL) to afford **258** (16 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 12.06 (s, 1H), 9.72 (s, 1H), 8.87 (t, J = 6.0 Hz, 2H), 8.56 (s, 1H), 8.51 (d, J = 8.8 Hz, 2H), 8.17-8.13 (m, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 4.76-4.49 (m, 2H), 3.64 (d, J = 7.6 Hz, 2H), 3.35-3.28 (m, 1H), 2.60-2.49 (m, 1H), 2.11-1.93 (m, 3H). MS (ESI): *m/z* 493.5 $[M+1]^+$. HPLC Purity: 87.07%

Scheme 58



Example 262

2-amino-3-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzamido) propanoic acid hydrochloride (262)

To a stirred solution of 3-amino-2-((tert-butoxycarbonyl)amino)propanoic acid (**HT**; 100 mg, 0.49 mmol) in DCM (5 mL) under nitrogen atmosphere were added (diazomethyl)trimethylsilane (0.26 mL, 0.53 mmol) and MeOH (0.5 mL). The reaction was stirred at RT for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to obtain compound **HV** (80 mg, 75%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.13-7.12 (m, 1H), 3.97-3.93 (m, 1H), 3.61 (s, 3H), 2.80-2.77 (m, 2H), 1.75 (br s, 1H), 1.41 (s, 9H). MS (ESI): *m/z* 219.4 $[M+1]^+$

To a stirred solution of 4-bromo-3-chlorobenzoic acid **HI** (500 mg, 2.12 mmol) in DMF (10 mL) under nitrogen atmosphere were added HATU (1.2 g, 3.18 mmol), DIPEA (1.56 mL, 8.49 mmol) and compound **HV** (510 mg, 2.33 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and the compound was extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water (100 mL), brine (50

mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography eluting with 20% EtOAc/hexane to afford compound **HW** (600 mg, 65%) as a pale yellow syrup. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71-8.70 (m, 1H), 8.00 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 4.25 (d, J = 7.0 Hz, 1H), 3.60 (s, 3H), 3.57 (d, J = 6.0 Hz, 2H), 1.39 (s, 9H). MS (ESI): m/z 436.3 $[M+1]^+$

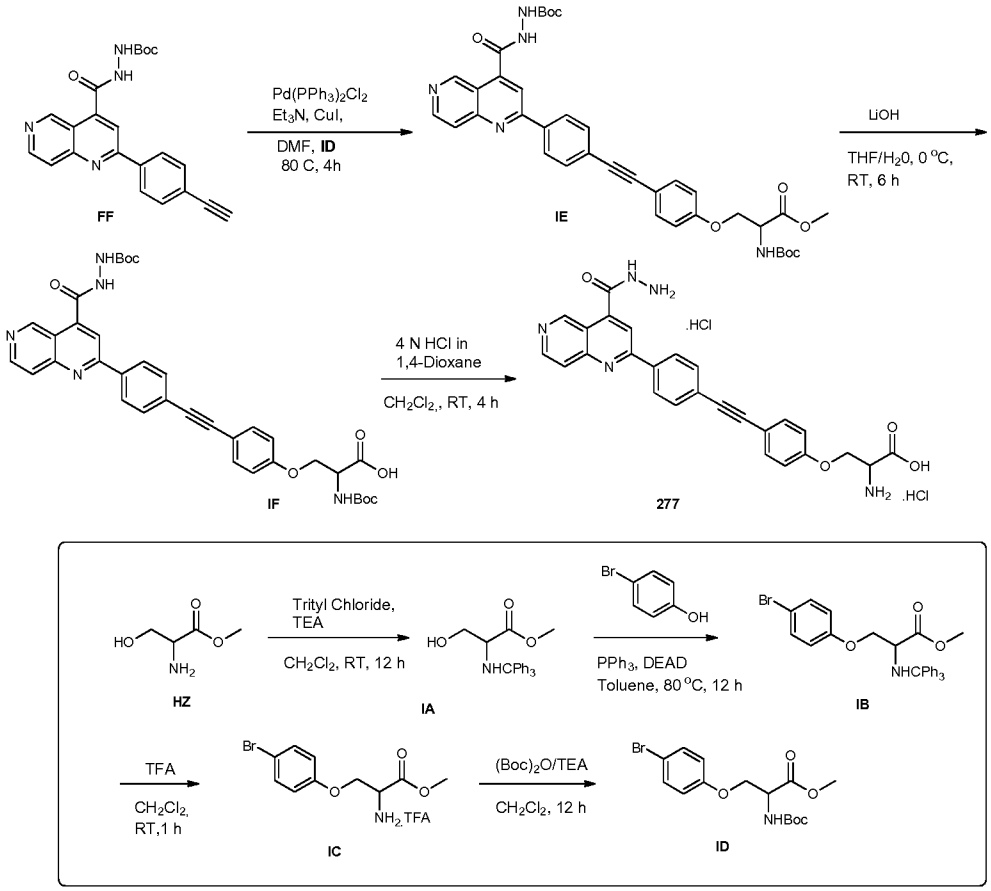
To a stirred solution of compound **FF** (250 mg, 0.64 mmol) in CH_3CN (20 mL) under argon atmosphere were added compound **HW** (308 mg, 0.70 mmol) and TEA (0.92 mL, 6.44 mmol). The reaction was purged with argon for 10 min followed by the addition of copper iodide (12 mg, 0.06 mmol) and $Pd(PPh_3)_2Cl_2$ (45 mg, 0.06 mmol). The reaction was heated to 90 °C and stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 2-5% MeOH/DCM to afford compound **HX** (150 mg, 31%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.72 (s, 1H), 9.29 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.74 (t, J = 7.0 Hz, 1H), 8.47 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 6.0 Hz, 1H), 8.00 (s, 1H), 7.87-7.83 (m, 3H), 7.26 (d, J = 8.0 Hz, 1H), 4.27 (q, 1H), 3.62-3.56 (m, 5H), 1.49 (s, 9H), 1.37 (s, 9H). MS (ESI): m/z 744.7 $[M+1]^+$

To a stirred solution of compound **HX** (50 mg, 0.06 mmol) in MeOH:THF:H_2O (4 mL:4 mL:2 mL) was added lithium hydroxide monohydrate (14 mg, 0.33 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was diluted with water and the pH was adjusted to ~3 using an acetic acid solution (0.2 mL). The solid precipitate was filtered and dried under reduced pressure to afford compound **HY** (35 mg, 71%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.67 (br s, 1H), 9.73 (br s, 1H), 9.29 (s, 1H), 9.12 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 8.5 Hz, 2H), 8.35 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.94 (s, 1H), 7.84-7.77 (m, 4H), 6.07 (s, 1H), 3.62-3.56 (m, 2H), 3.21-3.20 (m, 1H), 1.49 (s, 9H), 1.37 (s, 9H). MS (ESI): m/z 730.5 $[M+1]^+$

To a stirred solution of compound **HY** (35 mg, 0.04 mmol) in DCM (3 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and stir for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude residue was triturated with CH_3CN (2 mL) to afford **262** (18 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.44-12.39 (m, 1H), 9.70 (s, 1H), 9.28 (s, 1H), 9.06 (d, J = 5.6 Hz, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.65 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.50-8.45 (m, 2H), 7.94-7.85 (m,

3H), 4.16-4.12 (m, 1H), 3.71-3.67 (m, 1H), 3.50-3.47 (m, 1H). MS (ESI): *m/z* 529.4 $[M+1]^+$. UPLC Purity: 94.04%

Scheme 59



Example 277

O-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)serine dihydrochloride (277)

To a stirred solution of DL-serine methyl ester·HCl (**HZ**; 200 mg, 1.28 mmol) in DCM (10 mL) under nitrogen atmosphere were added TEA (0.9 mL, 6.40 mmol) and trityl chloride (442 mg, 1.53 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (15 mL) and extracted with EtOAc (2x20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 1% MeOH:DCM to afford compound **IA** (300 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41

(d, J = 7.2 Hz, 6H), 7.27 (t, J = 7.6 Hz, 6H), 7.19 (t, J = 7.2 Hz, 3H), 4.91 (s, 1H), 3.61-3.57 (m, 1H), 3.44-3.39 (m, 1H), 3.19 (s, 3H), 2.80 (d, J = 8.0 Hz, 1H), 2.50-2.47 (m, 1H)

To a stirred solution of triphenylphosphine (302 mg, 1.15 mmol) in toluene (10 mL) was added DEAD (200 mg, 1.15 mmol) under nitrogen atmosphere at 0 °C. After stirring for 10 min, compound **IA** (200 mg, 1.15 mmol) in toluene (2 mL) and 4-bromophenol (415 mg, 1.15 mmol) in toluene (2 mL) were added dropwise. After stirring for 10 min, the reaction was heated to 80 °C and stirred for 48h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 10% EtOAc:hexane to afford compound **IB** (250 mg, 42%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.42-7.38 (m, 5H), 7.33-7.17 (m, 14H), 6.82 (d, J = 8.5 Hz, 1H), 4.13-4.10 (m, 1H), 4.03-3.99 (m, 1H), 3.50-3.48 (m, 1H), 3.16 (s, 3H), 3.08 (d, J = 10.0 Hz, 1H). MS (ESI): m/z 516.43 $[M+1]^+$

To a stirred solution of compound **IB** (900 mg, 1.74 mmol) in DCM (10 mL) under nitrogen atmosphere was added TFA (1.98 g, 17.42 mmol) at 0 °C and the reaction was stirred for 10 min. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to obtain compound **IC** (800 mg, TFA salt) as a yellow solid.

To a stirred solution of compound **IC** (800 mg, 2.06 mmol) in DCM (10 mL) under nitrogen atmosphere was added TEA (2 mL, 14.47 mmol) at 0 °C. Boc anhydride (1.35 mL, 6.18 mmol) was added dropwise at 0 °C and the reaction was stirred for 10 min. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with DCM (2x30 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 15% EtOAc:hexane to afford compound **ID** (250 mg, 42%) as a viscous liquid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.43 (d, J = 9.0 Hz, 3H), 6.89 (d, J = 9.0 Hz, 2H), 4.45-4.42 (m, 1H), 4.19 (d, J = 5.5 Hz, 2H), 3.66 (s, 3H), 1.38 (s, 9H). MS (ESI): m/z 374.23 $[M+1]^+$

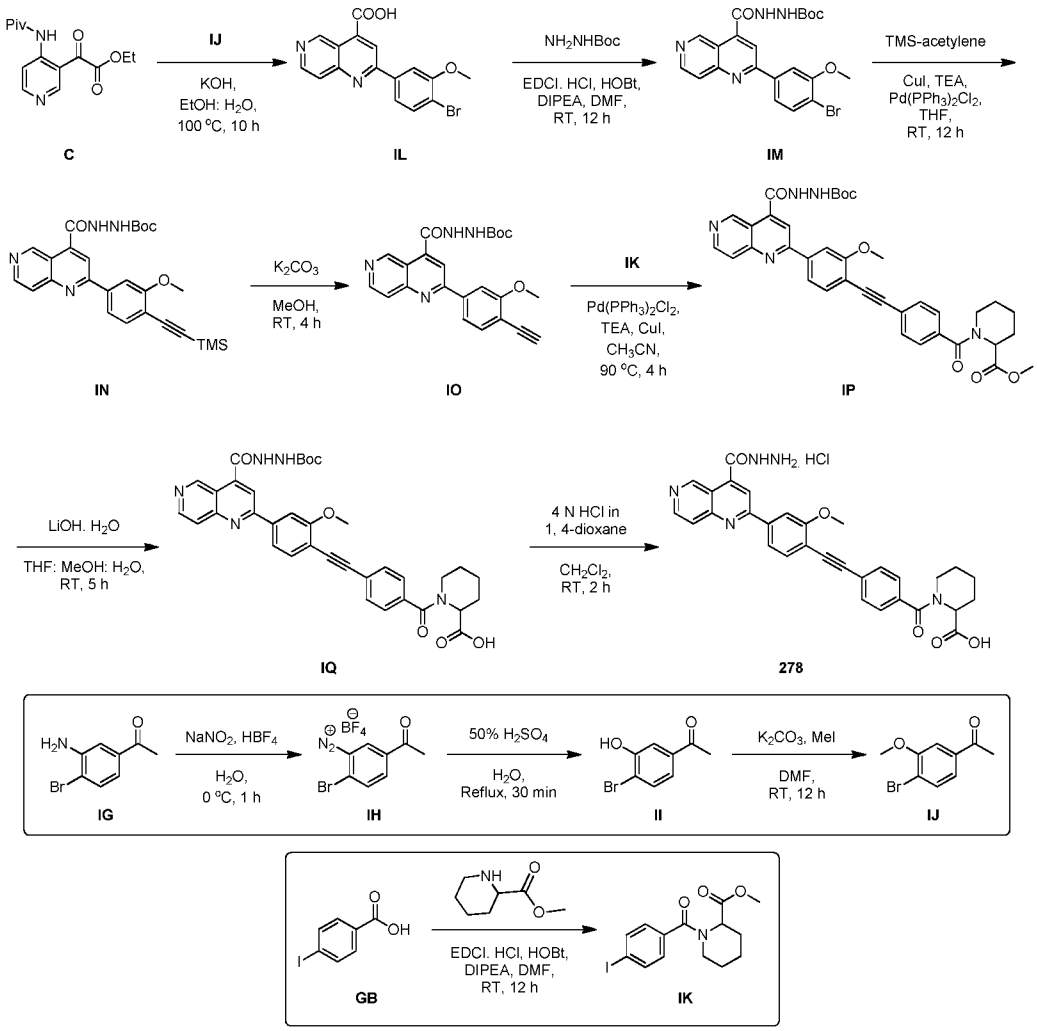
To a stirred solution of compound **FF** (300 mg, 0.77 mmol) in CH_3CN (15 mL) under argon atmosphere were added compound **ID** (345 mg, 0.92 mmol) and TEA (1.1 mL, 7.73 mmol) at RT. The reaction was purged under argon for 20 min followed by the addition of copper iodide (14.7 mg, 0.07 mmol) and $Pd(PPh_3)_2Cl_2$ (54 mg, 0.07 mmol). The reaction was heated

to 70 °C and stirred for 4h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with DCM (2 x 30 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM and further purified by preparative HPLC to afford compound **IE** (30 mg, 6%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.69 (s, 1H), 9.28 (s, 1H), 8.82 (d, J = 5.5 Hz, 1H), 8.40 (d, J = 8.5 Hz, 2H), 8.31 (s, 1H), 8.03 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 4.48 (d, J = 7.0 Hz, 1H), 4.26 (s, 2H), 3.68 (s, 3H), 1.49 (s, 9H), 1.40 (s, 9H). MS (ESI): m/z 681.75 $[M+1]^+$

To a stirred solution of compound **IE** (25 mg, 0.03 mmol) in THF:MeOH:H_2O (2 mL:2 mL:1 mL) were added lithium hydroxide monohydrate (7.7 mg, 0.18 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 6h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was diluted with water and acidified with acetic acid to pH~3. The precipicate was filtered and dried under reduced pressure to afford compound **IF** (20 mg, crude) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H), 10.00 (br s, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.83 (d, J = 5.0 Hz, 1H), 8.40-8.31 (m, 4H), 8.04 (d, J = 5.0 Hz, 1H), 7.79-7.72 (m, 2H), 7.54-7.42 (m, 2H), 6.99 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 4.22-4.15 (m, 3H), 1.49 (s, 9H), 1.39 (s, 9H). MS (ESI): m/z 667.26 $[M+1]^+$

To a stirred solution of compound **IF** (20 mg, crude) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (3 mL) and further purified through preparative HPLC to afford **277** (8 mg as an HCl salt) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.00 (s, 1H), 9.65 (s, 1H), 8.83 (d, J = 6.0 Hz, 1H), 8.52 (s, 3H), 8.41 (t, J = 8.0 Hz, 3H), 8.05 (d, J = 6.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 4.52-4.47 (m, 3H), 4.35 (d, J = 8.0 Hz, 2H). MS (ESI): m/z 468.3 $[M+1]^+$. UPLC Purity: 99.26%

Scheme 60



Example 278

1-(4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl)-2-methoxyphenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid hydrochloride (278)

To a stirred solution of 1-(3-amino-4-bromophenyl)ethan-1-one (**IG**; 3 g, 14.01 mmol) in H_2O (15 mL) were added sodium nitrate (1.93 g, 28.03 mmol) and 51-57% HBF_4 in diethyl ether (3 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered. The obtained solid was washed with water (2 x 5 mL) and dried under reduced pressure to afford compound **IH** (150 mg, crude) as an orange solid. The crude product was carried forward without further purification.

To a stirred solution of compound **IH** (3 g, 13.33 mmol) in H_2O (6 mL) under nitrogen atmosphere was added 50% sulphuric acid (39 mL) at RT. The reaction was heated to reflux and stirred for 30 min. After complete consumption of the starting material (by TLC), the

reaction mixture was extracted with EtOAc (2x40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 15-20% EtOAc/hexane to afford compound **II** (700 mg, 24%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 2.50 (d, J = 9.5 Hz, 3H). MS (ESI): m/z 216.2 $[M+1]^+$

To a stirred solution of compound **II** (500 mg, 2.33 mmol) in DMF (10 mL) under nitrogen atmosphere were added potassium carbonate (967 mg, 7.00 mmol) and methyl iodide (995 mg, 7.00 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography to afford compound **IJ** (500 mg, 93%) as a pale yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.5 Hz, 1H), 7.48 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H), 2.59 (s, 3H). MS (ESI): m/z 230.4 $[M+1]^+$

To a stirred solution of 4-iodobenzoic acid **GB** (500 mg, 2.01 mmol) in DMF (10 mL) under nitrogen atmosphere were added methyl piperidine-2-carboxylate (343 mg, 2.41 mmol), EDCI·HCl (967 mg, 5.04 mmol), HOBt (493 mg, 3.62 mmol), and DIPEA (1.3 g, 10.08 mmol) at RT. The reaction was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2x35 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography to afford compound **IK** (600 mg, 80%) as an off-white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.46 (br s, 1H), 4.41-4.38 (m, 1H), 3.91-3.88 (m, 1H), 3.78-3.75 (m, 3H), 3.60-3.57 (m, 1H), 3.32 (br s, 1H), 3.26-3.22 (m, 1H), 2.40 (br s, 1H), 1.25-1.22 (m, 2H). MS (ESI): m/z 374.5 $[M+1]^+$

To a stirred solution of ethyl 2-oxo-2-(4-pivalamidopyridin-3-yl) acetate (**C**; 500 mg, 1.79 mmol) in EtOH:H_2O (1:1, 20 mL) were added compound **IJ** (494 mg, 2.15 mmol) and potassium hydroxide (402 mg, 7.19 mmol) at 0 °C. The reaction was heated to reflux and stirred for 12h. The reaction mixture was concentrated under reduced pressure. The crude was diluted with water (25 mL) and acidified with acetic acid to pH~4. The precipitate was filtered and dried under reduced pressure to afford compound **IL** (510 mg, 65%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.98 (s, 1H), 8.78 (d, J = 6.0 Hz, 1H), 8.53 (s, 1H), 8.01 (d, J

= 6.0 Hz, 1H), 7.97 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 4.02 (s, 3H). MS (ESI): *m/z* 360.1 $[M+1]^+$

To a stirred solution of compound **IL** (500 mg, 1.38 mmol) in DMF (15 mL) under nitrogen atmosphere were added tert-butyl carbazate (548 mg, 4.15 mmol), EDCI·HCl (664 mg, 3.46 mmol), HOBt (339 mg, 2.49 mmol), and DIPEA (714 mg, 5.54 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2x25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to afford compound **IM** (430 mg, 66%) as an off-white solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.62 (br s, 1H), 9.70 (s, 1H), 9.28 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.32 (s, 1H), 8.03 (d, *J* = 6.0 Hz, 1H), 7.99 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 4.03 (s, 3H), 1.49 (s, 9H). MS (ESI): *m/z* 474.5 $[M+1]^+$

To a stirred solution of compound **IM** (430 mg, 0.91 mmol) in THF (15 mL) under nitrogen atmosphere were added TMS-acetylene (890 mg, 9.11 mmol) and TEA (920 mg, 9.11 mmol) at 0 °C. The reaction was purged with argon for 10 min followed by the addition of $Pd(PPh_3)_2Cl_2$ (63 mg, 0.09 mmol) and copper iodide (17 mg, 0.09 mmol) at RT. The reaction was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel chromatography to afford compound **IN** (320 mg, 84%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.62 (s, 1H), 9.70 (br s, 1H), 9.28 (br s, 1H), 8.82 (br s, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.95 (s, 1H), 7.91 (d, *J* = 6.5 Hz, 1H), 7.60-7.54 (m, 1H), 3.99 (s, 3H), 1.48 (s, 9H), 0.26 (s, 9H). MS (ESI): *m/z* 491.2 $[M+1]^+$

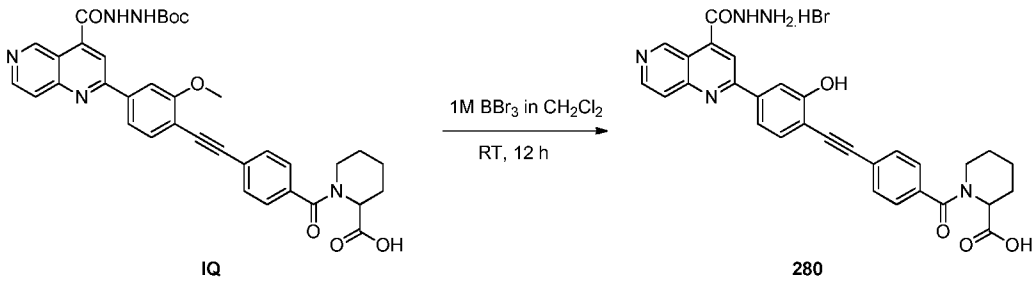
To a stirred solution of compound **IN** (200 mg, 0.40 mmol) in MeOH (10 mL) under nitrogen atmosphere was added potassium carbonate (168 mg, 1.22 mmol) at RT and the reaction was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2x25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography to afford compound **IO** (150 mg, 88%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.62 (s, 1H), 9.70 (s, 1H), 9.28 (s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.32 (s, 1H), 8.03 (d, *J* = 6.0 Hz, 1H), 7.95-7.91 (m, 2H), 7.62 (d, *J* = 7.5 Hz, 1H), 4.45 (s, 1H), 4.00 (s, 3H), 1.49 (s, 9H). MS (ESI): *m/z* 419.6 $[M+1]^+$

To a stirred solution of compound **IO** (150 mg, 0.35 mmol) in CH_3CN (20 mL) under nitrogen atmosphere were added compound **IK** (162 mg, 0.43 mmol) and TEA (0.5 mL, 3.58 mmol) at RT. The reaction was purged under argon for 10 min followed by the addition of copper iodide (6.8 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (25 mg, 0.03 mmol). The reaction was heated to 90 °C and stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was purified by silica gel chromatography to afford compound **IP** (200 mg, 63%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.73 (br s, 1H), 9.31 (s, 1H), 8.85 (br s, 1H), 8.37 (s, 1H), 8.07-8.00 (m, 4H), 7.82-7.55 (m, 3H), 7.45-7.40 (m, 1H), 5.28 (br s, 1H), 4.44-4.43 (m, 1H), 4.06 (s, 3H), 3.74-3.70 (m, 2H), 3.52-3.50 (m, 1H), 3.16-3.15 (m, 1H), 2.20-2.19 (m, 1H), 1.99-1.98 (m, 1H), 1.72-1.69 (m, 2H), 1.55 (s, 9H). MS (ESI): *m/z* 664.4 $[M+1]^+$

To a stirred solution of compound **IP** (100 mg, 0.15 mmol) in MeOH:THF:H_2O (2:2:1, 10 mL) was added lithium hydroxide monohydrate (32 mg, 0.75 mmol) at 0 °C. The reaction was allowed to warm to RT and stir for 5h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was diluted with water and the pH was adjusted to ~3 using an acetic acid solution (0.2 mL). The precipitate was filtered and dried under reduced pressure to afford compound **IQ** (55 mg, 57%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 9.71 (s, 1H), 9.28 (s, 1H), 8.82 (br s, 1H), 8.35 (s, 1H), 8.04-8.00 (m, 3H), 7.72-7.59 (m, 4H), 7.41-7.40 (m, 2H), 4.05 (s, 3H), 3.46-3.45 (m, 1H), 2.99-2.98 (m, 1H), 2.84-2.82 (m, 2H), 2.21-2.20 (m, 1H), 2.09-2.08 (m, 1H), 2.00-1.99 (m, 1H), 1.68-1.67 (m, 3H), 1.49-1.48 (m, 2H), 1.33-1.32 (m, 2H). MS (ESI): *m/z* 650.5 $[M+1]^+$

To a stirred solution of compound **IQ** (25 mg, 0.038 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with 10% MeOH/CH_3CN (2x5 mL) to afford **278** (13 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.01 (br s, 1H), 9.84 (br s, 1H), 8.98 (br s, 1H), 8.59 (s, 1H), 8.19 (br s, 1H), 8.09 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.66-7.65 (m, 2H), 7.44 (d, J = 7.5 Hz, 1H), 7.40 (br s, 1H), 5.19 (br s, 1H), 4.32-4.31 (m, 1H), 4.29-4.28 (m, 1H), 4.07 (s, 3H), 3.50-3.47 (m, 1H), 3.19-3.17 (m, 1H), 2.20-2.18 (m, 1H), 2.06-2.02 (m, 1H), 1.72-1.70 (m, 3H), 1.44-1.41 (m, 2H). MS (ESI): *m/z* 550.5 $[M+1]^+$. HPLC: 90.91%

Scheme 61



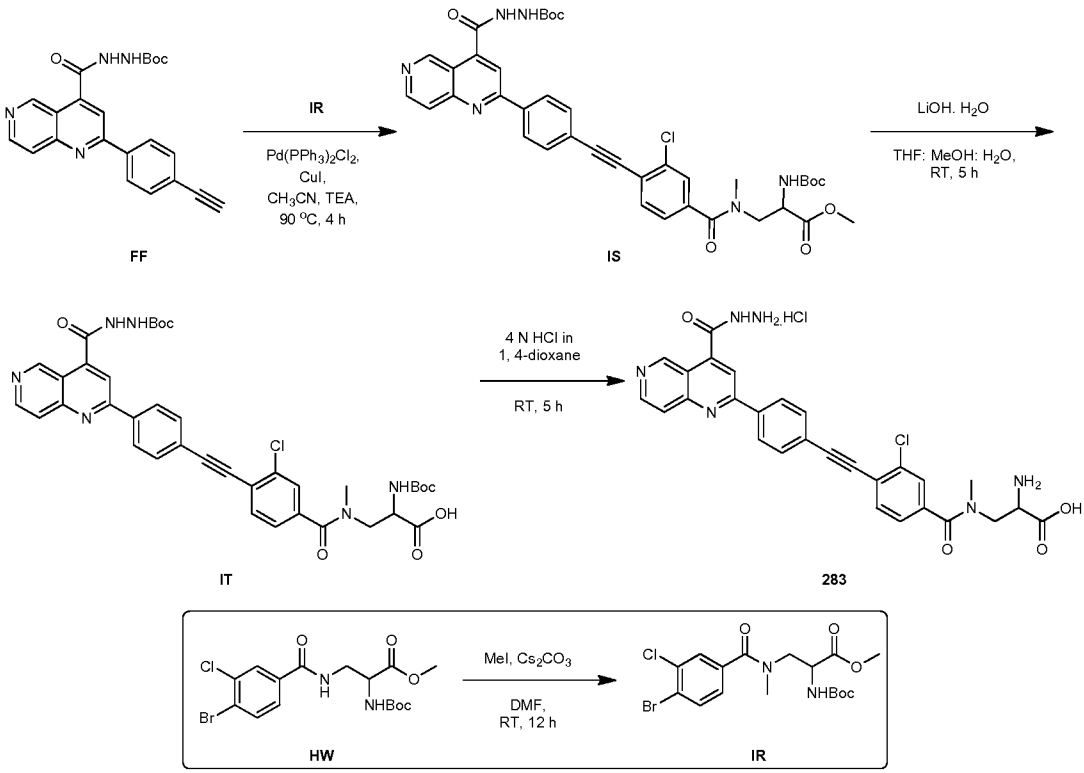
IQ 280

Example 280

1-(4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl)-2-hydroxyphenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid HBr salt (280)

To a stirred solution of compound **IQ** (20 mg, 0.03 mmol) in DCM (2 mL) was added 1M BBr_3 in DCM (45 mg, 0.18 mmol) at -78 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was quenched with MeOH (5 mL) and stirred for 2h. The volatiles were evaporated *in vacuo*. The crude material was purified by preparative HPLC to afford **280** (4 mg, 21% as an HBr salt) as a yellow solid. ^{1}H-NMR (400 MHz, CD_3OD-d_4): δ 9.73 (br s, 1H), 8.79-8.76 (m, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 5.38-5.37 (m, 1H), 4.57-4.45 (m, 1H), 3.67-3.55 (m, 1H), 2.99-2.94 (m, 1H), 2.40-2.22 (m, 1H), 1.81-1.78 (m, 2H), 1.67-1.56 (m, 1H), 1.51-1.44 (m, 2H). MS (ESI): *m/z* 536.6 $[M+1]^+$. UPLC Purity: 83.89%

Scheme 62



Example 283

2-amino-3-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl)-*N*-methylbenzamido) propanoic acid hydrochloride (283)

To a stirred solution of methyl 3-(4-bromo-3-chlorobenzamido)-2-((tert-butoxycarbonyl)amino) propanoate (**HW**; 700 mg, 1.61 mmol) in DMF (15 mL) under nitrogen atmosphere were added cesium carbonate (1.57 g, 4.83 mmol) and methyl iodide (687 mg, 4.83 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified through preparative HPLC to afford compound **IR** (350 mg, 48%) as a colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.47 (br s, 1H), 4.65 (br s, 1H), 4.09-4.08 (m, 1H), 3.78 (s, 3H), 3.67-3.64 (m, 1H), 3.03 (s, 3H), 1.45 (s, 9H). MS (ESI): *m/z* 450.5 $[M+1]^+$

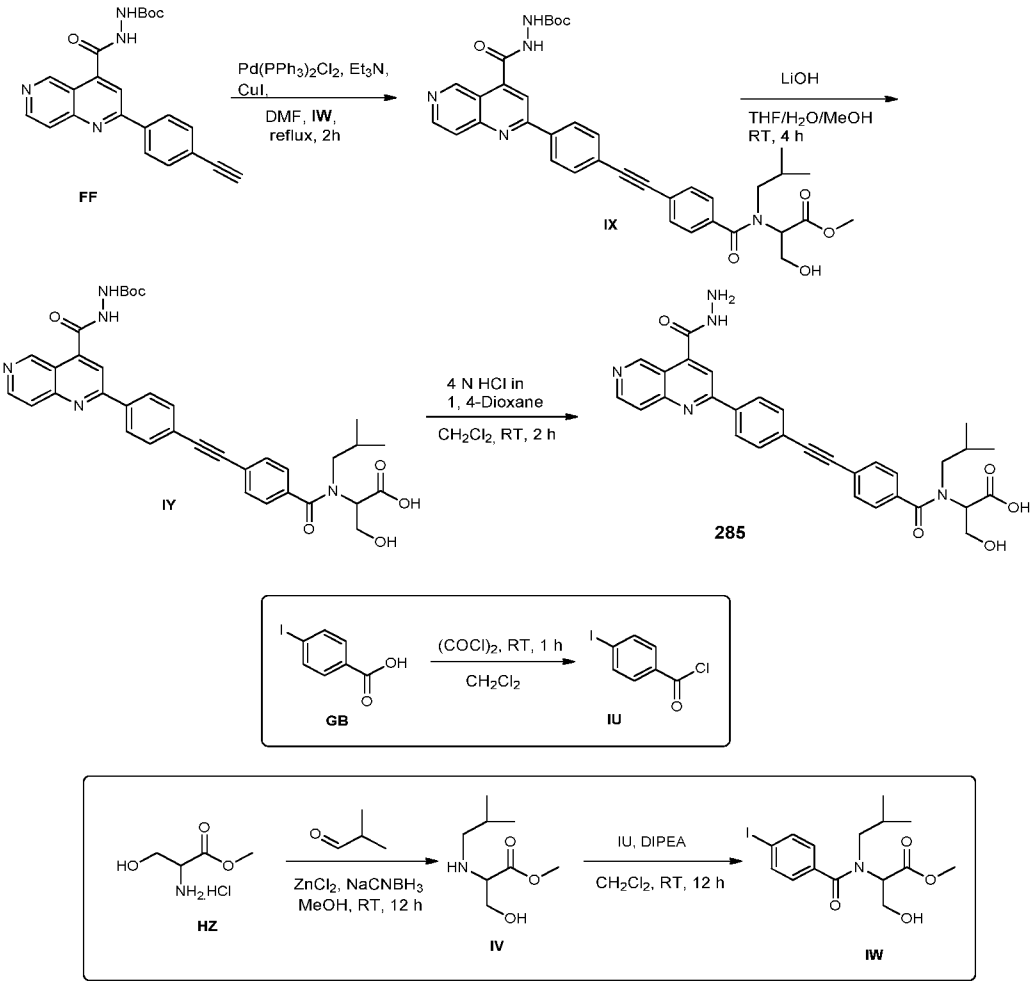
To a stirred solution of tert-butyl 2-(2-(4-ethynylphenyl)-1,6-naphthyridine-4-carbonyl)hydrazine-1-carboxylate (**FF**; 173 mg, 0.44 mmol) in CH_3CN:TEA (1:1, 20 mL) under nitrogen atmosphere was added compound **IR** (100 mg, 0.22 mmol). The reaction was degassed under argon for 10 min followed by the addition of copper iodide (4.2 mg, 0.044

mmol) and $Pd(PPh_3)_2Cl_2$ (15.6 mg, 0.022 mmol). The reaction was heated to 90 °C and stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were removed under reduced pressure. The crude was purified by silica gel chromatography to afford compound **IS** (103 mg, 61%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.71 (br s, 1H), 9.30 (s, 1H), 8.85 (br s, 1H), 8.47-8.46 (m, 2H), 8.34 (s, 1H), 8.07-8.06 (m, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.70-7.33 (m, 2H), 7.18-7.13 (m, 2H), 4.50-4.49 (m, 1H), 4.15-4.14 (m, 1H), 4.07-4.06 (m, 1H), 3.67-3.53 (m, 3H), 2.97-2.89 (m, 3H), 1.40 (s, 9H), 1.24 (s, 9H). MS (ESI): *m/z* 756.2 $[M+1]^+$

To a stirred solution of compound **IS** (50 mg, 0.066 mmol) in THF:MeOH:H_2O (2:2:1, 10 mL) under nitrogen atmosphere was added lithium hydroxide monohydrate (8.3 mg, 0.19 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 5h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was diluted with water (5 mL) and acidified with acetic acid. The precipitate was filtered and dried under reduced pressure to afford compound **IT** (28 mg, 57%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.80 (br s, 2H), 10.66 (br s, 1H), 9.71 (s, 1H), 9.30 (s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 7.0 Hz, 1H), 8.34 (s, 1H), 8.06-8.05 (m, 1H), 7.84-7.76 (m, 2H), 7.64-7.55 (m, 2H), 7.41-7.36 (m, 2H), 4.34-4.33 (m, 1H), 3.90-3.88 (m, 2H), 3.60-3.58 (m, 2H), 1.30 (s, 9H), 1.22 (s, 9H). MS (ESI): *m/z* 744.7 $[M+1]^+$

To a stirred solution of compound **IT** (25 mg, 0.033 mmol) in DCM (3 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 5h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with 10% MeOH/CH_3CN (2x5 mL) to afford **283** (12 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.09-11.99 (m, 1H), 9.71 (br s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 8.55 (s, 1H), 8.51-8.49 (m, 3H), 8.38-8.37 (m, 1H), 8.13 (d, J = 5.6 Hz, 1H), 7.83 (t, J = 4.8 Hz, 3H), 7.75 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 4.27 (br s, 1H), 4.03-3.99 (m, 2H), 3.77-3.75 (m, 1H), 2.95-2.92 (m, 4H). MS (ESI): *m/z* 543.6 $[M+1]^+$. UPLC Purity: 90.09%

Scheme 63



Example 285

***tert*-butyl 2-(2-(4-((4-((3-hydroxy-1-methoxy-1-oxopropan-2-yl)(isobutyl) carbamoyl) phenyl) ethynyl) phenyl)-1, 6-naphthyridine-4-carbonyl) hydrazine-1-carboxylate (285)**

To a stirred solution of DL-serine methylester·HCl (**HZ**; 2 g, 12.85 mmol) in MeOH (20 mL) under nitrogen atmosphere were added isobutyraldehyde (1.4 g, 19.27 mmol) and $ZnCl_2$ (874 mg, 6.42 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 30 min. Then $NaCNBH_3$ (2.43 g, 38.55 mmol) was added portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **IV** (850 mg, 38%) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.77 (t, J = 5.6 Hz, 1H), 3.62 (s, 3H), 3.57-

3.51 (m, 2H), 3.21 (t, J = 5.2 Hz, 1H), 2.35-2.31 (m, 1H), 2.23-2.18 (m, 1H), 1.84 (br s, 1H), 1.62-1.56 (m, 1H), 0.84 (d, J = 6.4 Hz, 6H).

To a stirred solution of 4-iodo benzoic acid **GB** (300 mg, 1.20 mmol) in DCM (5 mL) under nitrogen atmosphere were added oxalyl chloride (307 mg, 2.42 mmol) and DMF (0.01 mL) at 0 °C and the reaction was stirred for 10 min. The reaction was then allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to obtain compound **IU** (320 mg, crude) as a pale yellow solid.

To a stirred solution of compound **IV** (423 mg, 2.4 mmol) in DCM (10 mL) under nitrogen atmosphere was added DIPEA (2 mL, 12.0 mmol) at 0 °C. Then compound **IU** (320 mg, crude) in DCM (5 mL) was added under nitrogen atmosphere at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with DCM (2x30 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 30% EtOAc:hexane to afford compound **IW** (340 mg, crude) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.83-7.79 (m, 2H), 7.21-7.13 (m, 2H), 3.63 (s, 3H), 3.13 (d, J = 6.5 Hz, 2H), 2.96-2.88 (m, 2H), 1.86-1.80 (m, 1H), 1.33-1.23 (m, 2H), 0.77 (d, J = 6.5 Hz, 6H). MS (ESI): m/z 405.23 $[M+1]^+$

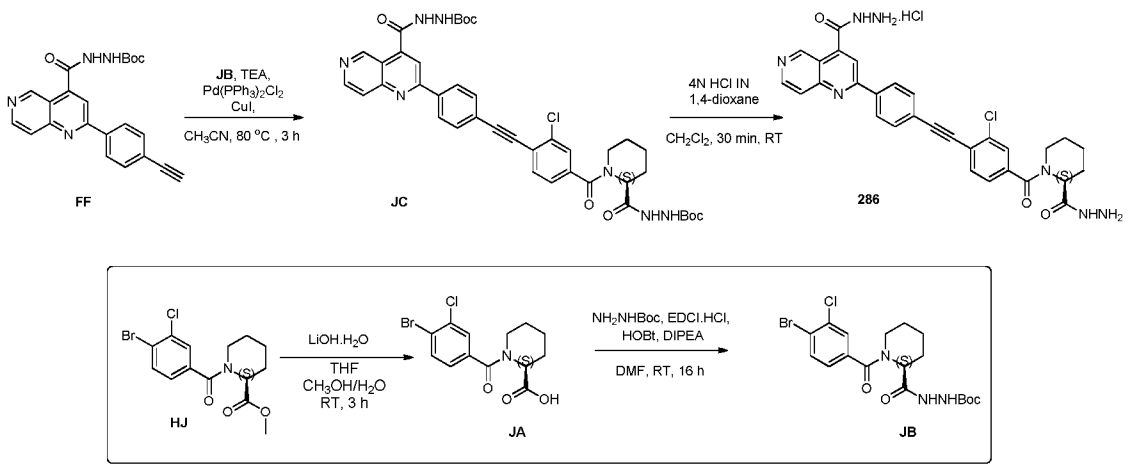
To a stirred solution of compound **FF** (200 mg, 0.51 mmol) in CH_3CN (10 mL) under argon atmosphere were added compound **IW** (250 mg, 0.61 mmol) and TEA (0.71 mL, 5.15 mmol). The reaction was purged under argon for 20 min followed by the addition of copper iodide (9.5 mg, 0.05 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol). The reaction was heated to reflux and stirred for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM and further purified by preparative HPLC to afford compound **IX** (80 mg, 23%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (br s, 1H), 9.29 (br s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.44 (d, J = 8.0 Hz, 3H), 8.34 (s, 1H), 8.04 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.49-7.41 (m, 2H), 5.02 (s, 1H), 4.18-3.98 (m, 3H), 3.65 (s, 3H), 3.17 (d, J = 5.2 Hz, 3H), 1.49 (s, 9H), 0.72 (d, J = 7.2 Hz, 6H). MS (ESI): m/z 665.75 $[M+1]^+$

To a stirred solution of compound **IX** (80 mg, 0.11 mmol) in THF:MeOH:H_2O (4 mL:2 mL: 4 mL) was added lithium hydroxide monohydrate (12.6 mg, 0.30 mmol) at 0 °C. The reaction

was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude was diluted with water and neutralized with acetic acid. The precipitate was filtered, washed with water and dried under reduced pressure to afford compound **IY** (62 mg, 79%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 10.66 (s, 1H), 9.71 (s, 1H), 9.31 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 8.05-7.99 (m, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 8.8 Hz, 2H), 7.49-7.33 (m, 2H), 4.08-3.97 (m, 2H), 3.88-3.67 (m, 2H), 3.13-3.09 (m, 2H), 1.90-1.87 (m, 2H), 1.49 (s, 9H), 0.87-0.71 (m, 6H). MS (ESI): *m/z* 651.72 $[M+1]^+$

To a stirred solution of compound **IY** (60 mg, 0.092 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was purified through preparative HPLC to afford **285** (10 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.0 (s, 1H), 9.67 (s, 1H), 8.83 (s, 1H), 8.54 (s, 1H), 8.44 (t, J = 8.0 Hz, 2H), 8.06 (d, J = 4.0 Hz, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 4.8 Hz, 2H), 7.26-7.01 (m, 3H), 4.31 (s, 1H), 4.07-3.98 (m, 2H), 3.70-3.62 (m, 1H), 3.30-3.16 (m, 2H), 2.06-1.88 (m, 1H), 0.91-0.73 (m, 6H). MS (ESI): *m/z* 552.5 $[M+1]^+$. UPLC Purity: 91.19%

Scheme 64



Example 286

(*S*)-2-(4-((2-chloro-4-(2-(hydrazinecarbonyl) piperidine-1-carbonyl) phenyl) ethynyl)phenyl)-1, 6-naphthyridine-4-carbohydrazide dihydrochloride (286)

To a stirred solution of compound **HJ** (500 mg, 1.36 mmol) in THF:MeOH:H_2O (8 mL:4 mL:4 mL) was added lithium hydroxide monohydrate (175 mg, 4.16 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was diluted with water and the pH was adjusted to ~3 using an acetic acid solution (0.2 mL). The crude compound was extracted with 10% MeOH/DCM (2x10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **JA** (450 mg, 94%) as a gummy colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.35 (brs, 1H), 7.86-7.82 (m, 1H), 7.58-7.49 (m, 1H), 7.25-7.20 (m, 1H), 5.12 (brs, 1H), 4.35-4.33 (m, 1H), 3.41-3.39 (m, 1H), 3.16-3.11 (m, 1H), 2.18-2.16 (m, 2H),1.76-1.65 (m, 3H).

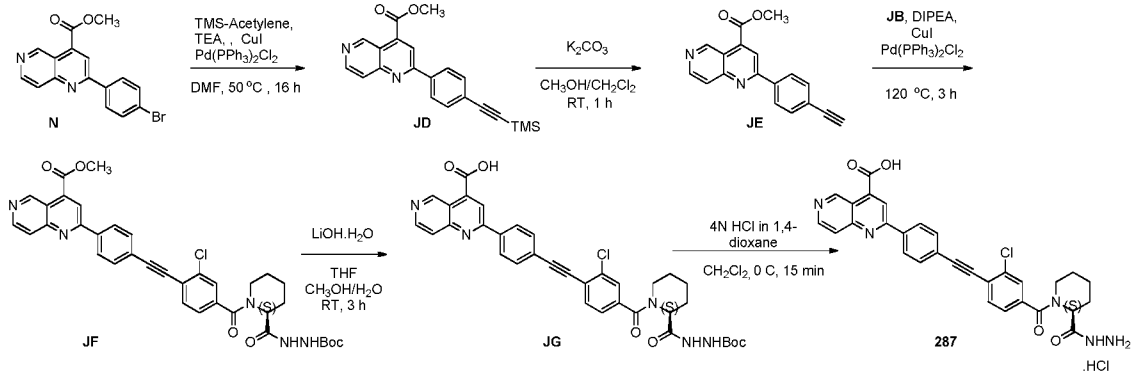
To a stirred solution of compound **JA** (450 mg, 1.29 mmol) in DMF (5 mL) under nitrogen atmosphere were added DIPEA (1.16 mL, 6.48 mmol), EDCI·HCl (498 mg, 2.59 mmol), HOBt (350 mg, 2.59 mmol) and tert-butyl carbazate (513 mg, 3.89 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (50 mL) and the compound was extracted with EtOAc (2x50 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography eluting with 2% MeOH/DCM to afford compound **JB** (350 mg, 59%) as a sticky colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 8.80 (s, 1H), 7.95 (s, 2H), 7.36 (d, J = 7.6 Hz, 1H), 5.13 (br s, 1H), 4.41-4.15 (m, 1H), 3.89 (s, 1H), 3.41-3.37 (m, 1H), 3.15-2.98 (m, 1H), 2.23 (d, J = 10.0 Hz, 1H), 1.79 (s, 1H), 1.61-1.58 (m, 2H), 1.41 (s, 9H). MS (ESI): m/z 461.75 $[M+1]^+$

To a stirred solution of compound **FF** (200 mg, 0.51 mmol) in CH_3CN (20 mL) under argon atmosphere were added compound **JB** (142 mg, 0.30 mmol) and TEA (0.72 mL, 5.15 mmol). The reaction was purged under argon for 20 min followed by the addition of CuI (9.8 mg, 0.05 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol). The reaction was heated to 80 °C and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite, the Celite bed was washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **JC** (70 mg, 18%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 9.69 (s, 1H), 9.30 (s, 1H), 8.80 (s, 1H), 8.46 (d, J = 6.4 Hz, 3H), 8.18-8.12 (m, 1H), 7.83 (d, J = 6.4 Hz, 1H), 7.51-7.39 (m, 3H), 5.15 (s, 1H), 4.51-4.36 (m, 1H), 3.61-3.57 (m, 2H), 2.26 (t, J = 4.4 Hz, 1H), 2.16-2.11

(m, 1H), 1.64-1.50 (m, 2H), 1.49 (s, 9H), 1.41 (s, 9H), 1.03 (d, J = 6.0 Hz, 1H). MS (ESI): *m/z* 769.27 $[M+1]^+$

To a stirred solution of compound **JC** (35 mg, 0.04 mmol) in DCM (0.5 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.02 mL) at 0 °C. The reaction was stirred for 15 min. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was purified through preparative HPLC to afford **286** (15 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.92 (s, 1H), 9.80 (s, 1H), 8.98 (br s, 1H), 8.46 (t, J = 8.4 Hz, 4H), 8.11 (br s, 1H), 7.84 (d, J = 8.4 Hz, 4H), 7.68 (s, 1H), 7.48 (d, J = 4.4 Hz, 1H), 5.22 (br s, 1H), 4.55-4.38 (m, 1H), 3.71-3.66 (m, 1H), 3.50-3.46 (m, 1H), 2.28-2.10 (m, 1H), 1.69-1.58 (m, 2H), 1.51-1.38 (m, 2H). MS (ESI): *m/z* 568.6 $[M+1]^+$. UPLC Purity: 96.41%

Scheme 65



Example 287

2-(4-((4-(2-oxooxazolidin-5-yl) phenyl) ethynyl) phenyl)-1, 6-naphthyridine-4-carbohydrazide HCl salt (287)

To a stirred solution of compound **N** (2 g, 5.84 mmol) in DMF (20 mL) under argon atmosphere were added TMS-acetylene (5.7 g, 58.4 mmol) and TEA (8.2 mL, 58.4 mmol). The reaction was purged under argon for 20 min followed by the addition of copper iodide (111 mg, 0.58 mmol) and $Pd(PPh_3)_2Cl_2$ (410 mg, 0.58 mmol). The reaction was heated to 50 °C and stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (100 mL) and extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water (2x100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 20% EtOAc:hexane to afford compound **JD** (1.3 g, 62%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.84 (s, 1H), 8.50 (s,

1H), 8.22 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 5.2 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 4.13 (s, 3H), 0.29 (s, 9H). MS (ESI): *m/z* 361.49 $[M+1]^+$

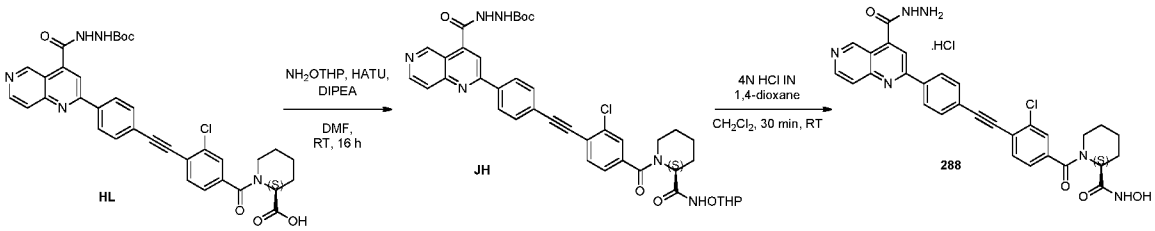
To a stirred solution of compound **JD** (1.3 g, 3.61 mmol) in MeOH:DCM (10 mL:10 mL) under nitrogen atmosphere was added K_2CO_3 (1.49 g, 10.83 mmol) portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with DCM (30 mL). The filtrate was concentrated under reduced pressure. The crude was diluted with cold water (20 mL) and extracted with DCM (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **JE** (800 mg, 77%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.63 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 5.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 4.44 (s, 1H), 4.06 (s, 3H). MS (ESI): *m/z* 289.3 $[M+1]^+$

To a stirred solution of compound **JE** (200 mg, 0.69 mmol) in DMF (5 mL) under argon atmosphere were added compound **JB** (191 mg, 0.41 mmol) and DIPEA (0.97 mL, 6.94 mmol). The solution was purged under argon for 20 min followed by the addition of copper iodide (13 mg, 0.06 mmol) and $Pd(PPh_3)_2Cl_2$ (49 mg, 0.06 mmol). The reaction was heated to 120 °C and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (30 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (2x30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **JF** (100 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.88 (s, 1H), 8.70 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 2H), 8.20 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.72-7.66 (m, 3H), 7.41-7.36 (m, 2H), 5.01 (s, 1H), 4.25-4.12 (m, 2H), 3.31 (s, 3H), 1.90-1.81 (m, 2H), 1.41 (s, 9H), 1.64 (d, *J* = 5.2 Hz, 2H), 1.28-1.23 (m, 2H). MS (ESI): *m/z* 669.15 $[M+1]^+$

To a stirred solution of compound **JF** (100 mg, 0.14 mmol) in THF/MeOH/H_2O (4 mL/2 mL/2 mL) were added $LiOH{\cdot}H_2O$ (19 mg, 0.44 mmol) at 0 °C. The reaction was allowed to warm to RT and stir for 3h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to ~3 by using AcOH. The resulting solids were filtered and washed with water, dried under reduced pressure to afford compound **JG** (40 mg, 41%) as a yellow solid. MS (ESI): *m/z* 655.12 $[M+1]^+$

To a stirred solution of compound **JG** (40 mg, 653 mmol) in DCM (0.5 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was stirred for 15 min. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was purified by preparative HPLC to afford **287** (4 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 10.50 (br s, 1H), 8.97 (d, *J* = 10.0 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 2H), 7.85-7.76 (m, 3H), 7.71 (s, 2H), 7.68-7.42 (m, 2H), 5.35 (s, 1H), 4.23 (d, *J* = 4.4 Hz, 2H), 2.35-2.10 (m, 1H), 1.99-1.85 (m, 1H), 1.72-1.65 (m, 2H), 1.64-1.55 (m, 2H). MS (ESI): *m/z* 555 $[M+1]^+$. UPLC Purity: 98.85%

Scheme 66



Example 288

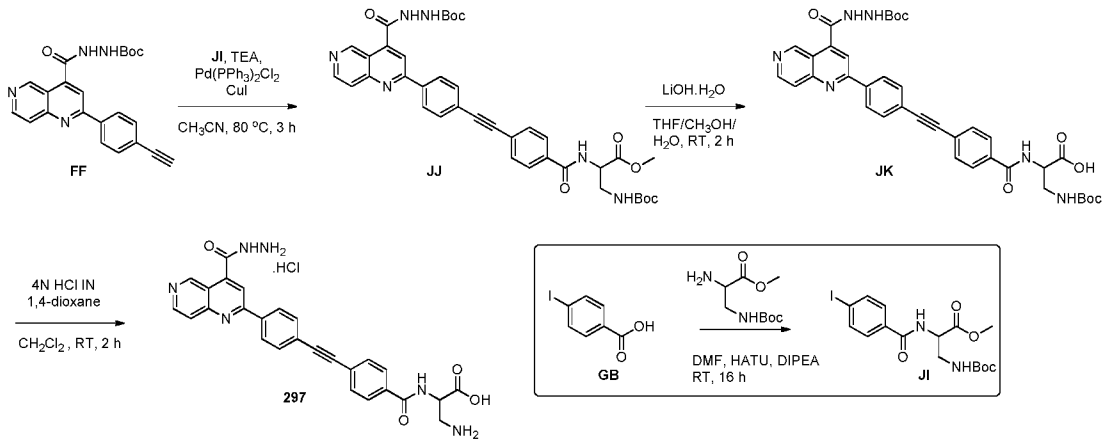
(*S*)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl)-N-hydroxypiperidine-2-carboxamide hydrochloride (288)

To a stirred solution of compound **HL** (55 mg, 0.084 mmol) in DMF (2 mL) under nitrogen atmosphere were added DIPEA (0.04 mL, 0.25 mmol), NH_2OTHP (19.5 mg, 0.168 mmol) and HATU (49 mg, 0.126 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (2x30 mL), brine (2x25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **JH** (30 mg, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.22 (br s, 1H), 10.80 (s, 1H), 9.74 (s, 1H), 9.29 (s, 1H), 8.84 (d, *J* = 6.0 Hz, 1H), 8.47-8.39 (m, 2H), 8.34 (s, 1H), 8.05 (d, *J* = 5.2 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.73-7.67 (m, 2H), 7.66-7.46 (m, 2H), 5.07 (s, 1H), 4.22 (t, *J* = 6.4 Hz, 2H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.53 (d, *J* = 11.2 Hz, 2H), 1.68-1.60 (m, 6H), 1.53-1.50 (m, 2H), 1.49 (s, 9H), 1.42-1.34 (m, 4H). MS (ESI): *m/z* 754.25 $[M+1]^+$

To a stirred solution of compound **JH** (30 mg, 0.039 mmol, crude) in DCM (0.5 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.02 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 30 min. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to afford **288** (15 mg

as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 10.70 (br s, 1H), 9.70 (s, 1H), 8.88 (d, J = 6.0 Hz, 1H), 8.51 (t, J = 10.0 Hz, 3H), 8.14 (d, J = 6.0 Hz, 1H), 7.87-7.80 (m, 2H), 7.73-7.69 (m, 1H), 7.68-7.47 (m, 2H), 7.38-7.15 (m, 2H), 5.12 (s, 1H), 4.22 (t, J = 6.8 Hz, 1H), 4.01 (d, J = 6.8 Hz, 1H), 3.44-3.29 (m, 2H), 2.30-2.19 (m, 1H), 2.01-1.85 (m, 1H), 1.40-1.34 (m, 3H). MS (ESI): 90.12%, *m/z* 569.5 $[M+1]^+$

Scheme 67



Example 297

3-amino-2-(4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzamido) propanoic acid hydrochloride (297)

To a stirred solution of 4-iodobenzoic acid (**GB**; 100 mg, 0.40 mmol) in DMF (5 mL) under nitrogen atmosphere were added DIPEA (0.2 mL, 1.20 mmol), methyl 2-amino-3-((tert-butoxycarbonyl)amino)propanoate (88 mg, 0.40 mmol) and HATU (235 mg, 0.60 mmol). The reaction was stirred at RT for 16h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (10 mL) and the compound was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography eluting with 40% EtOAc/hexane to afford compound **JI** (120 mg, crude) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 4.73-4.62 (m, 1H), 3.78 (s, 3H), 3.68-3.57 (m, 1H), 2.80 (s, 2H), 1.42 (s, 9H). MS (ESI): *m/z* 449.26 $[M+1]^+$

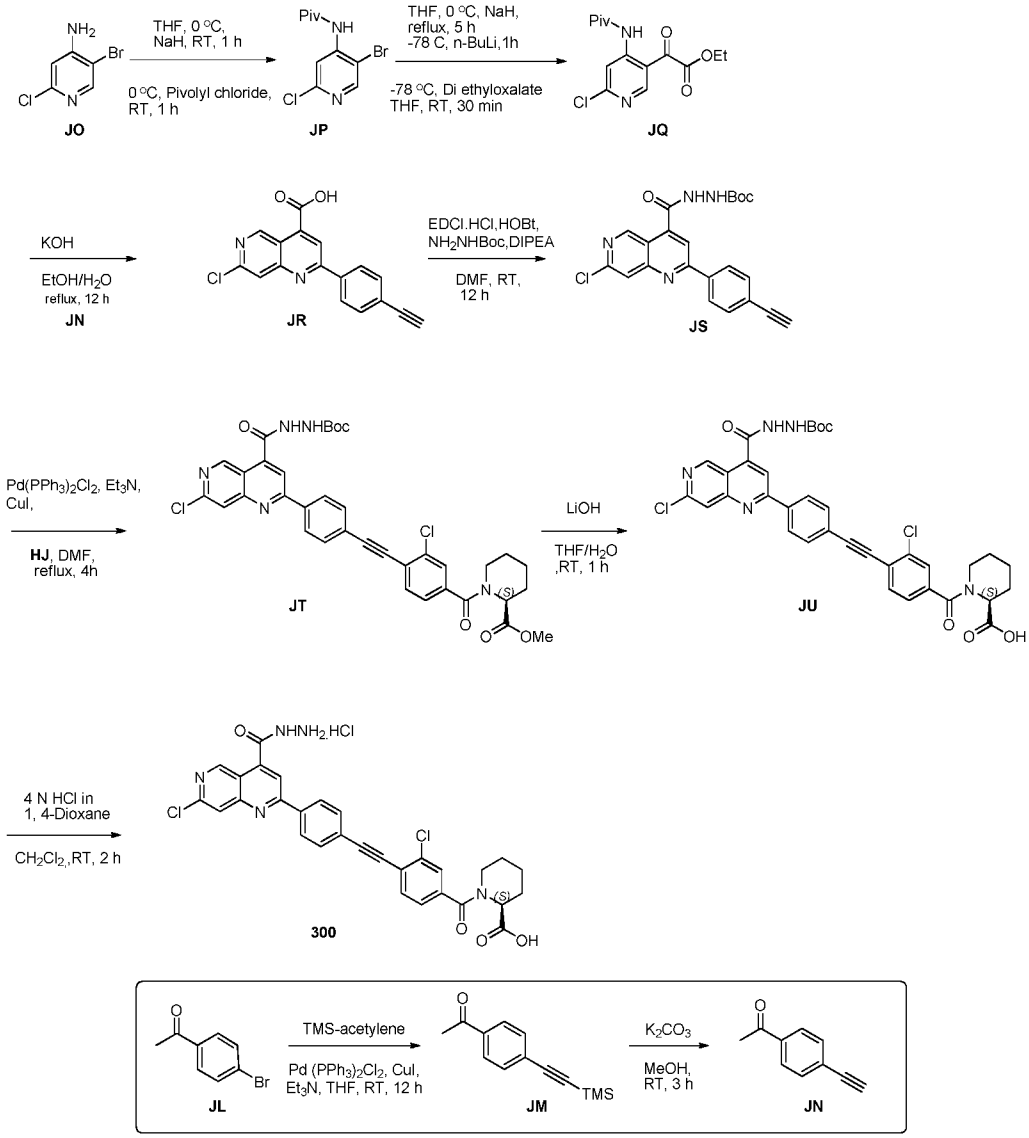
To a stirred solution of compound **FF** (100 mg, 0.25 mmol) in CH_3CN (10 mL) under argon atmosphere were added compound **JI** (115 mg, 0.25 mmol) and TEA (0.36 mL, 2.57 mmol). The solution was purged under argon for 20 min followed by the addition of copper iodide (5 mg, 0.025 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol). The reaction was heated to 80 °C

and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 2% MeOH:DCM to afford compound **JJ** (50 mg, 25%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 9.72 (s, 1H), 9.30 (br s, 1H), 8.89-8.73 (m, 2H), 8.70-8.63 (m, 1H), 8.62-8.50 (m, 1H), 8.48-8.34 (m, 1H), 8.05 (d, J = 5.6 Hz, 2H), 7.98-7.73 (m, 2H), 7.70-7.61 (m, 2H), 7.07-7.04 (m, 1H), 4.53-4.49 (m, 1H), 3.63 (s, 3H), 3.62-3.58 (m, 1H), 3.45 (d, J = 6.4 Hz, 2H), 1.49 (s, 9H), 1.37 (s, 9H). MS (ESI): *m/z* 709.77 $[M+1]^+$

To a stirred solution of compound **JJ** (50 mg, 0.06 mmol) in THF/MeOH/H_2O (4 mL/4 mL/2 mL) was added LiOH·H_2O (5.5 mg, 0.13 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was diluted with water and the pH was adjusted to pH~3 with AcOH. The precipitate was filtered, washed with water, and dried under reduced pressure to afford compound **JK** (35 mg, 71%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.65 (s, 1H), 9.71 (s, 1H), 9.29 (s, 1H), 8.83 (s, 1H), 8.45-8.33 (m, 4H), 8.05 (d, J = 6.4 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.73-7.56 (m, 2H), 6.89 (br s, 1H), 4.25 (br s, 1H), 3.40-3.32 (m, 2H), 1.49 (s, 9H), 1.36 (s, 9H). MS (ESI): *m/z* 695.75 $[M+1]^+$

To a stirred solution of compound **JK** (35 mg, 0.05 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to afford **297** (25 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.98 (s, 1H), 9.76 (br s, 1H), 9.06 (d, J = 8.0 Hz, 1H), 8.92 (s, 1H), 8.55 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.20-8.14 (m, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 4.78-4.72 (m, 1H), 3.35 (t, J = 6.0 Hz, 1H), 3.24 (d, J = 5.6 Hz, 1H). MS (ESI): *m/z* 495.4 $[M+1]^+$. UPLC Purity: 92.01%

Scheme 68



Example 300

(S)-1-(3-chloro-4-((4-(7-chloro-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid hydrochloride (300)

To a stirred solution of 1-(4-bromophenyl)ethan-1-one (**JL**; 5 g, 25.12 mmol) in THF (50 mL) under argon atmosphere were added TMS-acetylene (24.6 g, 251.2 mmol) and TEA (17.5 mL, 125.6 mmol) at 0 °C. The solution was purged under argon for 30 min followed by the addition of $Pd(PPh_3)_2Cl_2$ (1.76 g, 2.51 mmol) and CuI (478 mg, 2.51 mmol). The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 5% EtOAc/hexane to

afford compound **JM** (4.8 g, 88%) as a brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 2.59 (s, 3H), 0.26 (s, 9H). MS (ESI): *m/z* 216.36 $[M+1]^+$

To a stirred solution of compound **JM** (500 mg, 2.31 mmol) in MeOH (5 mL) under nitrogen atmosphere was added anhydrous K_2CO_3 (958 mg, 6.94 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The reaction was diluted with water (10 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 5% EtOAc/hexane to afford compound **JN** (280 mg, 84%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.90 (m, 2H), 7.58-7.56 (m, 2H), 3.24 (s, 1H), 2.60 (s, 3H). MS (ESI): *m/z* 144.17 $[M+1]^+$

To a stirred solution of 5-bromo-2-chloropyridin-4-amine (**JO**; 41 g, 197.63 mmol) in THF (600 mL) under nitrogen atmosphere was added NaH (20 g, 494.07 mmol) portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. Then pivaloyl chloride (29.16 mL, 237.16 mmol) in THF (20 mL) was added dropwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (500 mL) and the compound was extracted with EtOAc (2 x 500 mL). The combined organic extracts were washed with water (2x200 mL), brine (2x100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography eluting with 10% EtOAc/hexane to afford compound **JP** (46.25 g, 81%) as an off white solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.93 (s, 1H), 8.61 (s, 1H), 7.96 (s, 1H), 1.27 (s, 9H). MS (ESI): *m/z* 291.57 $[M+1]^+$

To a stirred solution of compound **JP** (5.5 g, 19.03 mmol) in THF (75 mL) under argon atmosphere was added NaH (3 g, 76.12 mmol) portionwise at 0 °C. The reaction was heated to reflux and was stirred for 5h. Then n-BuLi (15.3 mL, 38.06 mmol) was added dropwise at -78 °C and stirred for 2h. Diethyl oxalate (5.55 g, 38.06 mmol) was then added dropwise at -78°C over 30 min. The reaction was allowed to warm to RT and was stirred for 30 min. After complete consumption of the starting material (by TLC), the reaction was diluted with an NH_4Cl solution (100 mL) and the compound was extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel

column chromatography eluting with 5-7% EtOAc/hexane to afford compound **JQ** (4.8 g, 40.3%) as a white solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.70 (s, 1H), 8.70 (s, 1H), 8.11 (s, 1H), 4.31 (q, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.21 (s, 9H). MS (ESI): m/z 312.75 $[M+1]^+$

To a stirred solution of compound **JQ** (1 g, 3.20 mmol) in EtOH/H_2O (20 mL/ 20 mL) was added KOH (719 mg, 12.82 mmol). The reaction was heated to reflux and was stirred for 2h. Then 4- acetylene acetophenone **JN** (923 mg, 6.41 mmol) was added at RT and the reaction was heated to refluxed for 12h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure. The crude material was diluted with water (15 mL) and acidified using AcOH. The obtained solid was filtered and dried under reduced pressure to afford compound **JR** (801 mg, 81%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 8.40 (s, 1H), 8.31 (d, J = 8.0 Hz, 2H), 8.06 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 4.41 (s, 1H). MS (ESI): m/z 308.72 $[M+1]^+$

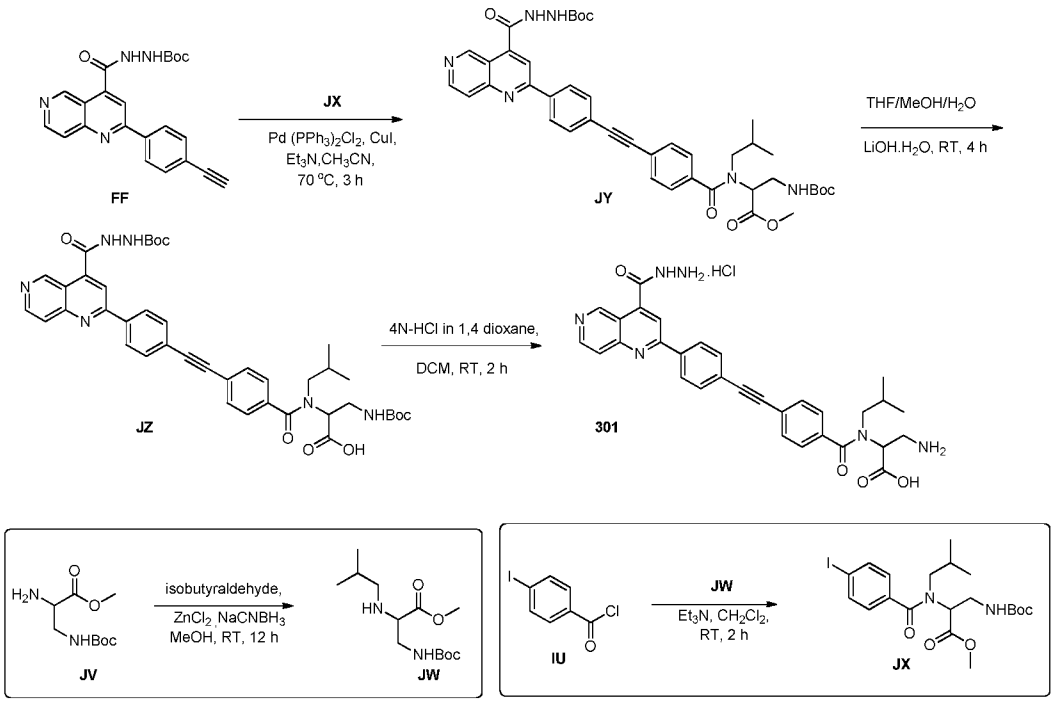
To a stirred solution of compound **JR** (250 mg, 0.81 mmol) in DMF (5 mL) under nitrogen atmosphere were added DIPEA (0.5 mL, 2.43 mmol), tert-butyl hydrazine carboxylate (320 mg, 2.43 mmol) and HATU (634 mg, 1.62 mmol). The reaction was stirred at RT for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2x50 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography 2% MeOH/DCM to afford compound **JS** (380 mg, 55%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 9.58 (s, 1H), 9.32 (s, 1H), 8.37 (t, J = 7.6 Hz, 3H), 8.20 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 4.45 (s, 1H), 1.48 (s, 9H). MS (ESI): m/z 422.87 $[M+1]^+$

To a stirred solution of compound **JS** (300 mg, 0.71 mmol) in CH_3CN (20 mL) under argon atmosphere were added **HJ** (383 mg, 1.06 mmol) and TEA (1 mL, 7.11 mmol). The solution was purged under argon for 20 min followed by the addition of copper iodide (13.5 mg, 0.071 mmol) and $Pd(PPh_3)_2Cl_2$ (50 mg, 0.071 mmol). The reaction was heated to reflux and stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **JT** (180 mg, 36%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 9.59 (s, 1H), 9.33 (s, 1H), 8.47 (d, J = 8.0 Hz, 3H), 8.22 (s, 1H), 7.85 (t, J = 9.2 Hz, 2H), 7.64-7.54 (m, 3H), 5.26 (s, 1H), 4.46-4.38 (m, 1H), 3.74 (s, 3H), 3.50-3.31 (m, 1H), 2.21-2.08 (m, 1H), 1.78-1.69 (m, 2H), 1.58-1.54 (m, 1H), 1.49 (s, 9H), 1.33-1.24 (m, 2H). MS (ESI): m/z 702.59 $[M+1]^+$

To a stirred solution of compound **JT** (100 mg, 0.14 mmol) in THF:H_2O (5 mL:5 mL) was added lithium hydroxide monohydrate (60 mg, 1.42 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and neutralized with an acetic acid solution (0.2 mL) to obtain the solid, which was filtered, washed with water, and dried under reduced pressure to afford compound **JU** (62 mg, 63%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 9.59 (s, 1H), 9.33 (s, 1H), 8.45 (d, J = 6.4 Hz, 2H), 8.38 (s, 1H), 8.21 (s, 1H), 7.89-7.76 (m, 3H), 7.62-7.58 (m, 2H), 7.40 (s, 1H), 4.31-4.22 (m, 1H), 4.10-3.99 (m, 1H), 3.41-3.31 (m, 1H), 2.24-2.12 (m, 1H), 1.65-1.54 (m, 2H), 1.49 (s, 9H), 1.10-1.01 (m, 3H). MS (ESI): *m/z* 688.46 $[M+1]^+$

To a stirred solution of compound **JU** (60 mg, 0.087 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with 20% IPA:CH_3CN (3 mL) to afford **300** (30 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 9.54 (s, 1H), 8.47 (d, J = 8.0 Hz, 3H), 8.21 (s, 1H), 7.90-7.81 (m, 3H), 7.59-7.55 (m, 1H), 7.42-7.04 (m, 1H), 5.17 (s, 1H), 4.41-4.31 (m, 1H), 3.46 (d, J = 12.8 Hz, 1H), 3.18 (t, J = 12.8 Hz, 1H), 2.19-2.05 (m, 1H), 1.71-1.55 (m, 2H), 1.46-1.22 (m, 2H). MS (ESI): *m/z* 624.90 $[M+1]^+$. UPLC Purity: 92.04%

Scheme 69



Example 301

3-amino-2-(4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl)-N-isobutylbenzamido) propanoic acid (301)

To a stirred solution of methyl 2-amino-3-((tert-butoxycarbonyl)amino)propanoate (**JV**; 1 g, 4.58 mmol) in MeOH (20 mL) under nitrogen atmosphere were added isobutyraldehyde (0.71 mL, 6.84 mmol) and $ZnCl_2$ (311 mg, 2.28 mmol) at RT. After stirring for 1h at RT, $NaCNBH_3$ (865 mg, 13.73 mmol) was added portionwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (5 mL) and the pH was adjusted to pH~8 by using a $NaHCO_3$ solution. The solution was extracted with EtOAc (2x50 mL) and the combined organic extracts were washed with water (50 mL), brine (50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford compound **JW** (1 g, 80%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 6.81 (br s, 1H), 3.59 (s, 3H), 3.25-3.18 (m, 1H), 3.15-3.08 (m, 2H), 2.32-2.14 (m, 2H), 1.87 (br s, 1H), 1.60-1.51 (m, 1H), 1.36 (s, 9H), 0.84 (d, J = 6.4 Hz, 6H). MS (ESI): *m/z* 275.36 $[M+1]^+$

To a stirred solution of **JW** (308 mg, 1.12 mmol) in DCM (5 mL) was added compound **IU** (300 mg, 1.12 mmol) in 5 mL DCM dropwis e at 0°C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and the compound was extracted with DCM

(2 x 10 mL). The combined organic extracts were washed with a 10% $NaHCO_3$ solution (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 20% EtOAc/hexane to afford compound **JX** (360 mg, 59%) as alow melting white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 5.21 (br s, 1H), 3.88 (s, 2H), 3.75 (s, 3H), 3.71-3.65 (m, 1H), 3.20-3.08 (m, 2H), 1.93 (t, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H). MS (ESI): *m/z* 505.37 $[M+1]^+$

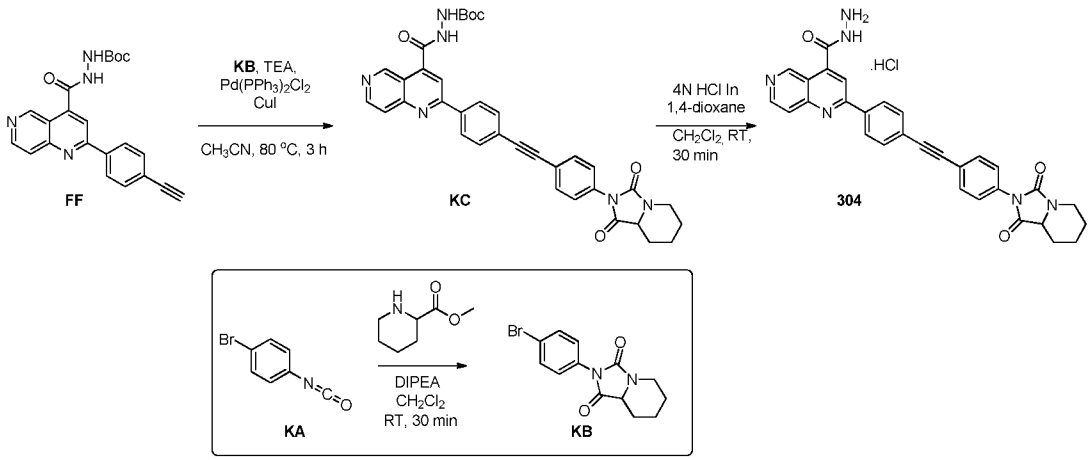
To a stirred solution of compound **FF** (250 mg, 0.64 mmol) in CH_3CN (15 mL) under argon atmosphere were added compound **JX** (357 mg, 0.70 mmol) and Et_3N (0.9 mL, 6.44 mmol) at 0 °C. The solution was purged under argon for 30 min followed by the addition of $Pd(PPh_3)_2Cl_2$ (4.5 mg, 0.06 mmol) and CuI (12.2 mg, 0.06 mmol). The reaction was purged under argon for 10 min and then heated to 70 °C and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite. The filterate was concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography eluting with 5% MeOH/DCM and further triturated with IPA: pentane (1 mL/4 mL) to afford compound **JY** (240 mg, 51%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (br s, 1H), 9.71 (br s, 1H), 9.30 (br s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 2H), 8.33 (s, 1H), 8.05 (d, *J* = 6.4 Hz, 1H), 7.96 (s, 1H), 7.83-7.62 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 4.08 (s, 1H), 3.67 (s, 3H), 3.63-3.57 (m, 2H), 3.13 (d, *J* = 10.4 Hz, 1H), 3.01-2.96 (m, 1H), 1.80-1.71 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H), 0.77 (d, *J* = 6.0 Hz, 3H), 0.72 (d, *J* = 6.4 Hz, 3H). MS (ESI): *m/z* 765.88 $[M+1]^+$

To a stirred solution of compound **JY** (80 mg, 0.10 mmol) in THF:MeOH:H_2O (4 mL:1 mL:1 mL) was added lithium hydroxide monohydrate (22 mg, 0.52 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was diluted with water (5 mL) and the pH was adjusted to pH~3 by using an acetic acid solution (0.2 mL). The product was extracted with 20% MeOH/DCM (2x10 mL) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was further triturated with IPA:pentane (2 mL/4 mL) to afford compound **JZ** (60 mg, 80%) as a brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.71 (br s, 1H), 9.29 (br s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.44 (d, *J* = 7.6 Hz, 2H), 8.33 (s, 1H), 8.05 (d, *J* = 5.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.64-7.52 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 4.33 (d, *J* = 3.2 Hz, 1H), 3.95-3.77 (m, 2H), 3.64-3.56 (m, 1H),

3.03-2.97 (m, 2H), 1.83-1.79 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H), 0.77 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H). MS (ESI): m/z 751.85 $[M+1]^+$

To a stirred solution of compound **JZ** (60 mg, 0.07 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with MeOH:CH_3CN (1 mL: 3 mL) to afford **301** (20 mg as an HCl salt) as a pale brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.64 (s, 1H), 9.70 (br s, 1H), 8.87 (br s, 1H), 8.48 (t, J = 4.0 Hz, 3H), 8.10 (t, J = 6.4 Hz, 4H), 7.83 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 4.30 (t, J = 6.4 Hz, 2H), 3.19 (d, J = 6.8 Hz, 3H), 1.92-1.85 (m, 1H), 0.78 (d, J = 6.4 Hz, 3H), 0.71 (d, J = 6.4 Hz, 3H). MS (ESI): m/z 551.8 $[M+1]^+$. UPLC: 87.77%

Scheme 70



Example 304

2-(4-((4-(1, 3-dioxohexahydroimidazo[1, 5-a]pyridin-2(3H)-yl) phenyl) ethynyl) phenyl)-1, 6-naphthyridine-4-carbohydrazide hydrochloride (304)

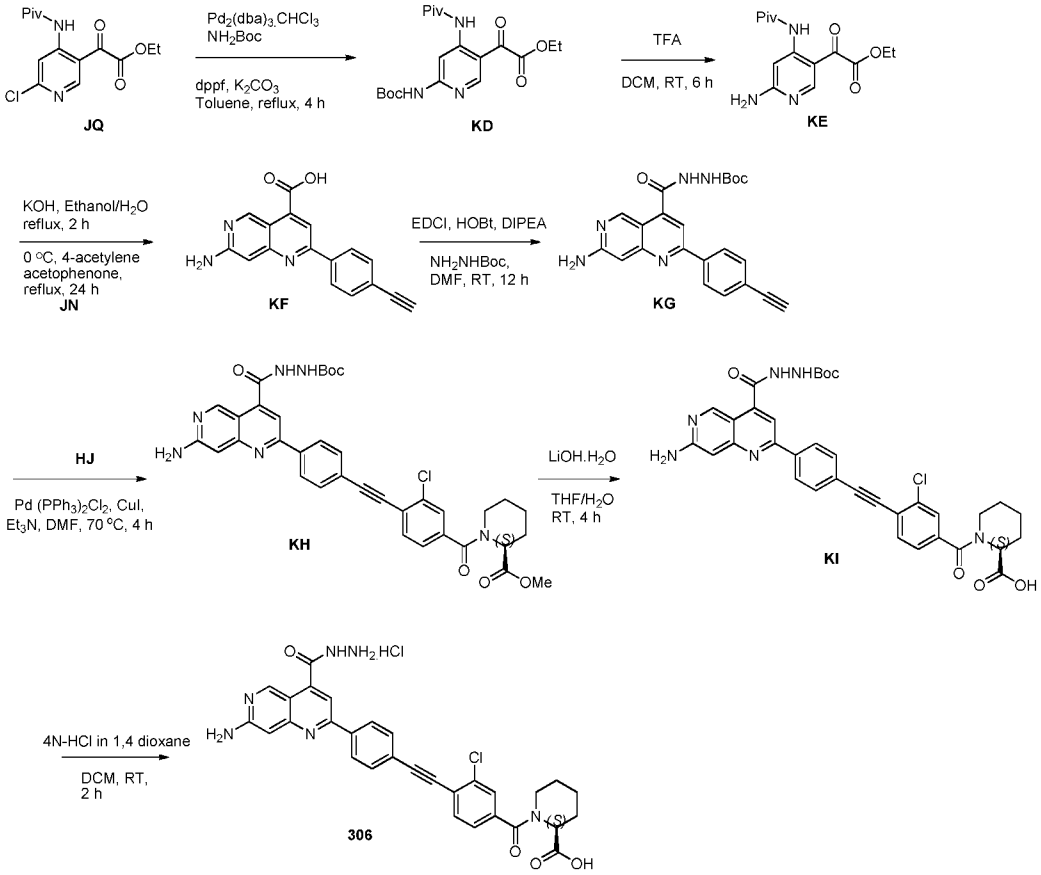
To a stirred solution of compound **KA** (500 mg, 3.49 mmol) in DCM (15 mL) under nitrogen atmosphere was added DIPEA (1.25 mL, 6.99 mmol) at 0 °C followed by the addition of methyl piperidine-2-carboxylate (690 mg, 3.49 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 30 min. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford compound **KB** (650 mg, crude) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.12-4.08 (m, 1H), 4.02-3.97 (m, 1H), 2.92-2.85 (m, 1H), 2.05

(d, J = 10.0 Hz, 1H), 1.89 (d, J = 12.4 Hz, 1H), 1.70 (d, J = 12.8 Hz, 1H), 1.54-1.45 (m, 2H), 1.37-1.23 (m, 1H). MS (ESI): *m/z* 310.16 $[M+1]^+$

To a stirred solution of compound **FF** (200 mg, 0.51 mmol) in CH_3CN (20 mL) under argon atmosphere was added compound **KB** (158 mg, 0.51 mmol) and Et_3N (0.72 mL, 5.15 mmol). The solution was purged under argon for 20 min followed by the addition of copper iodide (9.8 mg, 0.05 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol). The reaction was heated to 80 °C and stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography eluting with 2% MeOH:DCM to afford compound **KC** (60 mg, 19%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.30 (br s, 1H), 8.44 (d, J = 3.6 Hz, 2H), 7.98-7.89 (m, 2H), 7.80-7.61 (m, 6H), 7.59-7.43 (m, 2H), 4.15-4.11 (m, 2H), 2.94-2.87 (m, 1H), 2.07 (t, J = 4.0 Hz, 1H), 1.88-1.69 (m, 1H), 1.49 (s, 9H), 1.38-1.22 (m, 4H). MS (ESI): *m/z* 617.68 $[M+1]^+$

To a stirred solution of compound **KC** (60 mg, 0.09 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (3 mL) to afford **304** (22 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.96 (br s, 1H), 9.74 (br s, 1H), 8.89 (br s, 1H), 8.56 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.17 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.73-7.62 (m, 2H), 7.49 (t, J = 8.4 Hz, 2H), 4.14 (t, J = 4.0 Hz, 1H), 4.04-3.99 (m, 1H), 2.95-2.88 (m, 1H), 2.08-1.89 (m, 2H), 1.71 (d, J = 12.4 Hz, 1H), 1.56-1.23 (m, 3H). MS (ESI): *m/z* 517.58 $[M+1]^+$. UPLC Purity: 92.41%

Scheme 71



Example 306

(*S*)-1-(4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl) pyrrolidine-2-carboxylic acid hydrochloride (306)

To a stirred solution of compound **JQ** (500 mg, 1.60 mmol) in toluene (20 mL) under argon atmosphere were added tert-butyl carbamate (281 mg, 2.40 mmol) and potassium carbonate (662 mg, 4.80 mmol). The mixture was purged under argon for 10 min followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene (44.3 mg, 0.08 mmol) and $Pd_2(dba)_3CHCl_3$ (83 mg, 0.08 mmol). The reaction was heated to reflux and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc/hexane to afford compound **KD** (220 mg, 35%) as a pale yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.22 (s, 1H), 10.45 (s, 1H), 9.04 (s, 1H), 8.61 (s, 1H), 4.40 (q, 2H), 1.49 (s, 9H), 1.31 (t, J = 9.0 Hz, 3H), 1.25 (s, 9H). MS (ESI): *m/z* 393.44 $[M+1]^+$

To a stirred solution of compound **KD** (785 mg, 1.99 mmol) in DCM (5 mL) under nitrogen atmosphere was added TFA (5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 6h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure and the resulting residue was triturated with Et_2O (15 mL). The obtained solid was diluted with DCM (15 mL), basified with TEA, and washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 50% EtOAc/hexane to afford compound **KE** (500 mg, 85%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.41 (s, 1H), 8.29 (s, 1H), 7.66 (s, 1H), 7.46 (s, 2H), 4.37 (q, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.24 (s, 9H). MS (ESI): *m/z* 293.32 $[M+1]^+$

To a stirred solution of compound **KE** (500 mg, 1.70 mmol) in EtOH/H_2O (40 mL/8 mL) was added NaOH (682 mg, 17.06 mmol). The reaction was heated to reflux and was stirred for 2h. After cooling to RT, **JN** (489 mg, 3.30 mmol) was added, and the reaction mixture was heated at reflux for 24h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure and the residue was triturated with DCM (15 mL). The obtained solid was suspended in water and the pH was adjusted to pH~3 by using AcOH. The solid was filtered, washed with water, and dried under reduced pressure to afford compound **KF** (385 mg, 78%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.51 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 2H), 7.99 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 6.51-6.45 (m, 2H), 4.37 (s, 1H). MS (ESI): *m/z* 289.29 $[M+1]^+$

To a stirred solution of compound **KF** (380 mg, 1.31 mmol) in DMF (4 mL) under nitrogen atmosphere were added EDCI·HCl (502 mg, 2.62 mmol), HOBt (354 mg, 2.62 mmol), DIPEA (0.68 mL, 3.93 mmol), and tert-butyl carbazate (516 mg, 3.93 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (20 mL) and was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **KG** (280 mg, 53%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.47 (br s, 1H), 9.18 (br s, 2H), 8.25 (d, *J* = 8.0 Hz, 2H), 7.71 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 6.80 (s, 1H), 6.52-6.49 (m, 1H), 6.44-6.42 (m, 1H), 4.38 (s, 1H), 1.47 (s, 9H). MS (ESI): *m/z* 403.44 $[M+1]^+$

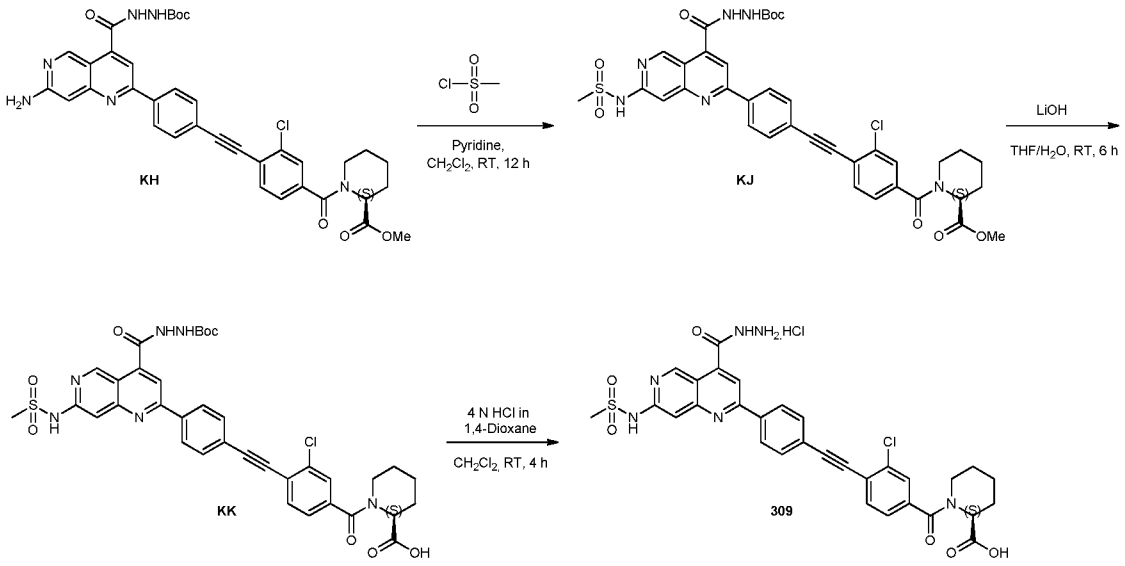
To a stirred solution of compound **KG** (100 mg, 0.24 mmol) in DMF (5 mL) under argon atmosphere were added compound **HJ** (130 mg, 0.36 mmol) and TEA (0.33 mL, 2.4 mmol).

The solution was purged with argon for 10 min followed by the addition of copper iodide (4.56 mg, 0.024 mmol) and $Pd(PPh_3)_2Cl_2$ (16.9 mg, 0.024 mmol). The reaction was then heated to 70 °C and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (20 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (2x20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2-5% MeOH/DCM to afford compound **KH** (100 mg, 61%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.49 (s, 1H), 9.18 (s, 2H), 8.90-8.82 (m, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.57-7.54 (m, 1H), 6.81-6.77 (m, 1H), 6.52-6.50 (m, 1H), 5.34-5.26 (m, 1H), 4.55-4.45 (m, 1H), 3.75-3.74 (m, 2H), 3.50-3.47 (m, 1H), 3.32-3.31 (m, 1H), 3.13-3.10 (m, 2H), 1.61-1.74 (m, 2H),1.47(s,9H),1.28-1.17(m,2H). MS (ESI): *m/z* 683.16 $[M+1]^+$

To a stirred solution of compound **KH** (100 mg, 0.14 mmol) in THF:H_2O (5 mL:5 mL) was added lithium hydroxide monohydrate (33 mg, 0.44 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The solid was suspended in water and the pH was adjusted to pH~3 by using an acetic acid solution (0.2 mL). The solid was filtered and dried under reduced pressure to afford compound **KI** (50 mg, crude) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.50 (br s, 1H), 9.18 (br s, 2H), 8.32 (br s, 1H), 8.14 (br s, 1H), 7.77-7.73 (m, 3H), 7.58 (s, 2H), 7.40-7.38 (m, 2H), 6.81 (s, 1H), 6.77-6.72 (m, 2H), 5.34-5.10 (m, 1H), 4.05 (d, J = 6.8 Hz, 1H), 2.90-2.84 (m, 1H), 2.18-2.10 (m, 1H), 1.67-1.65 (m, 3H), 1.35 (s, 9H), 1.29-1.23(m,2H). MS (ESI): *m/z* 669.13 $[M+1]^+$

To a stirred solution of compound **KI** (50 mg, 0.07 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with IPA:CH_3CN (5 mL) to afford **306** (40 mg as an HCl salt) as a brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 13.16 (s, 1H), 9.20 (s, 2H), 8.96 (s, 2H), 8.72 (s, 1H), 8.59 (s, 1H), 8.36 (d, J = 8.4 Hz, 2H), 7.81-7.76 (m, 3H), 7.58-7.54 (m, 2H), 7.41-7.34 (m, 1H), 5.17 (br s, 1H), 4.41-4.31 (m, 1H), 3.46 (d, J = 11.6 Hz, 1H), 3.18 (t, J = 12.0 Hz, 1H), 2.77-2.76 (m, 1H), 2.21 (d, J = 12.0 Hz, 1H), 1.71-1.69 (m, 2H), 1.45-1.30 (m, 2H). MS (ESI): *m/z* 569.6 $[M+1]^+$. UPLC Purity: 95.32%

Scheme 72



Example 309

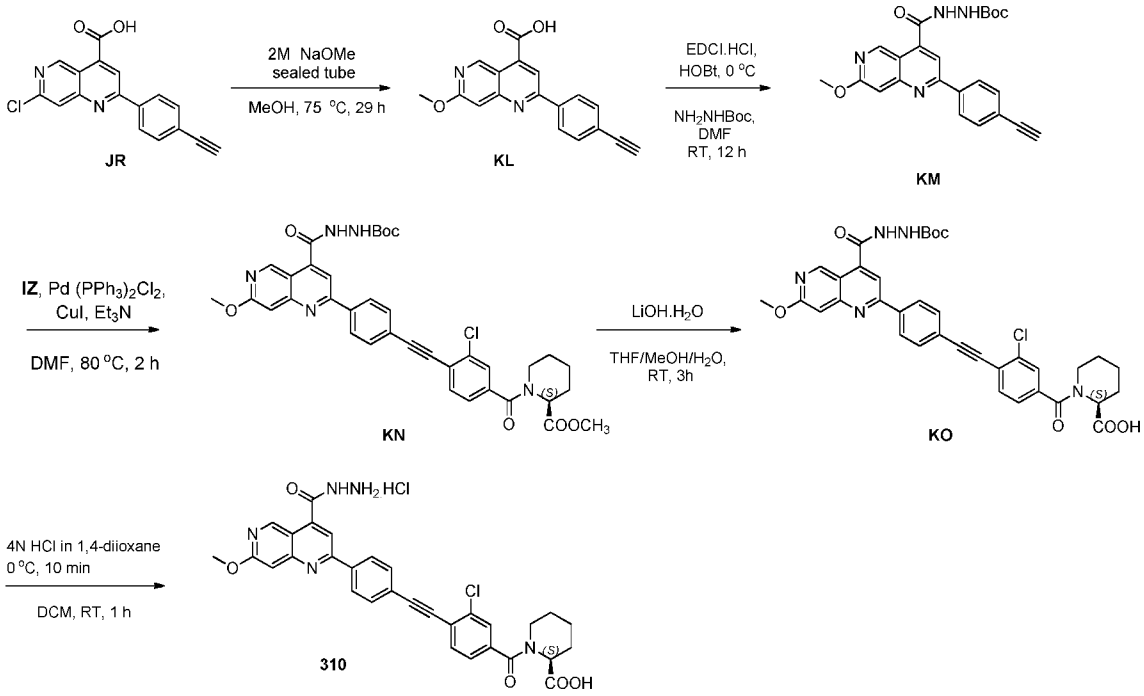
(*S*)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-7-(methylsulfonamido)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid hydrochloride (309)

To a stirred solution of compound **KH** (100 mg, 0.14 mmol) in DCM (5 mL) under nitrogen atmosphere were added pyridine (0.02 mL, 0.29 mmol) and $MeSO_2Cl$ (0.02 mL, 0.17 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 1% MeOH/DCM and further purified by preparative HPLC to afford compound **KJ** (50 mg, 20%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (br s, 1H), 10.60 (br s, 1H), 9.48 (s, 1H), 9.26 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 2H), 8.09 (br s, 1H), 7.81 (d, *J* = 8.0 Hz, 3H), 7.60-7.58 (m, 1H), 7.43 (s, 1H), 7.41-7.38 (m, 1H), 5.26 (br s, 1H), 4.49-4.45 (m, 1H), 3.74 (s, 3H), 3.49 (d, *J* = 13.6 Hz, 1H), 3.22-3.13 (m, 1H), 2.70-2.62 (m, 1H), 2.24-2.20 (m, 1H), 1.98 (s, 3H), 1.80-1.72 (m, 2H), 1.67-1.64 (m, 1H), 1.49 (s, 9H). MS (ESI): *m/z* 761.25 $[M+1]^+$

To a stirred solution of compound **KJ** (10 mg, 0.013 mmol) in THF:H_2O (3 mL: 2 mL) was added lithium hydroxide monohydrate (1.10 mg, 0.026 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 6h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH ~3 by using an acetic acid solution (0.02 mL). The precipitate was filtered and dried under reduced pressure to afford compound **KK** (8 mg, 82%) as a yellow solid. MS (ESI): *m/z* 747.22 $[M+1]^+$

To a stirred solution of compound **KK** (8 mg, 0.01 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 10% IPA:CH_3CN (3 mL) to afford **309** (7 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (br s, 1H), 9.46 (s, 1H), 8.45 (d, J = 8.0 Hz, 2H), 8.27 (s, 1H), 7.90-7.82 (m, 3H), 7.57-7.49 (m, 2H), 7.40 (s, 1H), 5.17 (s, 1H), 4.38-4.31 (m, 1H), 3.39-3.16 (m, 1H), 3.01 (s, 3H), 2.81-2.70 (m, 1H), 1.69-1.56 (m, 3H), 1.48-1.30 (m, 2H). MS (ESI): *m/z* 647.7.4 $[M+1]^+$. UPLC Purity: 90.20%

Scheme 73



Example 310

(*S*)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-7-methoxy-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid hydrochloride (310)

To a stirred solution of compound **JR** (1 g, 3.24 mmol) in MeOH (1 mL) was added 2M NaOMe (4 mL, 8.1 mmol) at 0 °C. The reaction was heated to 75 °C and was stirred for 12h. The reaction was cooled to RT, at which point, compound **9** (692 mg, 4.80 mmol) was added. The reaction was heated to 100 °C for 29h in sealed tube. After complete consumption of the starting material (by TLC), the reaction was diluted with cold water (10 mL) and the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the

pH was adjusted to pH~4 by using AcOH. The precipitate was filtered, washed with water, and dried under reduced pressure to afford compound **KL** (880 mg crude) as a yellow solid. MS (ESI): *m/z* 305.31 $[M+1]^+$

To a stirred solution of compound **KL** (880 mg, 2.89 mmol) in DMF (10 mL) under nitrogen atmosphere were added DIPEA (1.50 mL, 8.67 mmol), EDCI·HCl (1.10 g, 5.78 mmol), HOBt (780 mg, 5.78 mmol), and tert-butyl carbazate (757 mg, 5.78 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (50 mL) and was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexane to afford compound **KM** (300 mg, crude). Preparative HPLC purification afforded compound **KM** (110 mg) as a pale yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.59 (s, 1H), 9.45 (s, 1H), 9.27 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 2H), 8.06 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.34 (s, 1H), 4.42 (s, 1H), 4.03 (s, 3H), 1.48 (s, 9H). MS (ESI): *m/z* 419.45 $[M+1]^+$

IZ was synthesized from 3-chloro-4-iodobenzoic acid and (S)-methyl piperidine-2-carboxylate hydrochloride following a similar procedure used to synthesize **HJ**.

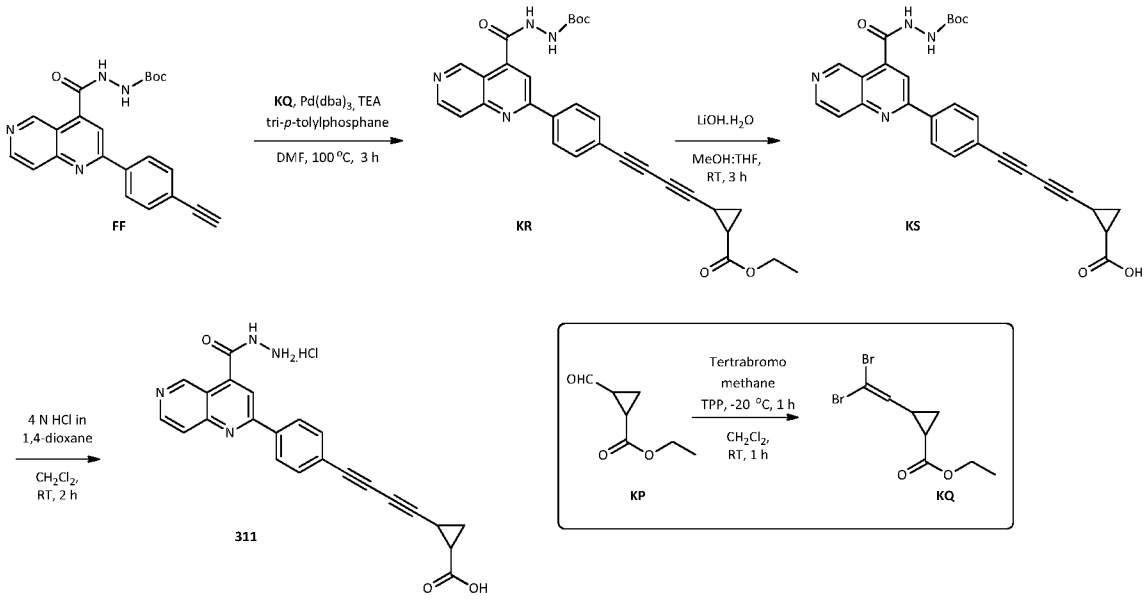
To a stirred solution of compound **KM** (80 mg, 0.19 mmol) in CH_3CN (10 mL) under argon atmosphere were added compound **IZ** (85 mg, 0.20 mmol) and TEA (0.26 mL, 1.91 mmol). The solution was purged under argon for 20 min followed by the addition of copper iodide (3 mg, 0.01 mmol) and $Pd(PPh_3)_2Cl_2$ (13 mg, 0.01 mmol). The reaction was heated to 80 °C and was stirred for 2h. After complete consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography eluting with 2% MeOH:DCM and further triturated with IPA: pentane (3 mL:2 mL) to afford compound **KN** (15 mg, 30%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 9.46 (s, 1H), 9.27 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 2H), 8.10 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 3H), 7.55 (s, 1H), 7.37 (s, 2H), 5.26 (s, 1H), 4.02 (s, 3H), 3.74 (s, 3H), 3.51-3.47 (m, 1H), 3.15 (t, *J* = 11.6 Hz, 1H), 2.21-2.18 (m, 1H), 1.72-1.68 (m, 3H), 1.58-1.54 (m, 1H), 1.49 (s, 9H), 1.03 (d, *J* = 6.0 Hz, 1H). MS (ESI): *m/z* 699.17 $[M+1]^+$

To a stirred solution of compound **KN** (30 mg, 0.04 mmol) in THF:MeOH:H_2O (2 mL:1 mL:1 mL) was added lithium hydroxide monohydrate (2 mg, 0.06 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (5 mL) and the pH was adjusted to pH~3 by using AcOH (0.1

mL). The product was extracted with 20% MeOH/DCM (2x10 mL) and the combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with 10% MeOH:DCM (2 mL) to afford compound **KO** (18 mg, 62%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (s, 1H), 10.61 (s, 1H), 9.46 (s, 1H), 9.27 (s, 1H), 8.43 (d, J = 7.6 Hz, 2H), 8.10 (s, 1H), 7.82 (d, J = 7.6 Hz, 3H), 7.58 (s, 1H), 7.41-7.36 (m, 2H), 5.15 (s, 1H), 4.17 (s, 3H), 3.46-3.43 (m, 1H), 3.23-3.17 (m, 1H), 2.83-2.76 (m, 1H), 2.22-2.07 (m, 1H), 1.67-1.52 (m, 4H), 1.49 (s, 9H). MS (ESI): m/z 685.15 $[M+1]^+$

To a stirred solution of compound **KO** (13 mg, 0.01 mmol) in DCM (0.4 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.1 mL) at 0 °C and the reaction was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure and the resulting solids were triturated with 30% CH_3OH:CH_3CN (0.5 mL) to afford **310** (10 mg as an HCl salt) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 9.39 (s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.21 (s, 1H), 7.83 (d, J = 8.0 Hz, 3H), 7.58 (s, 1H), 7.37 (s, 2H), 5.17-4.38 (s, 1H), 4.40 (m, 0.5H), 4.38 (m, 0.5 H), 4.31 (m, 3H), 4.03 (m, 0.5H), 3.36 (m, 0.5H), 2.76-2.72 (m, 0.5H), 2.22-2.05 (m, 1H), 1.71-1.55 (m, 3H), 1.35-1.23 (m, 2H). MS (ESI): m/z 584.8 $[M+1]^+$. HPLC Purity: 87.38%

Scheme 74



Example 311

2-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl)buta-1, 3-diyn-1-yl) cyclopropane-1-carboxylic acid hydrochloride (311)

To a stirred solution of tetrabromomethane (934 mg, 2.81 mmol) in DCM (5 mL) under nitrogen atmosphere was added triphenylphosphine (1.47 g, 5.63 mmol) in DCM (5 mL) dropwise over 10 min at -20 °C. Then ethyl 2-formylcyclopropane-1-carboxylate (**KP**; 200 mg, 1.40 mmol) in DCM (4 mL) was added dropwise over 10 min at -70 °C and was stirred for 30 min. The reaction was allowed to slowly warm to RT over 1h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by column chromatography eluting with 15% EtOAc/hexane to afford compound **KQ** (250 mg, 59%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (d, J = 9.0 Hz, 1H), 4.17-4.13 (m, 2H), 2.23-2.19 (m, 1H), 1.78-1.74 (m, 1H), 1.50-1.46 (m, 1H), 1.33-1.26 (m, 1H), 1.06-1.02 (m, 3H).

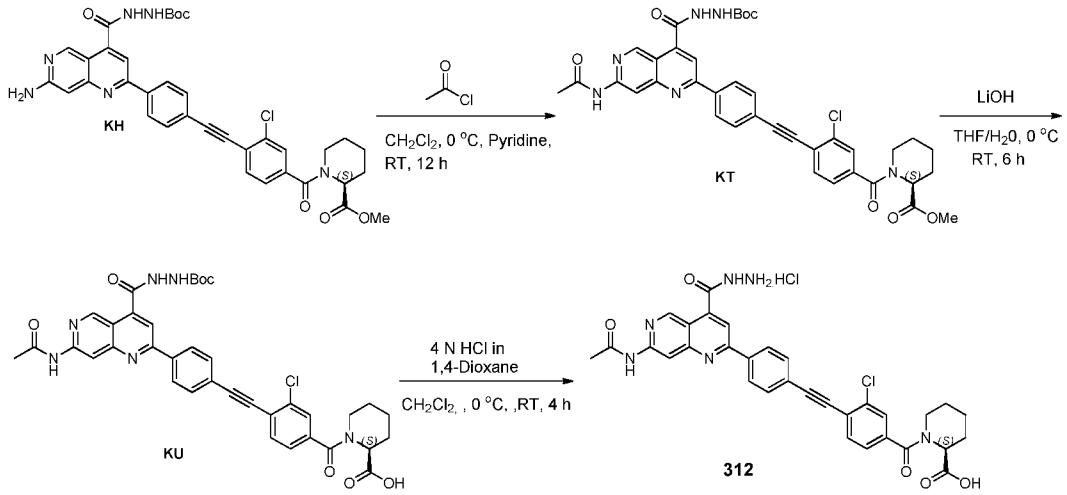
To a stirred solution of carboxylate **KQ** (100 mg, 0.33 mmol) in DMF (4 mL) under nitrogen atmosphere were added **FF** (130 mg, 0.33 mmol), TEA (0.14 mL, 0.99 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol) and tri-*p*-tolylphosphane (5 mg, 0.01 mmol). The reaction was heated to 100 °C and was stirred for 3h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (20 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (2x20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **KR** (60 mg, 35%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (br s, 1H), 9.71 (br s, 1H), 9.29 (br s, 1H), 8.84 (d, J = 6.0 Hz, 1H), 8.39 (d, J = 7.6 Hz, 2H), 8.31 (s, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.78-7.70 (m, 2H), 4.14-4.08 (m, 2H), 2.34 (d, J = 10.8 Hz, 1H), 2.32-2.19 (m, 2H), 2.18-1.97 (m, 1H), 1.49 (s, 9H), 1.41-1.32 (m, 3H).

To a stirred solution of compound **KR** (60 mg, 0.11 mmol) in THF/MeOH (1:1, 6 mL) were added lithium hydroxide monohydrate (9.6 mg, 0.22 mmol) and water (2 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was dissolved in water (5 mL) and acidified with acetic acid to pH~4. The precipitate was filtered and dried under reduced pressure to obtain compound **KS** (15 mg, 27%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br s, 1H), 9.70 (s, 1H), 9.29 (s, 1H), 8.83 (d, J = 5.6 Hz, 1H), 8.38 (d, J = 8.4 Hz, 2H), 8.30 (s, 1H), 8.03 (d, J = 6.0 Hz, 1H), 7.77-7.70 (m, 2H), 1.85 (d, J = 7.6 Hz, 2H), 1.48 (s, 9H), 1.30-1.22 (m, 1H), 0.96-0.99 (m, 1H). MS (ESI): 19.37%, *m/z* 491.8 $[M+1]^+$

To a stirred solution of compound **KS** (15 mg, 0.03 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.2 mL) at 0 °C. The reaction was allowed to

warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 20% CH_3OH/CH_3CN (4 mL) to afford **311** (10 mg as an HCl salt) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.79 (br s, 1H), 9.69 (s, 1H), 8.86 (d, J = 6.0 Hz, 1H), 8.50 (s, 1H), 8.42 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 6.0 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 2.08-2.00 (m, 2H), 1.36 (t, J = 8.0 Hz, 2H). HPLC Purity: 91.30%

Scheme 75



Example 312

(*S*)-1-(4-((4-(7-acetamido-4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl)ethynyl)-3-chlorobenzoyl)piperidine-2-carboxylic acid hydrochloride (312)

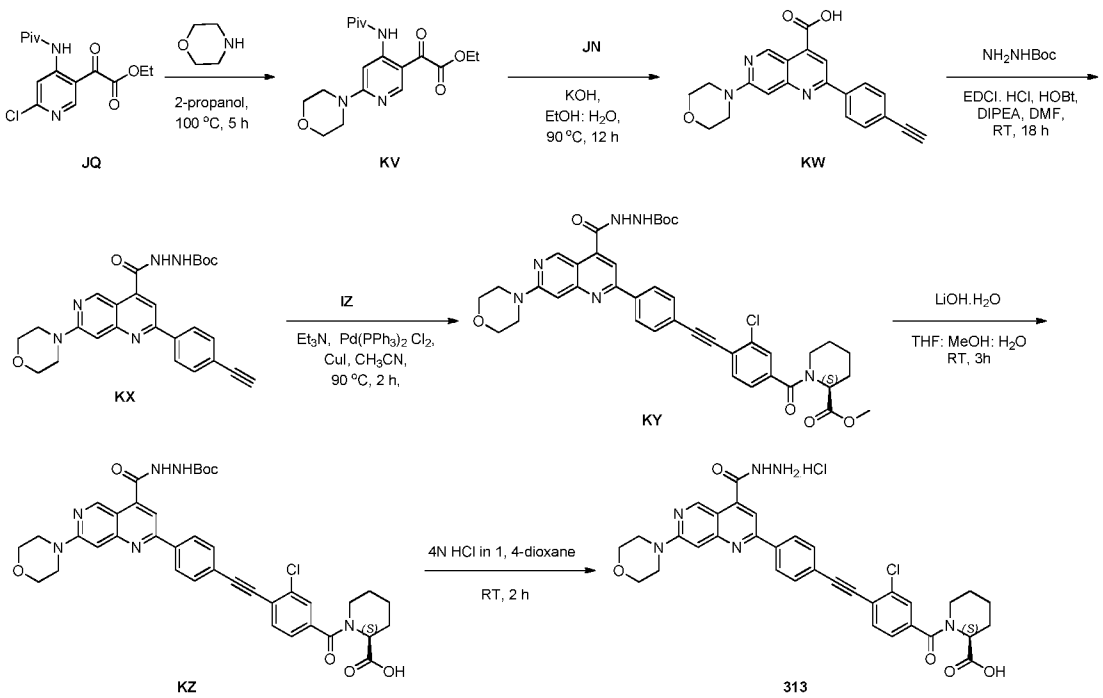
To a stirred solution of compound **KH** (100 mg, 0.14 mmol) in DCM (2 mL) under nitrogen atmosphere were added pyridine (0.03 mL, 0.28 mmol) and acetyl chloride (0.02 mL, 0.22 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were concentrated under reduced pressure. The crude material was purified by preparative TLC to afford compound **KT** (30 mg, 30%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 10.65 (s, 1H), 9.50 (s, 1H), 9.26 (s, 1H), 8.68 (s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.16 (s, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.60 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 5.26 (br s, 1H), 4.45-4.39 (m, 1H), 3.74 (s, 3H), 3.37-3.36 (m, 1H), 3.12 (s, 1H), 2.19 (s, 3H), 2.10-2.04 (m, 1H), 1.76-1.72 (m, 2H), 1.48 (s, 9H), 1.34-1.30 (m, 2H). MS (ESI): m/z 725.20 $[M+1]^+$

To a stirred solution of compound **KT** (70 mg, 0.096 mmol) in THF:H_2O (4 mL:2 mL) was added lithium hydroxide monohydrate (8.1 mg, 0.193 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting

material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (3 mL) and neutralized with an acetic acid solution (0.03 mL) and the resulting precipitate was filtered and dried under reduced pressure to afford compound **KU** (25 mg, 37%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 10.66 (s, 1H), 9.50 (s, 1H), 9.26 (s, 1H), 8.68 (s, 1H), 8.44 (d, J = 7.2 Hz, 2H), 8.25 (d, J = 7.6 Hz, 1H), 7.82-7.72 (m, 3H), 7.58 (s, 1H), 7.40-7.39 (m, 1H), 5.12 (br s, 1H), 4.37 (d, J = 10.4 Hz, 1H), 3.33-3.32 (m, 1H), 2.86-2.82 (m, 1H), 2.19 (s, 3H), 2.16-2.00 (m, 1H), 1.68-1.66 (m, 2H), 1.49 (s, 9H), 1.30-1.26 (m, 2H). MS (ESI): *m/z* 711.17 $[M+1]^+$

To a stirred solution of compound **KU** (40 mg, 0.056 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.4 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 30% MeOH:ACN (2 mL) to afford **312** (25 mg as an HCl salt) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 10.94 (s, 1H), 9.45 (s, 1H), 8.69 (s, 1H), 8.47 (d, J = 8.0 Hz, 2H), 8.37-8.33 (m, 1H), 7.84-7.82 (m, 3H), 7.58-7.55 (m, 1H), 7.40-7.36 (m, 1H), 5.17 (br s, 1H), 4.40-4.31 (m, 1H), 3.46 (d, J = 10.8 Hz, 1H), 3.18 (t, J = 12.0 Hz, 1H), 2.79-2.76 (m, 2H), 2.19 (s, 3H), 2.07-2.04 (m, 1H), 1.71-1.69 (m, 3H), 1.42-1.30 (m, 2H). MS (ESI): *m/z* 613.5 $[M+2]^+$. UPLC Purity: 80.05%

Scheme 76



Example 313

(*S*)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-7-morpholino-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid hydrochloride (313)

To a stirred solution of ethyl 2-(6-chloro-4-pivalamidopyridin-3-yl)-2-oxoacetate **JQ** (1 g, 3.20 mmol) in 2-propanol (15 mL) under nitrogen atmosphere was added morpholine (826 mg, 9.61 mmol). The reaction was heated to 100 °C in a sealed tube and was stirred for 5h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes to afford compound **KV** (800 mg, 69%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.49-8.44 (m, 1H), 7.99 (s, 1H), 4.40 (q, 2H), 3.8 (br s, 8H), 1.5 (t, 3H), 1.26 (s, 9H). MS (ESI): *m/z* 364.4 $[M+1]^+$

To a stirred solution of compound **KV** (800 mg, 2.20 mmol) in EtOH:H_2O (10 mL:10 mL) was added potassium hydroxide (495 mg, 8.83 mmol) at 0 °C. The reaction was heated to 90 °C and was stirred for 2h. The reaction was then cooled to 0 °C at which point **JN** (477 mg, 3.31 mmol) was added. The reaction was heated to 90 °C for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (1 mL) and the pH was adjusted to pH~3 using an acetic acid solution (0.2 mL). The precipitate was filtered and dried under reduced pressure to afford compound **KW** (600 mg, 75%) as a yellow solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.67 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 10.0 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.41-7.38 (m, 2H), 7.15 (s, 1H), 5.86 (s, 1H), 4.39 (s, 1H), 3.76-3.75 (m, 2H), 3.66-3.62 (m, 2H), 3.50-3.48 (m, 2H), 3.33-3.30 (m, 1H). MS (ESI): *m/z* 360.4 $[M+1]^+$

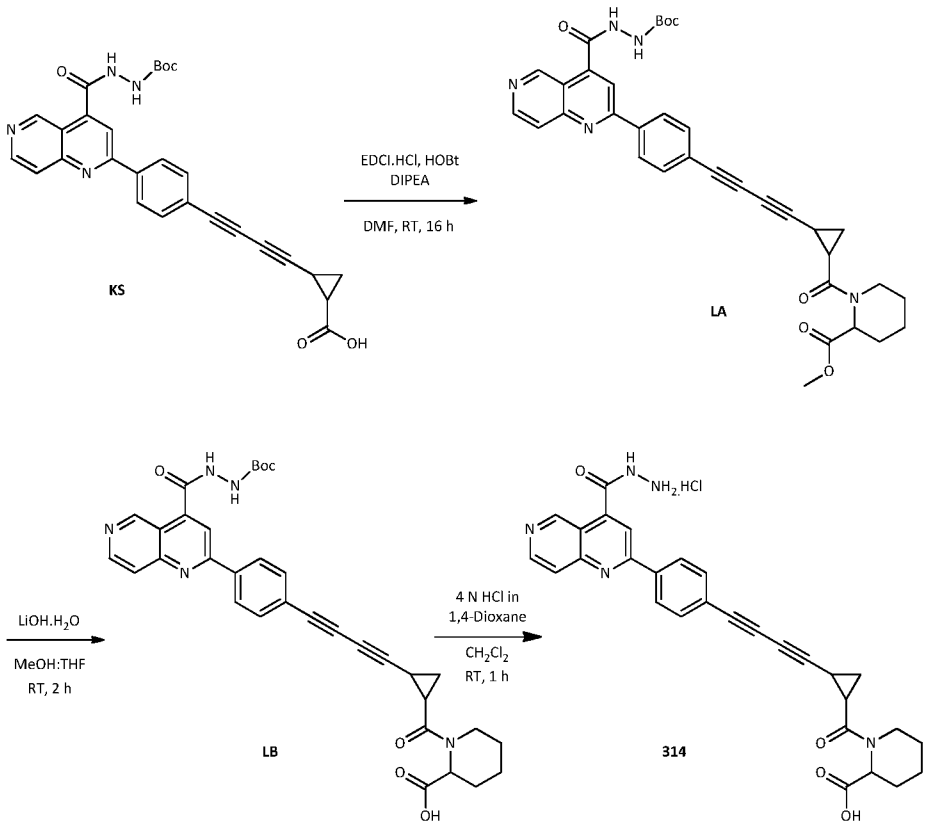
To a stirred solution of compound **KW** (200 mg, 0.55 mmol) in DMF (10 mL) under nitrogen atmosphere were added tert-butyl hydrazine carboxylate (220 mg, 1.67 mmol), EDCI·HCl (213 mg, 1.11 mmol), HOBt (151 mg, 1.11 mmol), and DIPEA (215 mg, 1.67 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 18h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography eluting with 30% EtOAc/hexanes to afford compound **KX** (60 mg, 23%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.37 (s, 1H), 9.22 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 7.85 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 4.40 (s, 1H), 3.76 (t, *J* = 4.8 Hz, 4H), 3.63 (t, *J* = 4.8 Hz, 4H), 1.47 (s, 9H). MS (ESI): *m/z* 474.3 $[M+1]^+$

To a stirred solution of compound **KX** (100 mg, 0.21 mmol) in CH_3CN (15 mL) under nitrogen atmosphere were added **IZ** (94 mg, 0.23 mmol) and TEA (0.3 mL, 2.11 mmol) at RT. After the reaction was purged under argon for 10 min, copper iodide (4 mg, 0.02 mmol) and $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol) were added. The reaction was then heated to 90 °C and stirred for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 50% EtOAc/hexanes to afford compound **KY** (54 mg, 34%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H), 9.38 (s, 1H), 9.23 (s, 1H), 8.38 (d, J = 7.6 Hz, 2H), 7.88 (s, 2H), 7.80 (d, J = 7.6 Hz, 2H), 7.60 (s, 1H), 7.15-7.13 (m, 1H), 5.26 (br s, 1H), 4.43 (br s, 1H), 3.78-3.71 (m, 7H), 3.67-3.63 (m, 4H), 3.50-3.48 (m, 1H), 3.20-3.17 (m, 1H), 1.80-1.72 (m, 3H), 1.60-1.54 (m, 2H), 1.46 (s, 9H). MS (ESI): *m/z* 754.1 $[M+1]^+$

To a stirred solution of compound **KY** (50 mg, 0.06 mmol) in MeOH:THF:H_2O (2:2:1, 5 mL) was added lithium hydroxide monohydrate (5.5 mg, 0.13 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~3 using an acetic acid solution (0.2 mL). The precipitate was filtered and dried under reduced pressure to afford compound **KZ** (28 mg, 57%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.55 (br s, 1H), 9.37 (s, 1H), 9.22 (s, 1H), 8.37 (d, J = 7.6 Hz, 2H), 7.89 (s, 1H), 7.79 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.56-7.55 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 4.93 (br s, 1H), 4.31-4.29 (m, 1H), 3.78-3.76 (m, 4H), 3.64-3.62 (m, 4H), 2.91-2.89 (m, 1H), 2.20-2.17 (m, 1H), 1.61-1.58 (m, 2H), 1.50 (s, 9H), 1.40-1.34 (m, 3H). MS (ESI): *m/z* 740.5 $[M+1]^+$

To a stirred solution of compound **KZ** (28 mg, 0.03 mmol) in DCM (3 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude residue was triturated with 10% MeOH:CH_3CN (2 mL) to afford **313** (11 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (400 MHz, CD_3OD-d_4): δ 8.66 (s, 1H), 8.59 (s, 1H), 8.25 (d, J = 8.4 Hz, 2H), 7.81-7.71 (m, 4H), 7.65-7.59 (m, 1H), 7.41-7.37 (m, 1H), 5.35-5.34 (m, 1H), 4.55-4.40 (m, 1H), 3.91-3.85 (m, 4H), 3.74-3.72 (m, 1H), 3.60 (s, 3H), 3.59-3.58 (m, 1H), 2.95-2.92 (m, 1H), 2.40-2.27 (m, 1H), 1.79 (d, J = 12.0 Hz, 2H), 1.67-1.64 (m, 2H), 1.54-1.43 (m, 2H). MS (ESI): 86.62%, *m/z* 639.7 $[M+1]^+$

Scheme 77



Example 314

1-(2-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) buta-1, 3-diyn-1-yl) cyclopropane-1-carbonyl) piperidine-2-carboxylic acid hydrochloride (314)

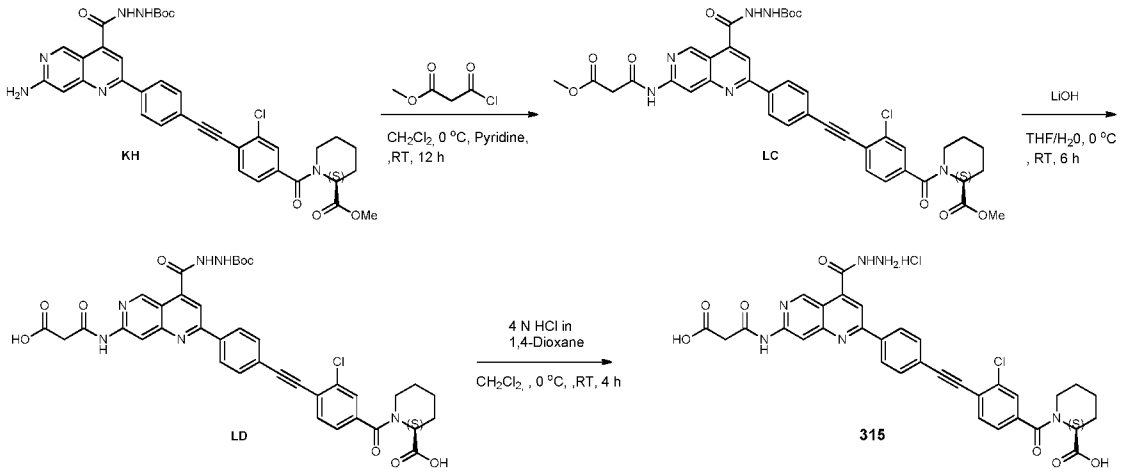
To a stirred solution of compound **KS** (25 mg, 0.05 mmol) in DMF (2 mL) under nitrogen atmosphere were added DIPEA (0.04 mL, 0.25 mmol), EDCI·HCl (14.3 mg, 0.075 mmol), HOBt (10 mg, 0.075 mmol) and methyl piperidine-2-carboxylate hydrochloride (9.81 mg, 0.055 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (5 mL) and was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain compound **LA** (30 mg) as a yellow solid. MS (ESI): *m/z* 622.6 $[M+1]^+$

To a stirred solution of compound **LA** (30 mg, 0.048 mmol) in THF/MeOH/H_2O (1 mL:1 mL:0.5 mL) was added lithium hydroxide monohydrate (6 mg, 0.14 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The

residue was diluted with water (2 mL) and acidified with acetic acid to pH~4. The obtained solid was filtered and triturated with CH_3CN (3 mL) to obtain compound **LB** (10 mg, 34%) as a yellow solid. MS (ESI): *m/z* 608.6 $[M+1]^+$

To a stirred solution of compound **LB** (10 mg, 0.016 mmol) in DCM (0.5 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 1h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to afford **314** (6 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 9.68 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.42 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.10 (s, 1H), 5.03 (d, J = 4.8 Hz, 2H), 4.28-4.19 (m, 1H), 3.27-3.21 (m, 1H), 2.24-2.01 (m, 1H), 1.91-1.86 (m, 1H), 1.84-1.79 (m, 2H), 1.69-1.53 (m, 4H), 1.48-1.23 (m, 2H). MS (ESI): *m/z* 508.9 $[M+1]^+$

Scheme 78



Example 315

(*S*)-1-(4-((4-(7-(2-carboxyacetamido)-4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl)-3-chlorobenzoyl) piperidine-2-carboxylic acid hydrochloride (315)

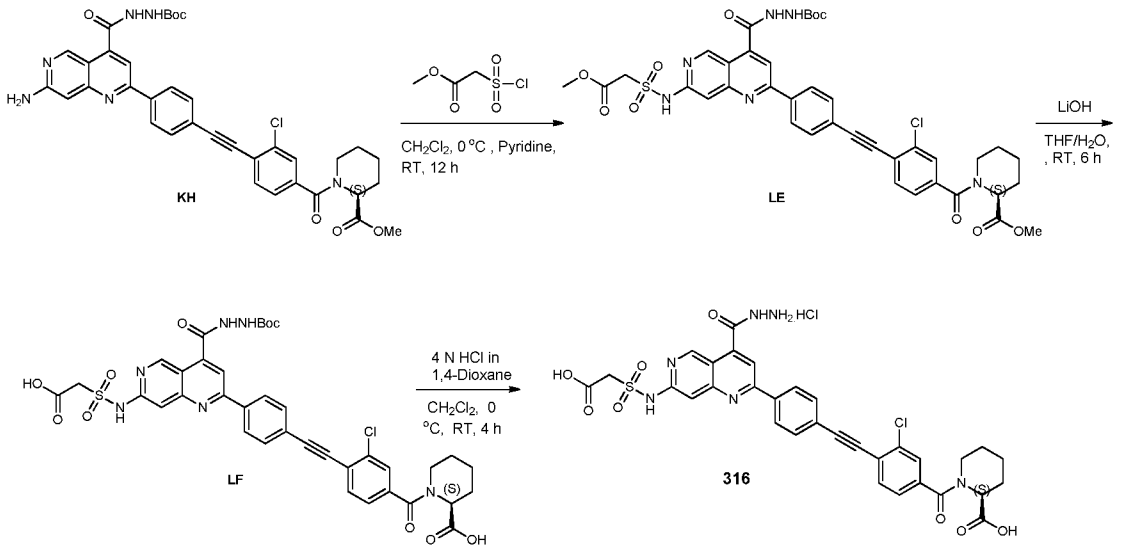
To a stirred solution of compound **KH** (90 mg, 0.13 mmol) in DCM (5 mL) under nitrogen atmosphere were added pyridine (0.03 mL, 0.39 mmol) and methyl 3-chloro-3-oxopropanoate (0.02 mL, 0.14 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (5 mL) and the compound was extracted with DCM (2x5 mL). The combined organic extracts were washed with water (2x5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by

preparative HPLC to afford compound **LC** (50 mg, 20%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 9.42 (s, 1H), 8.72 (s, 1H), 8.39 (br s, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 7.99 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.53-7.52 (m, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.94 (br s, 1H), 5.47 (br s, 1H), 4.63-4.42 (m, 1H), 3.83 (s, 6H), 3.63-3.59 (m, 3H), 3.28 (t, *J* = 11.2 Hz, 1H), 2.36 (d, *J* = 12.8 Hz, 1H), 1.78-1.72 (m, 2H), 1.60 (s, 9H), 1.43-1.37 (m, 2H). MS (ESI): *m/z* 783.24 $[M+1]^+$

To a stirred solution of compound **LC** (15 mg, 0.019 mmol) in THF:H_2O (4 mL:1 mL) were added lithium hydroxide monohydrate (2.4 mg, 0.05 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~3 by using an acetic acid solution (0.02 mL). The precipitate was filtered and dried under reduced pressure to afford compound **LD** (10 mg, 71%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.01 (s, 1H), 11.67 (s, 1H), 10.66 (s, 1H), 9.51 (s, 1H), 9.27 (s, 1H), 9.18 (s, 1H), 8.67 (s, 1H), 8.45 (d, *J* = 7.2 Hz, 2H), 8.16 (s, 1H), 7.99-7.81 (m, 3H), 7.73-7.58 (m, 1H), 7.25-7.16 (m, 1H), 6.51-6.42 (m, 1H), 5.16 (s, 1H), 4.39-4.22 (m, 2H), 3.42-3.39 (m, 2H), 2.23-2.18 (m, 1H), 2.08 (d, *J* = 9.6 Hz, 3H), 1.48 (s, 9H), 1.21-1.10 (m, 1H). MS (ESI): *m/z* 755.18 $[M+1]^+$

To a stirred solution of compound **LD** (10 mg, 0.013 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.2 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 10% IPA:CH_3CN (2 mL) to afford **315** (8 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ 9.48 (s, 1H), 8.79 (s, 1H), 8.67-8.61 (m, 2H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.81-7.73 (m, 2H), 7.59-7.55 (m, 2H), 7.42-7.38 (m, 4H), 5.36 (d, *J* = 6.0 Hz, 1H), 4.41 (s, 2H), 3.66-3.52 (m, 3H), 2.95-2.90 (m, 1H), 2.40-2.23 (m, 1H), 1.81-1.65 (m, 4H), 1.55-1.43 (m, 3H). MS (ESI): *m/z* 692.52 $[M+1]^+$. UPLC Purity: 90.68%

Scheme 79



Example 316

(*S*)-1-(4-((4-(7-((carboxymethyl) sulfonamido)-4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl)-3-chlorobenzoyl) piperidine-2-carboxylic acid hydrochloride (316)

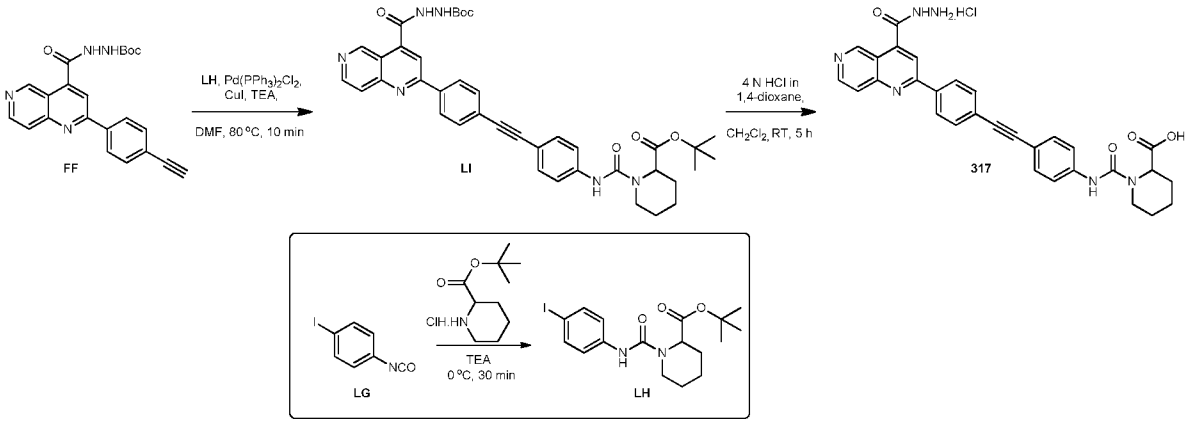
To a stirred solution of compound **KH** (50 mg, 0.073 mmol) in DCM (5 mL) under nitrogen atmosphere were added pyridine (0.03 mL, 0.36 mmol) and methyl 2-(chlorosulfonyl)acetate (31 mg, 0.18 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 6h. After complete consumption of the starting material (by TLC), the volatiles were concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH:DCM to afford compound **LE** (33 mg, 55%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 10.64 (s, 1H), 9.50 (s, 1H), 9.28 (s, 1H), 8.45 (d, J = 8.0 Hz, 2H), 8.16 (s, 1H), 7.82-7.62 (m, 3H), 7.60-7.35 (m, 5H), 5.26 (s, 1H), 4.72 (s, 2H), 4.45-4.39 (m, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.19-3.12 (m, 1H), 1.72-1.68 (m, 1H), 1.49 (s, 9H), 1.38-1.33 (m, 3H). MS (ESI): *m/z* 819.28 $[M+1]^+$

To a stirred solution of compound **LE** (33 mg, 0.04 mmol) in THF:H_2O (3 mL:1 mL) was added lithium hydroxide monohydrate (3.4 mg, 0.08 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (3 mL), neutralized with an acetic acid solution (0.03 mL), and the resulting solids were filtered and dried under reduced pressure to afford compound **LF** (28 mg, 90%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (s, 2H), 10.64 (s, 1H), 9.50 (s, 1H), 9.28 (s, 1H), 8.45 (d, J = 7.6 Hz, 2H), 8.15 (s, 1H), 7.81 (d, J = 6.4 Hz, 3H), 7.64-7.58 (m, 2H), 7.41-7.36 (m, 2H), 5.17 (s, 1H), 4.54 (s, 2H), 4.35-4.28 (m, 1H), 3.78-3.60 (m, 1H), 2.80-2.78 (m,

1H), 2.22-2.16 (m, 1H), 2.08-1.97 (m, 1H), 1.71-1.69 (m, 3H), 1.49 (s, 9H). MS (ESI): *m/z* 791.23 $[M+1]^+$

To a stirred solution of compound **LF** (25 mg, 0.031 mmol) in DCM (3 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.3 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 30% MeOH:ACN (2 mL) to afford **316** (19 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (br s, 2H), 9.46 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 2H), 8.26 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 3H), 7.58-7.55 (m, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 5.17 (br s, 1H), 4.61 (s, 2H), 4.39-4.31 (m, 1H), 3.21-3.19 (m, 1H), 2.79-2.76 (m, 1H), 2.22-2.19 (m, 1H), 1.71-1.69 (m, 3H), 1.35-1.30 (m, 1H). MS (ESI): *m/z* 691.5 $[M+1]^+$. UPLC Purity: 82.47%

Scheme 80



Example 317

1-((4-((4-(4-(hydrazinecarbonyl)-1, 6-naphthyridin-2-yl)phenyl) ethynyl) phenyl) carbamoyl) piperidine-2-carboxylic acid hydrochloride (317)

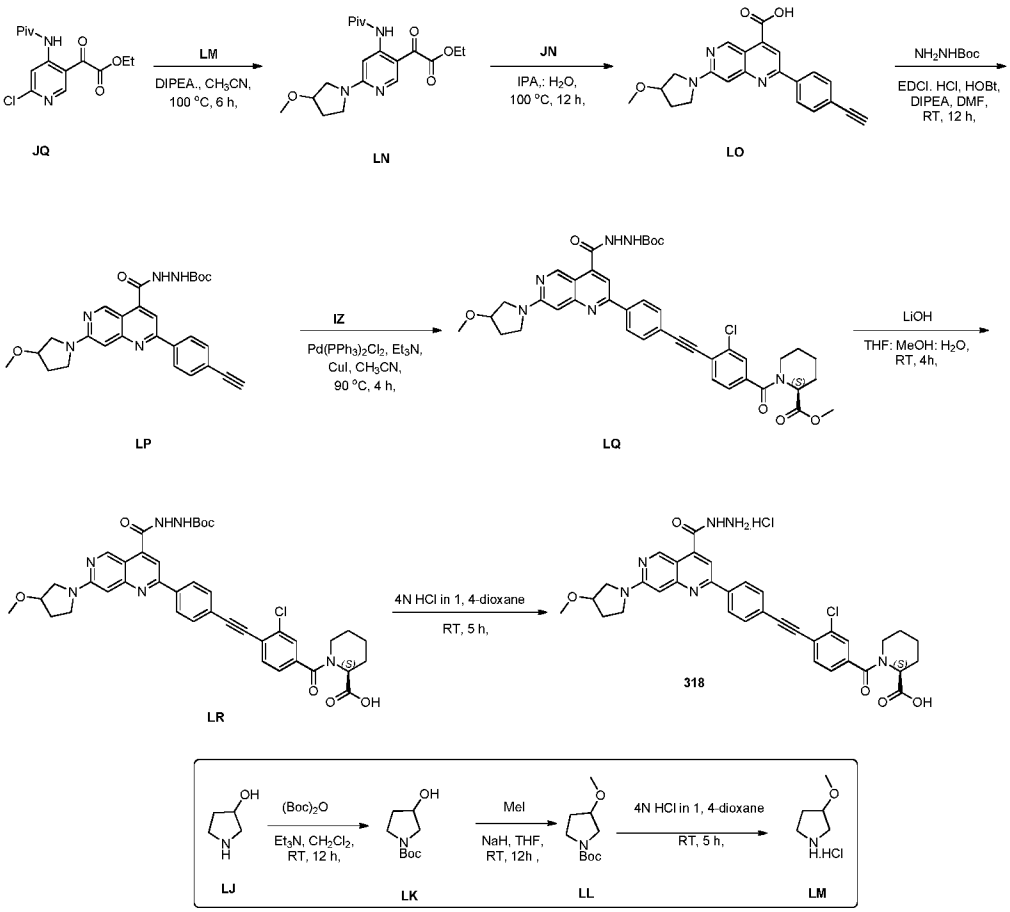
To a stirred solution of tert-butyl piperidine-2-carboxylate hydrochloride (500 mg, 2.25 mmol) in DCM (20 mL) under nitrogen atmosphere were added TEA (0.31 mL, 2.25 mmol) and 1-iodo-4-isocyanatobenzene (**LG**; 551 mg, 2.25 mmol) at 0 °C. After the reaction mixture was stirred for 30 min,. the reaction mixture was washed with water (15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH/DCM to afford compound **LH** (550 mg, 57%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 4.91 (d, *J* = 4.5 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.25-3.19

(m, 1H), 2.23 (d, *J* = 14.0 Hz, 1H), 1.73-1.67 (m, 3H), 1.54-1.50 (m, 1H), 1.46 (s, 9H), 1.39-1.33 (m, 1H).

To a stirred solution of **FF** (100 mg, 0.25 mmol) in DMF (3 mL) under nitrogen atmosphere were added compound **LH** (107 mg, 0.25 mmol), TEA (0.35 mL, 2.57 mmol), copper iodide (7.3 mg, 0.025 mmol) and $Pd(PPh_3)_2Cl_2$ (27.1 mg, 0.025 mmol). The reaction mixture was heated in a microwave at 80 °C and stirred for 10 min. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (20 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (2x20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 3-5% MeOH/DCM and further purified by preparative HPLC to afford compound **LI** (18 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 9.70 (s, 1H), 9.30 (s, 1H), 8.83 (d, *J* = 6.0 Hz, 1H), 8.77 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 2H), 8.32 (s, 1H), 8.04 (d, *J* = 5.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 4.83 (d, *J* = 3.6 Hz, 1H), 3.97 (d, *J* = 12.4 Hz, 1H), 3.03-2.97 (m, 1H), 2.12 (d, *J* = 13.2 Hz, 1H), 1.67-1.59 (m, 4H), 1.49 (s, 9H), 1.41 (s, 9H), 1.28-1.15 (m, 1H)

To a stirred solution of compound **LI** (18 mg, 0.026 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.2 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 5h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (3 mL) to afford **317** (12 mg as an HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H), 9.74 (s, 1H), 8.89 (d, *J* = 6.0 Hz, 1H), 8.60 (s, 1H), 8.50 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.73-7.71 (m, 2H), 7.52-7.49 (m, 2H), 4.16-4.12 (m, 1H), 4.04-3.99 (m, 1H), 2.95-2.87 (m, 1H), 2.06 (t, *J* = 4.4 Hz, 1H), 1.91 (t, *J* = 2.8 Hz, 1H), 1.71 (d, *J* = 12.4 Hz, 1H), 1.56-1.48 (m, 2H), 1.47-1.34 (m, 1H). HPLC Purity: 88.01%

Scheme 81



Example 318

(2*S*)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-7-(3-methoxypyrrolidin-1-yl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl) benzoyl) piperidine-2-carboxylic acid hydrochloride (318)

To a stirred solution of pyrrolidin-3-ol (**LJ**; 1 g, 11.47 mmol) in DCM (20 mL) under nitrogen atmosphere were added TEA (3.31 mL, 22.95 mmol) and Boc anhydride (1.48 g, 12.62 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and was extracted with 10% MeOH/DCM (2x100 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/DCM to afford compound **LK** (1.2 g, 56%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.89-4.88 (m, 1H), 4.21 (br s, 1H), 3.33 (s, 3H), 3.11-3.09 (m, 1H), 1.84-1.81 (m, 2H), 1.39 (s, 9H).

To a stirred solution of compound **LK** (350 mg, 1.87 mmol) in THF (10 mL) under nitrogen atmosphere was added sodium hydride (54 mg, 2.24 mmol) at 0 °C. The mixture was stirred

for 15 minutes, then methyl iodide (0.13 mL, 2.24 mmol) was added and the reaction was stirred at RT for 12h. After complete consumption of the starting material (by TLC), the reaction was quenched with ice cold water (10 mL) and the compound was extracted with DCM (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/DCM to afford compound **LL** (300 mg, 80%) as a colorless liquid. ^{1}H NMR (400 MHz, DMSo-d_6): δ 3.98 (br s, 1H), 3.31 (s, 3H), 3.29-3.25 (m, 1H), 3.22 (s, 3H), 1.89-1.88 (m, 2H), 1.39 (s, 9H).

To a stirred solution of compound **LL** (300 mg, 1.49 mmol) in DCM (10 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 5h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with ether (2 mL) to afford compound **LM** (110 mg as an HCl salt) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.61 (br s, 1H), 9.29 (br s, 1H), 4.07-4.05 (m, 1H), 3.34 (s, 3H), 3.23-3.05 (m, 3H), 2.04-2.00 (m, 1H), 1.92-1.85 (m, 1H).

To a stirred solution of compound **JQ** (500 mg, 1.60 mmol) in CH_3CN (10 mL) under nitrogen atmosphere were added DIPEA (1.77 mL, 9.61 mmol) and compound **LM** (329 mg, 2.40 mmol). The reaction mixture was stirred at 100 °C for 6 h in a sealed tube. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexanes to afford compound **LN** (500 mg, 83%) as a colorless liquid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.52 (s, 1H), 8.45 (s, 1H), 7.69 (s, 1H), 4.42-4.37 (m, 2H), 3.81-3.79 (m, 1H), 3.80-3.61 (m, 3H), 3.31 (s, 3H),3.28-3.29 (m, 1H), 2.08-2.06 (m, 2H), 1.32 (t, J = 7.5 Hz, 3H), 1.26 (s, 9H).

To a stirred solution of compound **LN** (500 mg, 1.32 mmol) in IPA:H_2O (10 mL:10 mL) was added sodium hydroxide (530 mg, 13.26 mmol) at 0 °C. The reaction mixture was heated to 100 °C for 2h. The reaction was cooled to 0 °C, **JN** (530 mg, 13.26 mmol) was added, and then the reaction was heated to 100 °C for 12h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~3 by using an acetic acid solution (0.2 mL). The precipitate was filtered, washed with ether (2 mL) and dried under reduced pressure to afford compound **LO** (350 mg, 71%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ

9.70 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.61 (s, 1H), 4.47 (s, 1H), 3.60-3.46 (m, 7H), 1.66 (s, 3H).

To a stirred solution of compound **LO** (350 mg, 0.93 mmol) in DMF (10 mL) under nitrogen atmosphere were added EDCI·HCl (360 mg, 1.87 mmol), HOBt (255 mg, 1.87 mmol) and DIPEA (0.52 mL, 2.81 mmol) at 0 °C. The reaction was stirred for 5 min, tert-butyl hydrazinecarboxylate (371 mg, 2.81 mmol) was added, and the reaction was stirred at RT for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL) and the compound was extracted with EtOAc (2x20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexanes to afford compound **LP** (160 mg, 35%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.50 (s, 1H), 9.48-9.21 (m, 2H), 8.29 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 4.39 (s, 1H), 4.14 (s, 1H), 3.90 (br s, 1H), 3.64-3.62 (m, 3H), 3.50-3.49 (m, 1H), 2.14-2.12 (m, 2H), 1.79 (s, 2H), 1.47 (s, 9H).

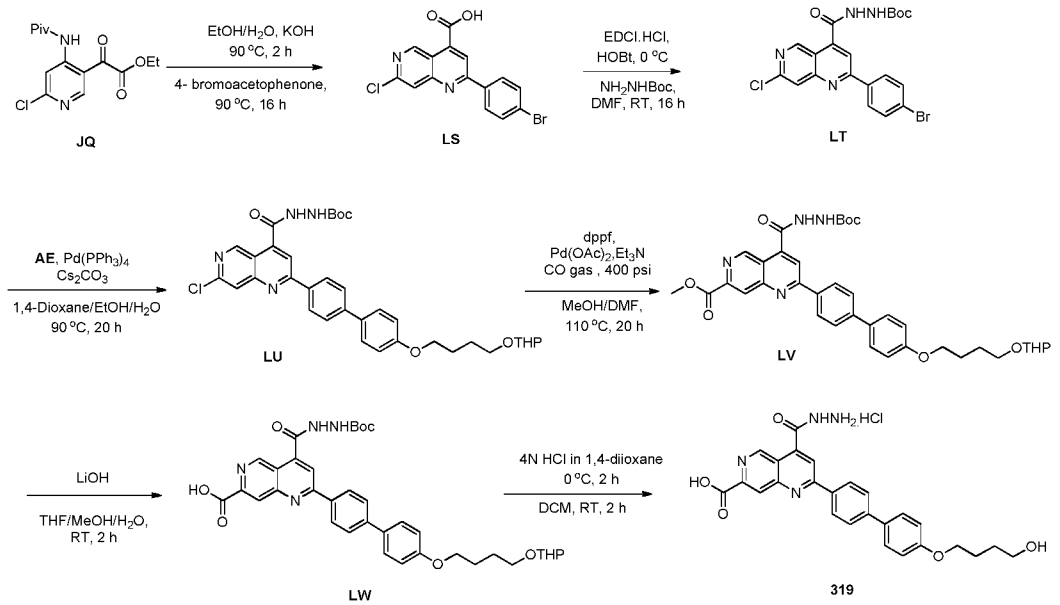
To a stirred solution of compound **LP** (160 mg, 0.32 mmol) in CH_3CN (15 mL) under nitrogen atmosphere were added **IZ** (147 mg, 0.36 mmol) and TEA (0.47 mL, 3.28 mmol). The solution was purged with argon for 10 min followed by the addition of copper iodide (6.25 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (23 mg, 0.32 mmol). The reaction was heated to 90 °C and stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 4% MeOH/DCM to afford compound **LQ** (84 mg, 33%) as a yellow solid. ^{1}H NMR (400 MHz, DMSo-d_6): δ 10.51 (s, 1H), 9.47 (s, 1H), 9.32 (s, 1H), 9.21 (s, 1H), 8.63 (s, 1H), 8.36 (d, 2H), 7.80-7.76 (m, 4H), 6.76 (s, 1H), 5.26-5.24 (m, 1H), 4.41-4.38 (m, 1H), 4.15-4.11 (m, 1H), 3.74-3.72 (m, 5H), 3.69-3.64 (m, 3H), 3.51-3.47 (m, 2H), 3.17-3.13 (m, 1H), 2.17-2.14 (m, 4H), 1.79 (s, 4H), 1.48 (s, 9H).

To a stirred solution of compound **LQ** (80 mg, 0.10 mmol) in THF:MeOH:H_2O (5 mL:5 mL:5 mL) was added lithium hydroxide monohydrate (13 mg, 0.31 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~3 by using an acetic acid solution (0.2 mL). The precipitate was filtered, washed with ether (2 mL) and dried under reduced pressure to afford compound **LR** (64 mg, 82%) as a yellow solid. MS (ESI): *m/z* 753 $[M+1]^+$.

To a stirred solution of compound **LR** (20 mg, 0.02 mmol) in DCM (3 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to

warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (2 mL) to afford **318** (9 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 13.18 (s, 1H), 9.37 (s, 1H), 8.83-8.60 (m, 2H), 8.40-8.27 (m, 2H), 7.94-7.74 (m, 3H), 7.49-7.33 (m, 4H), 6.80 (s, 1H), 5.16 (br s, 1H), 4.86-4.69 (m, 1H), 4.37-4.03 (m, 3H), 3.80-3.69 (m, 2H), 3.30-3.29 (m, 2H), 3.20-3.18 (m, 1H), 3.10 (s, 1H), 2.26-2.09 (m, 3H), 1.99-1.71 (m, 3H), 1.68-1.29 (m, 2H). MS (ESI): *m/z* 569.6 $[M+1]^+$. UPLC Purity: 95.32%

Scheme 82



Example 319

4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1, 1'-biphenyl]-4-yl)-1, 6-naphthyridine-7-carboxylic acid hydrochloride (319)

To a stirred solution of compound **JQ** (4 g, 12.82 mmol) in EtOH/H_2O (40 mL/10 mL) was added KOH (2.87 g, 51.28 mmol). The reaction was heated to 90 °C and was stirred for 2h. The reaction was cooled to RT, 4-bromo acetophenone (5.11 g, 25.64 mmol) was added, and the reaction was heated to 90 °C for 16h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude was triturated with diethylether (30 mL). The obtained solid was diluted with water and the pH was adjusted to pH~3 using AcOH. The precipitate was filtered, washed with water, and dried under reduced pressure to afford compound **LS** (3.7 g, 79%) as an off-white solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.96 (s, 1H), 8.36 (s, 1H), 8.26-8.20 (m, 2H), 8.05 (s, 1H), 7.80-7.76 (m, 2H). MS (ESI): *m/z* 364.59 $[M+1]^+$

To a stirred solution of compound **LS** (3.7 g, 10.17 mmol) in DMF (30 mL) under nitrogen atmosphere were added EDCI·HCl (3.90 g, 20.34 mmol), HOBt (2.76 g, 20.34 mmol), DIPEA (5.3 mL, 30.52 mmol) and tert-butyl carbazate (4.02 g, 30.52 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (50 mL) and the compound was extracted with EtOAc (2 x 50mL). The combined organic extracts were washed with water (50 mL), brine (50 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **LT** (3.5 g, 72%) as a pale yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.68 (s, 1H), 9.58 (s, 1H), 9.32 (s, 1H), 8.36 (d, *J*=5.2Hz, 2H), 8.3 (s, 1H), 8.19 (s, 1H), 7.84-7.79 (m, 2H), 1.48 (s, 9H). MS (ESI): *m/z* 478.74 $[M+1]^+$

To a stirred solution of compound **LT** (1 g, 2.09 mmol) in 1,4-dioxane:EtOH:H_2O (10 mL:5 mL:2.5 mL) under argon atmosphere were added compound **AE** (1.18 g, 3.13 mmol) and Cs_2CO_3 (2.38 g, 7.30 mmol). The solution was purged under argon for 20 min followed by the addition of $Pd(PPh_3)_4$ (240 mg, 0.20 mmol). The reaction was heated to 90 °C and stirred for 20h. After complete consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 35% EtOAc/hexane to afford compound **LU** (700 mg with 64% HPLC purity). Preparative HPLC purification gave **LU** (300 mg, 22%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.71 (s, 1H), 9.57 (s, 1H), 9.33 (s, 1H), 8.46-8.28 (m, 3H), 8.19 (s, 1H), 7.90-7.85 (m, 2H), 7.74 (t, *J* = 8.5 Hz, 2H), 7.08 (t, *J* = 15.0 Hz, 2H), 4.57 (s, 1H), 4.10-4.05 (m, 1H), 3.76-3.67 (m, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 1.82-1.68 (m, 8H), 1.62-1.50 (m, 2H), 1.49 (s, 9H), 1.06-1.01 (m, 1H). MS (ESI): *m/z* 648.17 $[M+1]^+$

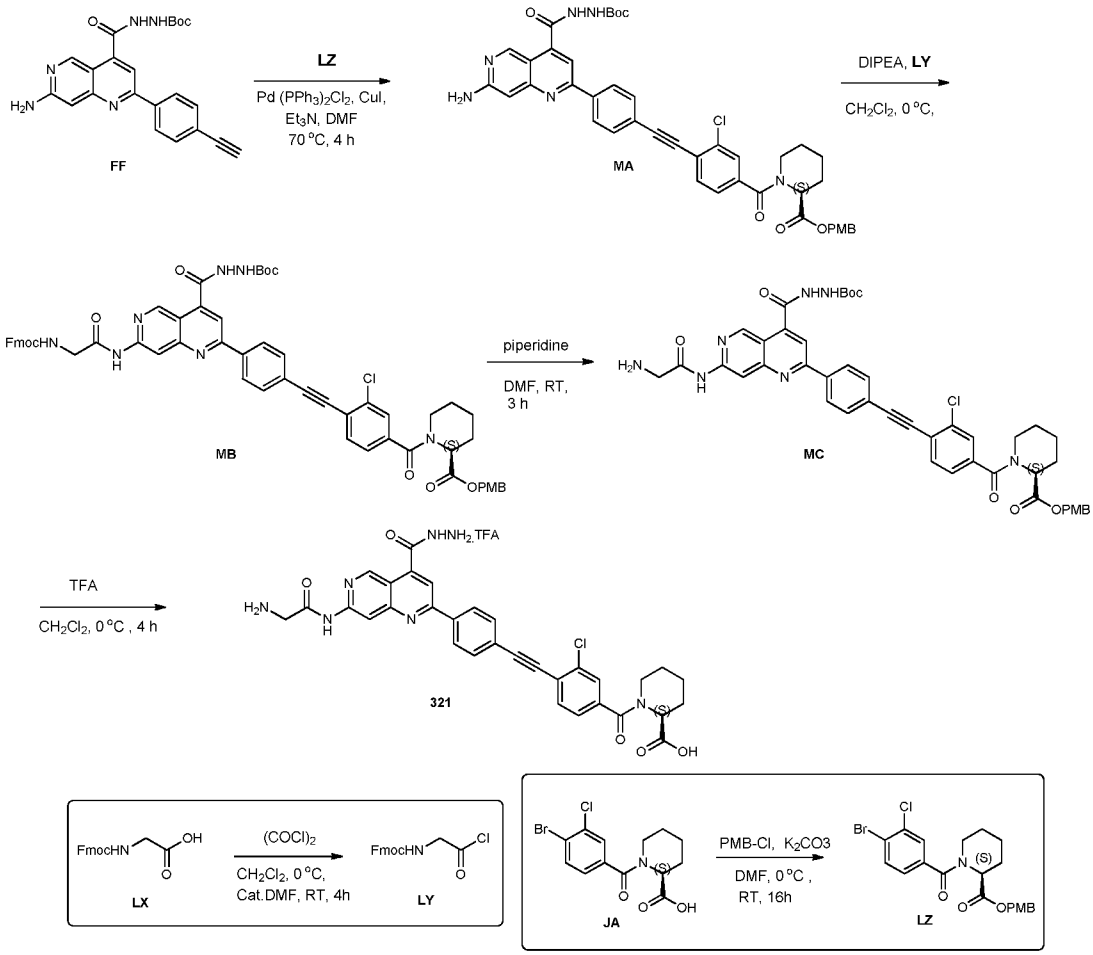
To a stirred solution of compound **LU** (80 mg, 0.12 mmol) in MeOH:DMF (9 mL:1 mL) under argon atmosphere were added TEA (0.08 mL, 0.61 mmol), dppf (34 mg, 0.06 mmol), and $Pd(OAc)_2$ (1 mg, 0.06 mmol). The solution was purged under argon in a steel bomb for 20 min followed by pressurizing the system with CO gas (at 200 psi). The reaction was heated to 100 °C and stirred for 20h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with 10% MeOH:DCM. The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH:DCM and further triturated with 5% IPA:pentane (3 mL) to afford compound **LV** (35 mg, 42%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 9.78 (s, 1H), 9.34 (s, 1H), 8.63 (s, 1H), 8.47-8.09 (m, 2H), 8.06 (t, *J* = 4.4 Hz, 1H), 7.91-7.72 (m, 2H), 7.60 (s, 1H), 7.53-7.30 (m,

1H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.58 (d, *J* = 4.0 Hz, 1H), 3.98 (s, 3H), 3.77-3.67 (m, 3H), 3.45-3.41 (m, 3H), 1.81-1.59 (m, 10H), 1.50 (s, 9H). MS (ESI): *m/z* 671.76 $[M+1]^+$

To a stirred solution of compound **LV** (30 mg, 0.04 mmol) in THF:MeOH:H_2O (2 mL:0.5 mL:0.5 mL) was added lithium hydroxide monohydrate (3 mg, 0.07 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was triturated with diethylether (2 mL). The obtained solid was diluted with water and the pH was adjusted to pH~3 by using AcOH. The precipitate was filtered,washed with water and dried under reduced pressure. The solid was triturated with diethylether:CH_3CN (2 mL:0.5 mL) to afford compound **LW** (16 mg, 55%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (s, 1H), 10.71 (s, 1H), 9.77 (s, 1H), 9.33 (s, 1H), 8.59 (s, 2H), 8.51-8.44 (m, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.55-7.48 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.57-4.49 (m, 2H), 4.21-4.05 (m, 2H), 3.77-3.66 (m, 2H), 3.44-3.30 (m, 2H), 1.81-1.69 (m, 8H), 1.68-1.50 (m, 1H), 1.49 (s, 9H). MS (ESI): *m/z* 657.74 $[M+1]^+$

To a stirred solution of compound **LW** (16 mg, 0.02 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1 mL) at 0 °C for 2h. The reaction was allowed to warm to RT and was stirred for 2h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The solid was triturated with 10% CH_3OH:CH_3CN (1 mL) to afford **319** (9 mg as an HCl salt) as a brick red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.34 (s, 1H), 9.71 (s, 1H), 8.61 (s, 1H), 8.54 (s, 1H), 8.47 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 1.81-1.74 (m, 2H), 1.62-1.55 (m, 2H). MS (ESI): 81.30%, *m/z* 473.4 $[M+1]^+$

Scheme 83



Example 321

(*S*)-1-(4-((4-(7-(2-aminoacetamido)-4-(2-(2, 2, 2-trifluoroacetyl)-2l4-diazane-1-carbonyl)-1, 6-naphthyridin-2-yl) phenyl) ethynyl)-3-chlorobenzoyl) piperidine-2-carboxylic acid (321)

To a stirred solution of compound **LX** (370 mg, 1.24 mmol) in DCM:DMF (5 mL:0.01 mL) was added oxalyl chloride (315 mg, 2.48 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 3h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure to afford compound **LY** (370 mg, crude).

To a stirred solution of compound **JA** (850 mg, 2.45 mmol) in DCM (5 mL) under nitrogen atmosphere were added potassium carbonate (1.01 g, 7.35 mmol) and PMB-Cl (769 mg, 4.90 mmol) at 0 °C. The reaction was heated to 80 °C and was stirred for 8h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (30 mL) and extracted with EtOAc (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 10% EtOAc:hexane to afford compound **LZ** (1 g, 88%) as a

white sticky liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.43-7.28 (m, 2H), 7.10 (d, *J* 7.6 Hz, 1H), 6.92-6.87 (m, 2H), 5.22-5.10 (m, 1H), 4.62 (s, 2H), 3.81 (s, 3H), 3.53-3.15 (m, 1H), 2.38-2.20 (m, 1H), 1.40-1.29 (m, 6H). MS (ESI): *m/z* 466.76 $[M+1]^+$

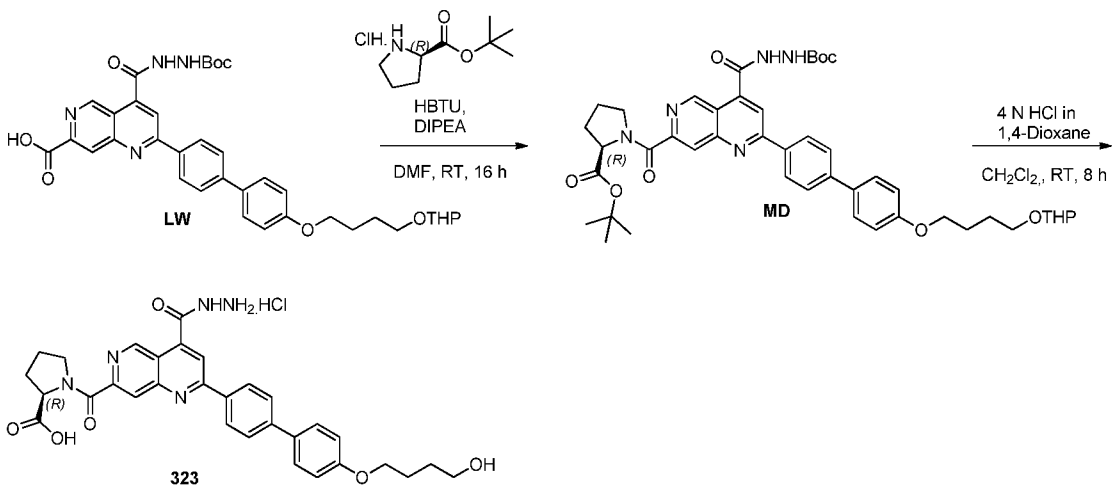
To a stirred solution of compound **FF** (170 mg, 0.42 mmol) in DMF (10 mL) under argon atmosphere were added compound **LZ** (393 mg, 0.84 mmol) and TEA (0.61 mL, 4.21 mmol) at RT. The reaction was purged under argon for 20 min followed by the addition of copper iodide (8 mg, 0.04 mmol) and $Pd(PPh_3)_2Cl_2$ (29 mg, 0.04 mmol). The reaction was heated to 70 °C and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (20 mL) and extracted with DCM (2x30 mL). The combined organic extracts were washed with water (2x20 mL), brine (2x15 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 3% MeOH:DCM and further purified by preparative HPLC to afford compound **MA** (140 mg, 41%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 9.18 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.73-7.70 (m, 2H), 7.69-7.68 (m, 2H), 7.54-7.51 (m, 2H), 7.34-7.31 (m, 4H), 6.92 (s, 1H), 6.50 (br s, 2H), 5.28 (br s, 1H), 5.15 (s, 2H), 4.44-4.40 (m, 1H), 4.13-4.12 (m, 1H), 3.77 (s, 3H), 3.43-3.41 (m, 1H), 3.14-3.10 (m, 1H), 2.21-2.18 (m, 1H), 1.69-1.66 (m, 2H), 1.47 (s, 9H). MS (ESI): *m/z* 789.29 $[M+1]^+$

To a stirred solution of compound **MA** (140 mg, 0.177 mmol) in DCM (10 mL) and DIPEA (0.3 ml, 1.7 mmol) was added compound **LY** (370 mg, 1.17 mmol (crude) in 5 mL DCM dropwise at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (15 mL), brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MB** (20 mg, 11%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (br s, 1H), 10.65 (br s, 1H), 9.51 (s, 1H), 9.26 (s, 1H), 8.65 (s, 1H), 8.44 (d, *J* = 7.2 Hz, 1H), 8.16 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 3H), 7.75-7.73 (m, 3H), 7.70-7.65 (m, 3H), 7.46-7.33 (m, 6H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.26-5.20 (br s, 1H), 5.14 (s, 2H), 4.34-4.32 (m, 2H), 4.28-4.26 (m, 2H), 3.98-3.96 (m, 2H), 3.76 (s, 3H), 3.50-3.46 (m, 1H), 3.09-3.05 (m, 1H), 2.20-2.10 (m, 2H), 1.68 (d, *J* = 12.8 Hz, 3H), 1.48 (s, 9H). MS (ESI): *m/z* 1068.58 $[M+1]^+$

To a stirred solution of compound **MB** (20 mg, 0.018 mmol) in DMF (3 mL) under argon atmosphere was added piperidine (4.78 mg, 0.056 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the reaction was diluted with water (10 mL) and extracted with EtOAc (2x10 mL). The combined extractions were washed with water (3x10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 5% MeOH/DCM to afford compound **MC** (10 mg, 88%) as a pale yellow solid. MS (ESI): *m/z* 846.34 $[M+1]^+$

To a stirred solution of compound **MC** (10 mg, 0.01 mmol) in DCM (2 mL) under nitrogen atmosphere was added TFA (1 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with 10% IPA:MeOH (2 mL) to afford **321** (8 mg as a TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 11.50 (br s, 1H), 9.50 (s, 1H), 8.63 (s, 1H), 8.46-8.24 (m, 3H), 7.83-7.76 (m, 4H), 7.59-7.55 (m, 2H), 7.40-7.35 (m, 2H), 5.17 (s, 1H), 4.38-4.30 (m, 1H), 3.92 (s, 2H), 3.31-3.29 (m, 1H), 2.70-2.61 (m, 1H), 2.23-2.19 (m, 2H), 2.00-1.95 (m, 3H), 1.71-1.43 (m, 2H). MS (ESI): *m/z* 626.6 $[M+1]^+$. UPLC Purity: 71.45%

Scheme 84



Example 323

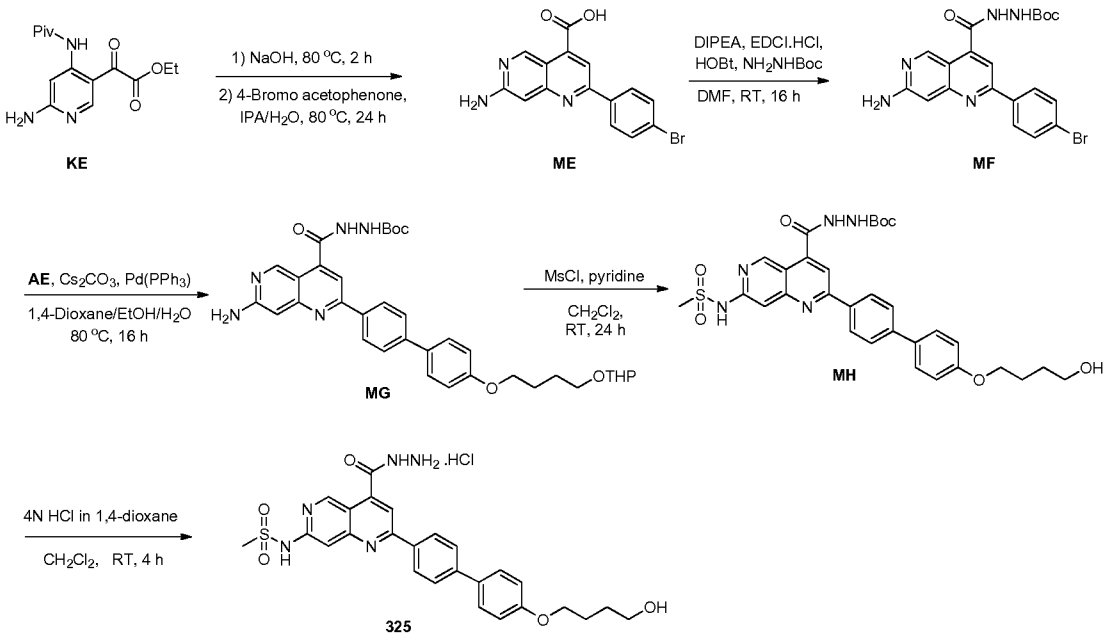
(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1, 1'-biphenyl]-4-yl)-1, 6-naphthyridine-7-carbonyl)-D-proline hydrochloride (323)

To a stirred solution of compound **LW** (40 mg, 0.06 mmol) in DMF (2 mL) under nitrogen atmosphere were added DIPEA (0.04 mL, 0.24 mmol) and HBTU (27 mg, 0.07 mmol). The

solution was stirred for 15 min at which point D-proline t-butylester.HCl (19 mg, 0.09 mmol) was added at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and was extracted with 10% MeOH:EtOAc (2x20 mL). The combined organic extracts were washed with water (5 mL), brine (5 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM and was further triturated with DCM:pentane (1 mL:4 mL) to afford compound **MD** (20 mg, 41%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (d, J = 12.4 Hz, 1H), 9.71 (s, 1H), 9.38 (s, 1H), 8.80 (s, 1H), 8.46-8.38 (m, 3H), 7.89 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 6.0 Hz, 1H), 4.57 (s, 1H), 4.48 (d, J = 4.8 Hz, 1H), 4.09-4.05 (m, 1H), 3.82-3.68 (m, 2H), 3.50-3.60 (m, 2H), 3.45-3.41 (m, 2H), 2.28-2.21 (m, 1H), 1.96-1.90 (m, 7H), 1.88-1.59 (m, 6H), 1.50 (s, 9H), 1.49 (s, 9H). MS (ESI): *m/z* 810.96 $[M+1]^+$

To a stirred solution of compound **MD** (18 mg, 0.02 mmol) in DCM (1 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (2.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 8h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure and the resulting solid was triturated with 10% CH_3OH:CH_3CN (1 mL) to afford **323** (10 mg as an HCl salt) as a brick red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.0 (s, 1H), 9.66 (s, 1H), 8.48-8.45 (m, 4H), 8.40 (s, 1H), 7.89 (t, J = 4.4 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 5.12-5.09 (m, 1H), 4.53-4.50 (m, 1H), 4.05 (t, J = 6.4 Hz, 2H), 3.74 (d, J = 7.2 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 1.93 (d, J = 6.4 Hz, 4H), 1.81-1.55 (m, 4H). MS (ESI): 82.21%, *m/z* 570.5 $[M+1]^+$

Scheme 85



Example 325

***N*-(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1, 1'-biphenyl]-4-yl)-1, 6-naphthyridin-7-yl) methanesulfonamide hydrochloride (325)**

To a stirred solution of compound **KE** (4 g, 13.65 mmol) in IPA/H_2O (80 mL/ 20 mL) was added NaOH (5.4 g, 27.30 mmol) at 0 °C. The reaction was heated to 80 °C and was stirred for 2h. The reaction was cooled to RT, 4-bromo acetophenone (5.4 g, 27.30 mmol) was added, and the reaction was heated to 80 °C for 24h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure. The crude material was triturated with diethylether (50 mL), the obtained solid was diluted with water, and the pH was adjusted to pH~4 by using AcOH. The precipitate was filtered, washed with water and dried under reduced pressure to afford compound **ME** (4 g, 86%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 12.00 (br s, 1H), 9.53 (s, 1H), 8.15 (d, J = 8.0 Hz, 2H), 7.77 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 6.74 (s, 1H), 6.24 (s, 2H). MS (ESI): *m/z* 345.17 $[M+1]^+$

To a stirred solution of compound **ME** (4.5 g, 13.11 mmol) in DMF (25 mL) under nitrogen atmosphere were added EDCI·HCl (5 g, 26.23 mmol), HOBt (3.54 g, 26.23 mmol), DIEPA (6.8 mL, 39.35 mmol), and tert-butyl carbazate (5.1 g, 39.35 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (100 mL) and was extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water (2x100 mL), brine (100 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography

eluting with 2% MeOH/DCM to afford compound **MF** (3.5 g, 58%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.47 (s, 1H), 9.18 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 7.95 (s, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 6.80 (s, 1H), 6.49 (s, 2H), 1.48 (s, 9H). MS (ESI): m/z 459.32 $[M+1]^+$

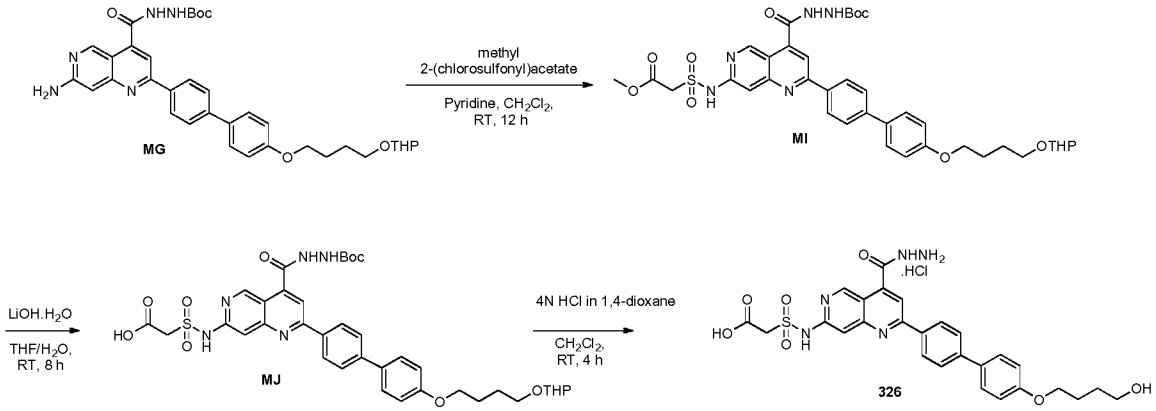
To a stirred solution of compound **MF** (1 g, 2.18 mmol) in 1,4-dioxane:EtOH:H_2O (20 mL:10 mL:5 mL) under argon atmosphere were added compound **AE** (1.23 g, 3.28 mmol) and cesium carbonate (2.5 g, 7.65 mmol). The mixture was purged with argon for 10 min followed by the addition of $Pd(PPh_3)_4$ (253 mg, 0.21 mmol). The reaction was heated to 80 °C and was stirred for 16h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MG** (300 mg, 22%) as a pale yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.49 (s, 1H), 9.17 (s, 2H), 8.30 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 6.81 (s, 2H), 6.46 (s, 2H), 4.57 (s, 1H), 4.07 (t, J = 6.5 Hz, 2H), 3.75-3.69 (m, 2H), 3.43 (t, J = 6.5 Hz, 2H), 1.83-1.73 (m, 4H), 1.71-1.62 (m, 6H), 1.48 (s, 9H). MS (ESI): m/z 628.74 $[M+1]^+$

To a stirred solution of compound **MG** (80 mg, 0.12 mmol) in DCM (5 mL) under nitrogen atmosphere were added pyridine (99 mg, 1.27 mmol) and methanesulfonylchloride (0.02 mL, 0.25 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 24h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MH** (30 mg, with some impurities) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.00 (s, 1H), 10.65 (s, 1H), 9.49 (s, 1H), 9.27 (s, 1H), 8.39 (d, J = 8.4 Hz, 2H), 8.00 (t, J = 6.4 Hz, 2H), 7.86 (d, J = 7.6 Hz, 3H), 7.73 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 4.05 (t, J = 6.4 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 3.38 (s, 3H), 1.77 (t, J = 7.2 Hz, 2H), 1.58 (t, J = 8.0 Hz, 2H), 1.48 (s, 9H). MS (ESI): m/z 622.71 $[M+1]^+$

To a stirred solution of compound **MH** (30 mg, impure) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.3 mL) at 0 °C. The reaction was allowed to warm to RT and and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude product was

triturated with CH_3CN (2 mL) to afford **325** (15 mg as an HCl salt) as a brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.53 (s, 1H), 10.98 (s, 1H), 9.43 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.55 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 4.05 (s, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.39 (s, 3H), 1.81-1.74 (m, 2H), 1.62-1.55 (m, 2H). MS (ESI): m/z 522.59 $[M+1]^+$. HPLC: 92.29%

Scheme 86



Example 326

2-(*N*-(4-(hydrazinecarbonyl)-2-(4'-(4-hydroxybutoxy)-[1, 1'-biphenyl]-4-yl)-1, 6-naphthyridin-7-yl) sulfamoyl) acetic acid hydrochloride (326)

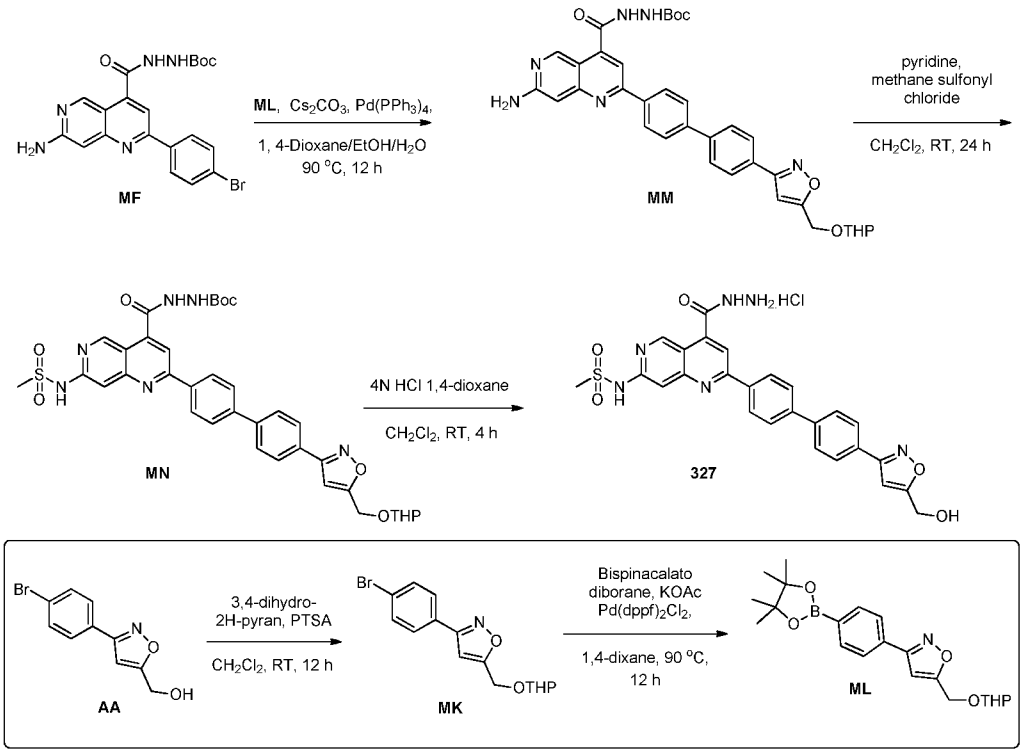
To a stirred solution of compound **MG** (100 mg, 0.15 mmol) in DCM (5 mL) under nitrogen atmosphere were added pyridine (0.14 mL, 1.59 mmol) and methyl 2-(chlorosulfonyl)acetate (69 mg, 0.39 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MI** (30 mg, 25%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.40 (br s, 1H), 10.64 (br s, 1H), 9.48 (s, 1H), 9.27 (s, 1H), 8.40 (d, J = 8.4 Hz, 2H), 8.14 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), , 4.73 (s, 2H), 4.58 (d, J = 4.0 Hz, 1H), 4.07 (t, J = 6.4 2H), 3.78-3.67 (m, 2H), 3.65 (s, 3H), 3.46-3.39 (m, 2H), 1.81-1.78 (m, 4H), 1.73-1.58 (m, 6H), 1.49 (s, 9H). MS (ESI): m/z 764.86 $[M+1]^+$

To a stirred solution of compound **MI** (30 mg, 0.03 mmol) in THF:H_2O (5 mL:1 mL) were added lithium hydroxide monohydrate (6.6 mg, 0.15 mmol) at 0 °C. The reaction was allowed

to warm to RT and was stirred for 8h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~4 by using an acetic acid solution (0.1 mL). The precipitate was filtered and dried under reduced pressure to afford compound **MJ** (15 mg, 52%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.61 (br s, 1H), 9.48 (s, 1H), 9.44 (s, 1H), 9.25 (s, 1H), 8.39 (d, J = 7.6 Hz, 2H), 8.12 (s, 1H), 8.08 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 12.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 4.58 (d, J = 3.6 Hz, 1H), 4.07 (t, J = 6.4 Hz, 1H), 3.77-3.67 (m, 4H), 3.45-3.38 (m, 3H), 1.79 (t, J = 6.4 Hz, 4H), 1.73-1.59 (m, 6H), 1.49 (s, 9H). MS (ESI): *m/z* 750.84 $[M+1]^+$

To a stirred solution of compound **MJ** (15 mg, 0.02 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.2 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (2 mL) to afford **326** (5 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.28 (br s, 1H), 10.99 (s, 1H), 9.43 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 8.23 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.06 (s, 2H), 4.05 (t, J = 6.8 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 1.80-1.75 (m, 2H), 1.62-1.57 (m, 2H). MS (ESI): *m/z* 566.6 $[M+1]^+$. HPLC:74.97 %

Scheme 87



Example 327

_N_-(4-(hydrazinecarbonyl)-2-(4'-(5-(hydroxymethyl) isoxazol-3-yl)-[1, 1'-biphenyl]-4-yl)-1, 6-naphthyridin-7-yl) methanesulfonamide hydrochloride (327)

To a stirred solution of compound **AA** (500 mg, 1.97 mmol) in DCM (20 mL) under nitrogen atmosphere were added 3,4-dihydro-2H-pyran (249 mg, 2.96 mmol) and *p*-TSA (187 mg, 0.98 mmol) at 0 °C for 15 min. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (25 mL) and the compound was extracted with DCM (2x25 mL). The combined organic extracts were washed with water (2x30 mL) dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography eluting with 8% EtOAc/hexane to afford compound **MK** (310 mg, 46%) as a colorless thick syrup. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.85-7.82 (m, 2H), 7.74-7.70 (m, 2H), 7.10 (s, 1H), 4.80 (s, 2H), 4.76-4.69 (m, 1H), 3.80-3.72 (m, 1H), 3.48-3.40 (m, 1H), 1.78-1.61 (m, 2H), 1.56-1.42 (m, 4H). MS (ESI): *m/z* 338 $[M]^+$, 340 $[M+2]^+$

To a stirred solution of compound **MK** (300 mg, 0.89 mmol) in 1,4-dioxane (10 mL) under argon atmosphere were added bispinacalatodiborane (271 mg, 1.06 mmol) and potassium acetate (261 mg, 2.67 mmol). The solution was purged with argon for 10 min followed by the addition of $Pd(dppf)_2Cl_2$ (65 mg, 0.08 mmol). The reaction was heated to 90 °C and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction

mixture was filtered through Celite and the Celite bed washed with ethyl acetate (25 mL). The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 10% EtOAc/hexane to afford compound **ML** (220 mg, 64%) as an off-white solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.91 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.11 (s, 1H), 4.80 (s, 2H), 4.78-4.67 (m, 1H), 3.81-3.76 (m, 1H), 3.52-3.49 (m, 1H), 1.76-1.65 (m, 2H), 1.55-1.49 (m, 4H), 1.23 (s, 12H). MS (ESI): *m/z* 386.27 $[M+1]^+$

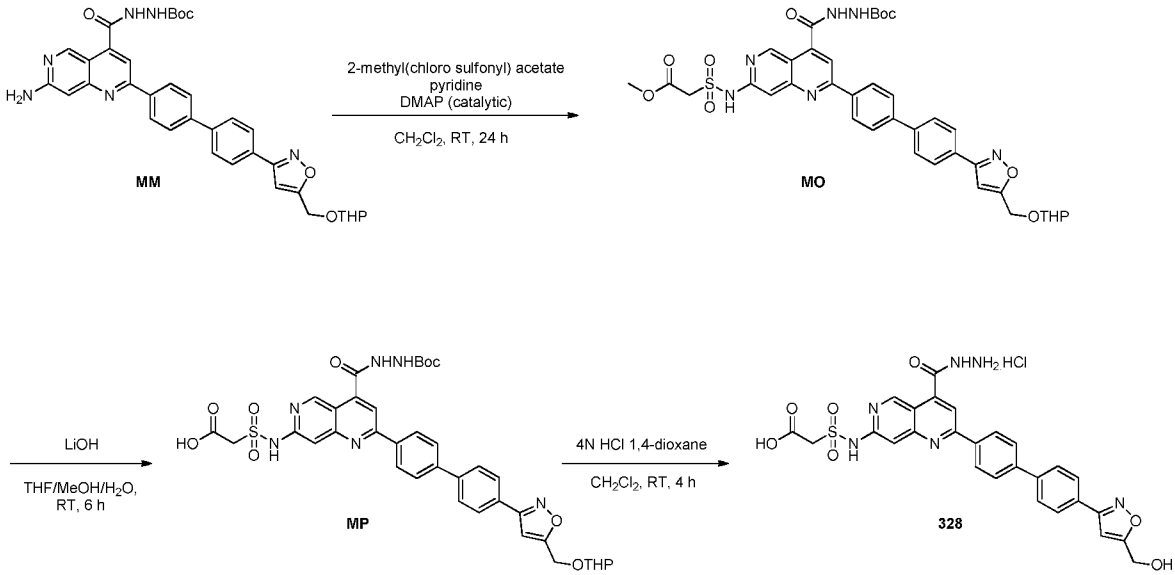
To a stirred solution of compound **MF** (500 mg, 1.09 mmol) in 1,4-dioxane:EtOH:H_2O (12 mL:3 mL:1 mL) under argon atmosphere were added compound **ML** (631 mg, 1.64 mmol) and cesium carbonate (1.25 g, 3.82 mmol). The solution was purged with argon for 10 min followed by the addition of $Pd(PPh_3)_4$ (126 mg, 0.10 mmol). The reaction was heated to 90 °C and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was filtered through Celite and the Celite bed washed with ethyl acetate (25 mL). The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MM** (210 mg, 30%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.57 (s, 1H), 9.18 (s, 2H), 8.36 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.95 (t, J = 8.0 Hz, 4H), 7.57-7.55 (m, 1H), 7.16 (s, 1H), 6.80 (s, 1H), 6.47 (s, 2H), 4.83 (s, 2H), 4.78 (t, J = 4.8 Hz, 1H), 3.83-3.77 (m, 1H), 3.54-3.49 (m, 1H), 1.77-1.64 (m, 2H), 1.56-1.50 (m, 4H), 1.48 (s, 9H). MS (ESI): *m/z* 637.7 $[M+1]^+$

To a stirred solution of compound **MM** (50 mg, 0.07 mmol) in DCM (3 mL) under nitrogen atmosphere were added pyridine (18.6 mg, 0.23 mmol) and methanesulfonylchloride (22.4 mg, 0.19 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 24h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MN** (26 mg, 52%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.98 (s, 1H), 10.64 (s, 1H), 9.51 (s, 1H), 9.28 (s, 1H), 8.54-8.45 (m, 2H), 8.16 (d, J = 7.6 Hz, 1H), 8.05-7.90 (m, 5H), 7.64-7.51 (m, 2H), 7.16 (s, 1H), 4.83 (s, 2H), 4.72-4.64 (m, 1H), 3.83-3.75 (m, 1H), 3.54-3.49 (m, 1H), 3.43 (s, 3H), 1.77-1.68 (m, 2H), 1.66-1.53 (m, 4H), 1.49 (s, 9H). MS (ESI): 80% *m/z* 715.79 $[M+1]^+$

To a stirred solution of compound **MN** (23 mg, 0.03 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to

warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN:pentane (2 mL:2 mL) to afford **327** (11 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.62 (s, 1H), 11.00 (s, 1H), 9.46 (s, 1H), 8.49 (d, J = 8.4 Hz, 2H), 8.31 (s, 1H), 8.03-7.94 (m, 6H), 7.58 (s, 1H), 7.01 (s, 1H), 4.64 (s, 2H), 3.39 (s, 3H). MS (ESI): 80%; m/z 531.56 $[M+1]^+$

Scheme 88



Example 328

2-(N-(4-(hydrazinecarbonyl)-2-(4'-(5-(hydroxymethyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-7-yl)sulfamoyl)acetic acid hydrochloride (328)

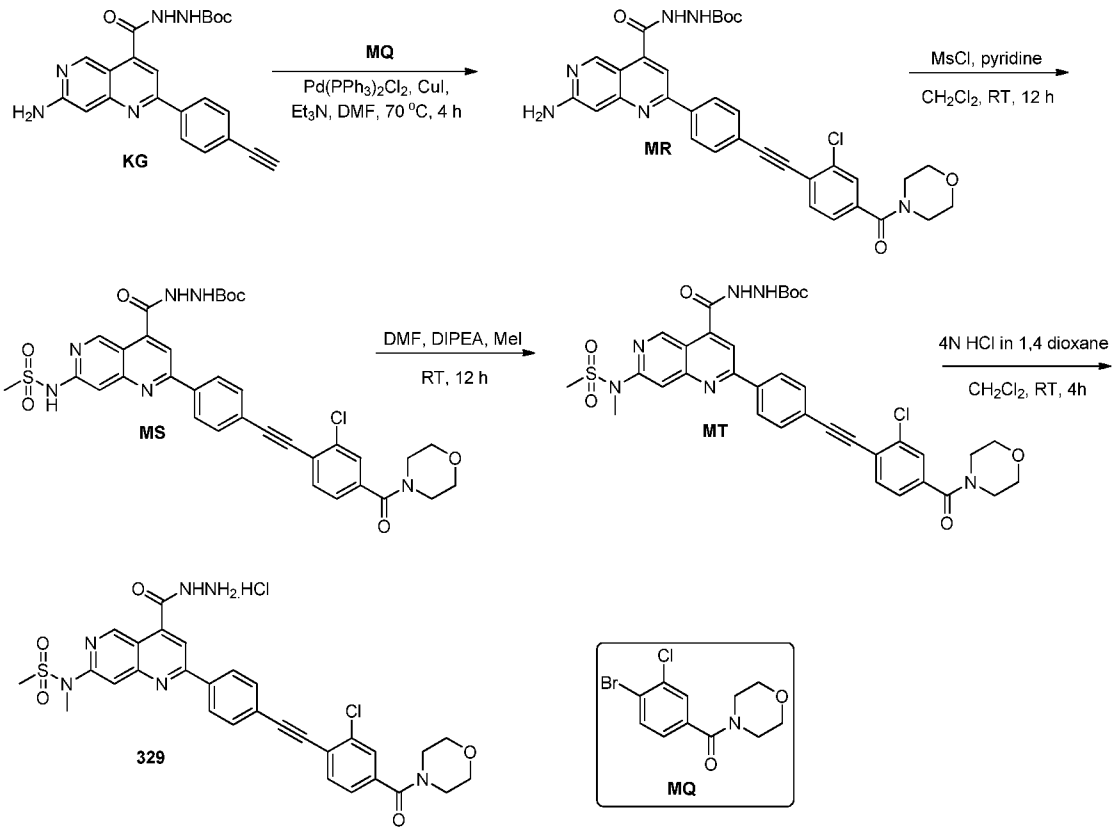
To a stirred solution of compound **MM** (300 mg, 0.47 mmol) in DCM (15 mL) under nitrogen atmosphere were added pyridine (372 mg, 4.7 mmol), DMAP (catalytic) and 2-methyl(chloro sulfonyl) acetate (203 mg, 1.17 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 24h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and was extracted with DCM (2x30 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MO** (45 mg) as a yellow solid. MS (ESI): 70% m/z 773.83 $[M+1]^+$

To a stirred solution of compound **MO** (45 mg, impure material) in THF:MeOH:H_2O (2 mL:1 mL:1 mL) were added lithium hydroxide monohydrate (7.3 mg, 0.17 mmol) at 0 °C. The

reaction was allowed to warm to RT and was stirred for 6h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude product mixture was diluted with water and the pH was adjusted to pH~4 by using an acetic acid solution (0.1 mL). The precipitate was filtered and dried under reduced pressure to afford compound **MP** (35 mg, 0.04 mmol, 10% over two steps) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.60 (br s, 1H), 9.34 (s, 1H), 9.22 (d, J = 11.6 Hz, 1H), 8.43 (t, J = 7.6 Hz, 2H), 8.04-7.94 (m, 6H), 7.57-7.50 (m, 1H), 7.16 (s, 1H), 4.83 (s, 2H), 4.79-4.68 (m, 1H), 3.83-3.77 (m, 2H), 3.38 (s, 2H), 1.75-1.68 (m, 4H), 1.56-1.53 (m, 2H), 1.49 (s, 9H). MS (ESI): *m/z* 759.80 $[M+1]^+$

To a stirred solution of compound **MP** (35 mg, 0.04 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The crude material was triturated with CH_3CN (2 mL) to afford **328** (15 mg as an HCl salt) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.34 (s, 2H), 9.45 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.30 (s, 1H), 8.03-7.94 (m, 6H), 7.56 (s, 1H), 7.01 (s, 1H), 4.62 (d, J = 11.6 Hz, 4H). MS (ESI): 81.1%; *m/z* 575.57 $[M+1]^+$

Scheme 89



Example 329

Synthesis of N-(2-(4-((2-chloro-4-(morpholine-4-carbonyl)phenyl)ethynyl)phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl)-N-methylmethanesulfonamide hydrochloride (329)

MQ is synthesized from 4-bromo-3-chlorobenzoic acid and morpholine following a similar procedure as used to synthesize **HJ**.

To a stirred solution of compound **KG** (1 g, 2.4 mmol) in DMF (5 mL) under argon atmosphere were added compound **MQ** (1.2 g, 3.7 mmol) and TEA (3.6 mL, 24.8 mmol). The solution was purged with argon for 10 min followed by the addition of copper iodide (47 mg, 0.24 mmol) and $Pd(PPh_3)_2Cl_2$ (174 mg, 0.24 mmol). The reaction was heated to 70 °C and was stirred for 4h. After complete consumption of the starting material (by TLC) the reaction mixture was diluted with ice cold water (20 mL) and was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with water (2x20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2-5% MeOH/DCM to afford compound **MR** (500 mg, 33 %) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.49 (br s, 1H), 9.19 (br s, 2H),

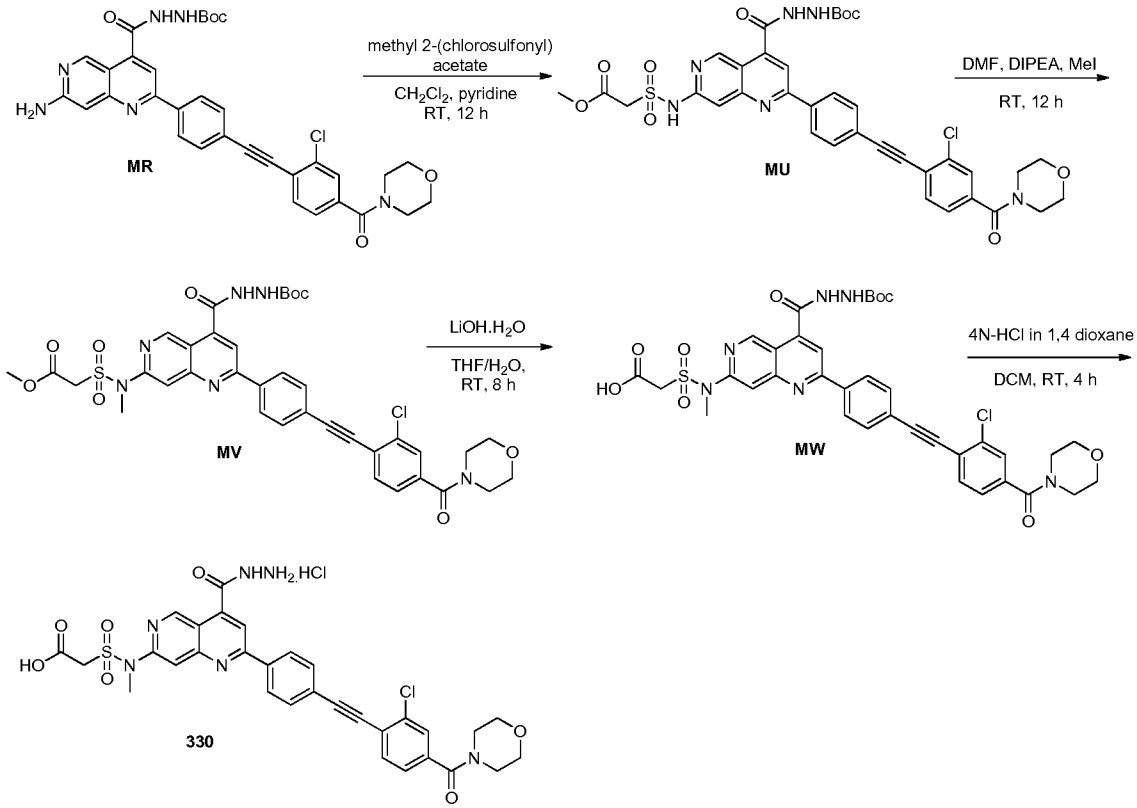
8.34 (d, J = 7.0 Hz , 2H), 7.81-7.68 (m, 5H), 7.46 (d, J = 7.5 Hz, 2H), 6.82 (S, 1H), 6.51(br s, 2H), 3.62-3.51 (m, 6H), 3.32-3.30 (m, 2H), 1.50 (s, 9H). MS (ESI): *m/z* 627.10 $[M+1]^+$

To a stirred solution of compound **MR** (200 mg, 0.31 mmol) in DCM (25 mL) under nitrogen atmosphere were added pyridine (0.05 ml, 0.63 mmol) and methanesulfonylchloride (0.03 mL, 0.38 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC) the reaction mixture was diluted with ice cold water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 3% MeOH/DCM to afford compound **MS** (100 mg, 45 %) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.00 (br s, 1H), 10.63(br s, 1H), 9.51 (br s, 1H), 9.28 (br s, 1H), 8.44 (d, J=8 Hz, 2H), 8.15 (s, 1H), 7.82-7.79 (m, 3H), 7.68 (s, 1H), 7.55 (s, 1H), 7.47-7.44 (m, 1H), 3.69-3.54 (br s, 6H), 3.40-3.37 (m, 5H), 1.49 (s, 9H). MS (ESI): *m/z* 705.18 $[M+1]^+$

To a stirred solution of compound **MS** (60 mg, 0.08 mmol) in DMF (10 mL) under nitrogen atmosphere were added DIPEA (21.95 mg, 0.17 mmol) and MeI (12 mg, 0.08 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MT** (42 mg, 69 %) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.56 (s, 1H), 8.23 (d, J = 8.4 Hz, 2H), 8.20-8.19 (m, 1H), 8.03(s, 1H), 7.86 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H), 7.29 (s, 1H), 6.80 (br s, 1H), 3.90-3.71 (br s, 6H), 3.51 (s, 5H), 3.25 (s, 3H), 1.55 (s, 9H). MS (ESI): *m/z* 719.21 $[M+1]^+$

To a stirred solution of compound **MT** (20 mg, 0.027 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (0.5 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure. The crude product was triturated with CH_3CN (2 mL) to afford **329** (20 mg as an HCl salt) as a brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.69 (m, 1H), 11.65 (br s, 1H), 9.54 (s, 1H), 8.48 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H), 7.95 (s, 1H), 7.86-7.79 (m, 3H), 7.68 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 3.73-3.63 (br s, 8H), 3.47 (s, 3H), 3.31 (s, 3H). MS (ESI): *m/z* 619.09 $[M+1]^+$. HPLC: 85.87 %

Scheme 90



Example 330

Synthesis of 2-(N-(2-(4-((2-chloro-4-(morpholine-4-carbonyl)phenyl)ethynyl)phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl)-N-methylsulfamoyl)acetic acid hydrochloride (330)

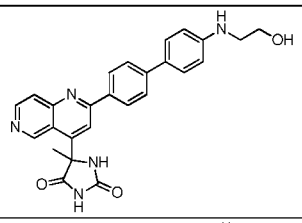
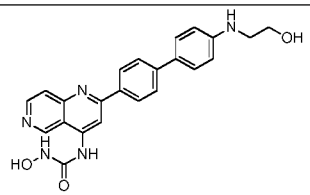
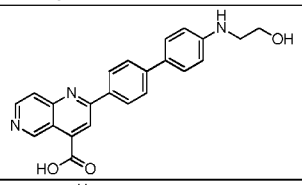
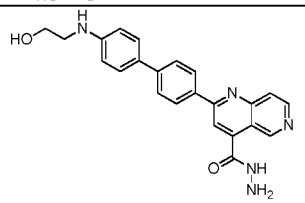
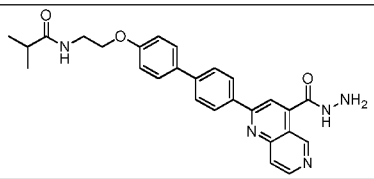
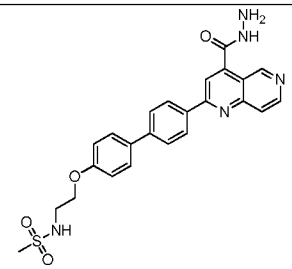
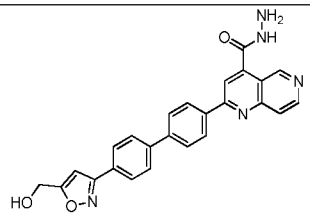
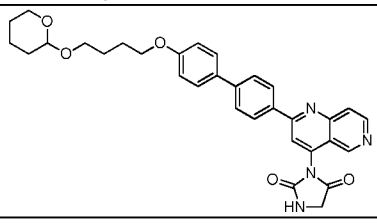
To a stirred solution of compound **MR** (200 mg, 0.31 mmol) in DCM (25 mL) under nitrogen atmosphere were added pyridine (0.05 ml, 0.63 mmol) and methyl 2-(chlorosulfonyl)acetate (0.03 mL, 0.31 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and the compound was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MU** (100 mg, 41 %) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.45 (br s, 1H), 10.64 (br s, 1H), 9.51 (br s, 1H), 9.29 (s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.17 (s, 1H), 7.83-7.80 (m, 3H), 7.72-7.66 (m, 3H), 7.54 (s, 1H), 6.71 (s, 1H), 5.99 (s,1H), 4.15-4.10 (m, 2H), 3.65 (s, 3H), 3.57 (br s, 8H),1.49 (s, 9H). MS (ESI): m/z 763.22 $[M+1]^+$

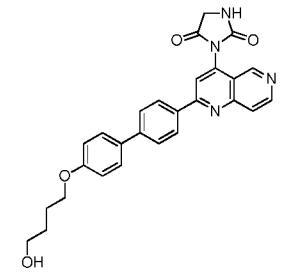
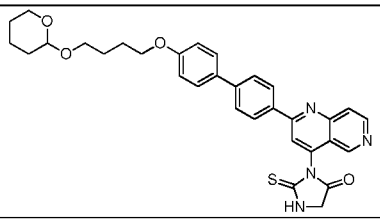
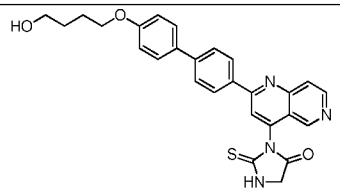
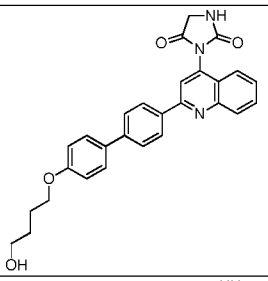
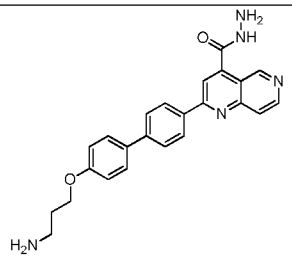
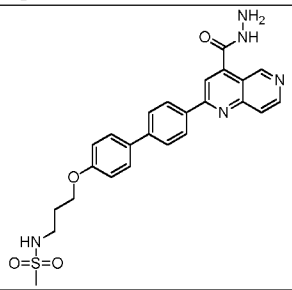
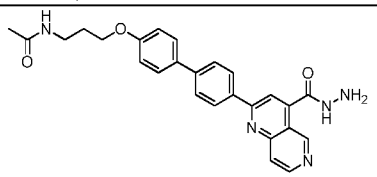
To a stirred solution of compound **MU** (100 mg, 0.18 mmol) in DMF (10 mL) under nitrogen atmosphere were added DIPEA (0.07 ml, 0.37 mmol) and MeI (0.012 ml, 0.18 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 12h. After complete consumption of the starting material (by TLC), the reaction mixture was diluted with ice cold water (10 mL) and was extracted with DCM (2x10 mL). The combined organic extracts were washed with water (2x20 mL), brine (20 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford compound **MV** (75 mg, 74 %) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.55 (s, 1H), 8.23 (d, J=8.4 Hz, 1H), 8.03 (s, 1H), 7.75-7.69 (m,3H), 7.62 (d, J = 8.4 Hz, 1H), 7.53-7.50 (m, 2H), 7.29 (s, 1H), 6.83 (br s, 1H), 4.69(s, 2H), 4.23-4.20 (m, 1H), 3.77 (s, 9H), 3.72 (s, 3H), 3.57(s, 2H), 1.57 (s, 9H). MS (ESI): *m/z* 777.25 $[M+1]^+$

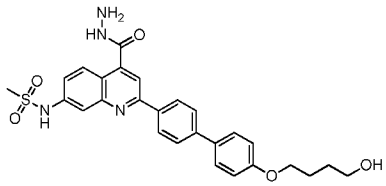
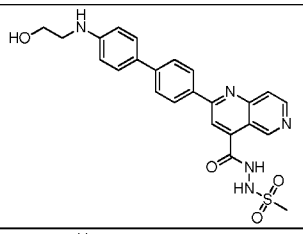
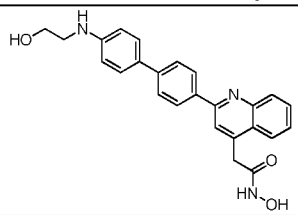
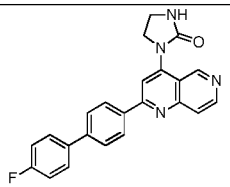
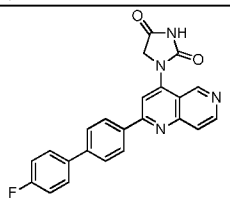
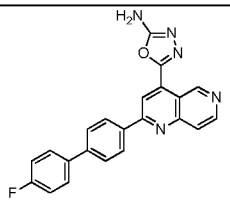
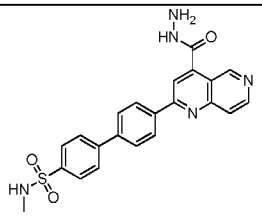
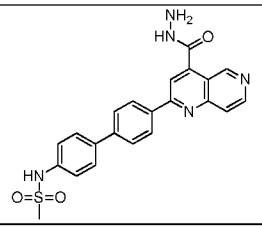
To a stirred solution of compound **MV** (70 mg, 0.09 mmol) in THF:H_2O (5 mL:1 mL) was added lithium hydroxide monohydrate (7.6 mg, 0.18 mmol) at 0 °C. The reaction was allowed to warm to RT and was stirred for 8h. After complete consumption of the starting material (by TLC) the volatiles were evaporated under reduced pressure. The crude material was diluted with water and the pH was adjusted to pH~4 by using an acetic acid solution (0.1 mL). The precipitate was filtered and dried under reduced pressure to afford compound **MW** (51.5 mg, 75%) as a yellow solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.66 (br s, 1H), 9.56 (br s, 1H), 9.29 (br s, 1H), 8.47 (d, J = 8 Hz, 2H), 8.24 (br s, 1H), 7.92 (s, 1H), 7.83-7.79 (m, 3H), 7.71-7.68 (m, 2H), 7.46 (d, J = 7.6 Hz, 1H), 4.52 (br s, 2H), 3.61 (br s, 8H), 3.51(s, 3H), 1.49 (s, 9H). MS (ESI): *m/z* 763.22 $[M+1]^+$

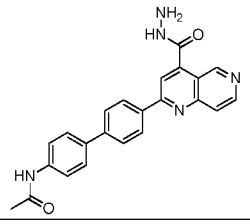
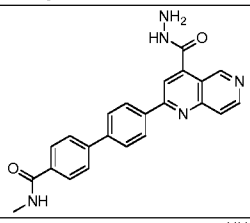
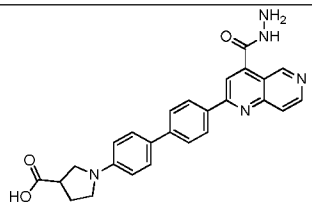
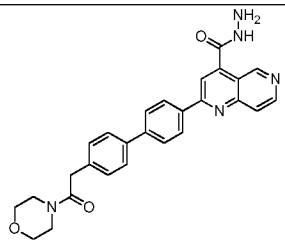
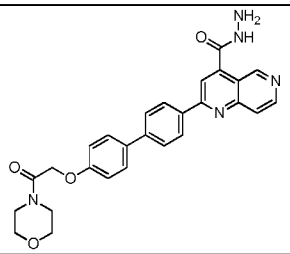
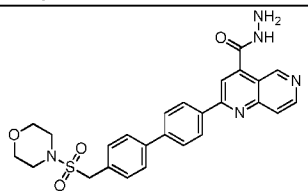
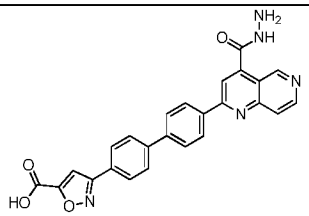
To a stirred solution of compound **MW** (40 mg, 0.05 mmol) in DCM (2 mL) under nitrogen atmosphere was added 4N HCl in 1,4-dioxane (1.0 mL) at 0 °C. The reaction was allowed to warm to RT and was stirred for 4h. After complete consumption of the starting material (by LC-MS), the volatiles were evaporated under reduced pressure. The crude product was triturated with CH_3CN (2 mL) to afford **330** (20 mg as an HCl salt) as a brown solid. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 11.62 (br s, 1H), 9.53 (s, 1H), 8.48 (d, J = 8.0 Hz, 2H), 8.40 (s, 1H), 7.93 (s 1H), 7.86-7.79 (m, 3H), 7.68 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 4.70 (s, 2H), 3.61 (br s, 8H), 3.37 (s, 3H). MS (ESI): *m/z* 663.05 $[M+1]^+$. HPLC: 90.05 %.

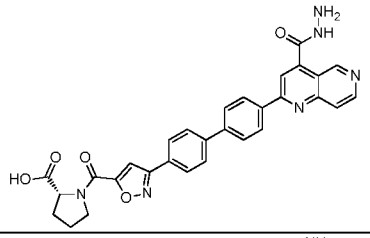
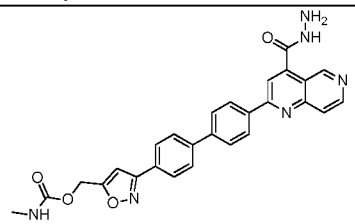
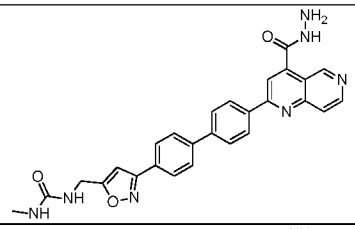
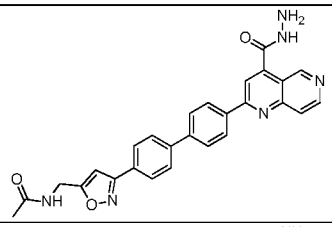
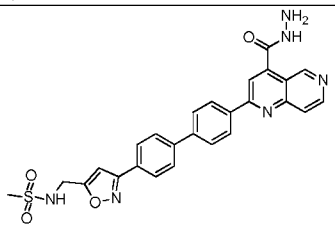
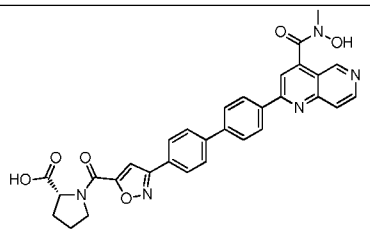
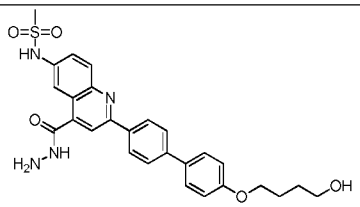
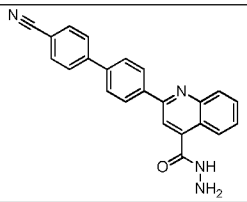
Table 1. Analytical Data

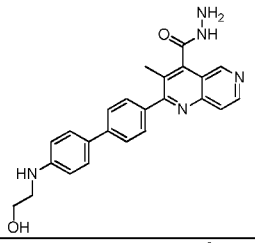
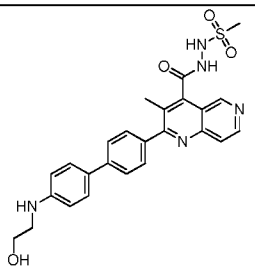
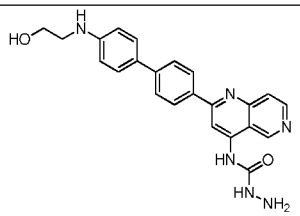
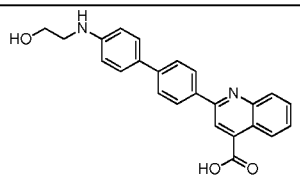
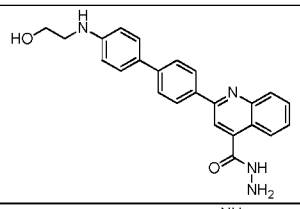
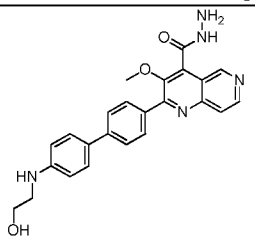
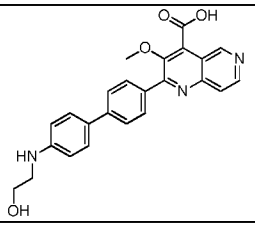
Example #	HPLC Method	HPLC RT	MS(ESI) (M+H)	Chirality	Structure
1	A	1.47	454.6	Racemate	
2	A	1.38	416		
3	A	1.45	386.2		
4	A	1.41	400.2		
5	A	1.85	470		
6	A	1.70	478		
7	A	1.61	437		
8	A	2.63	552.8	Racemate	

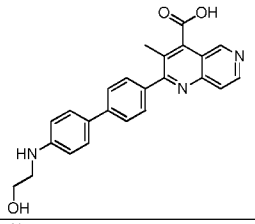
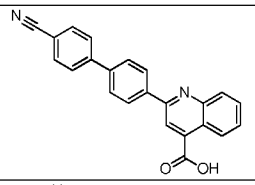
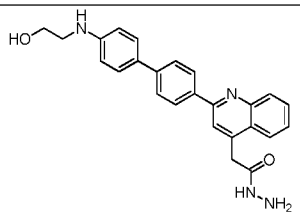
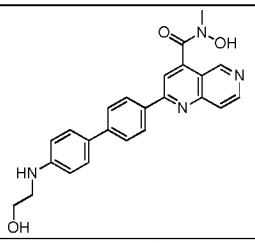
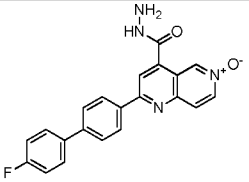
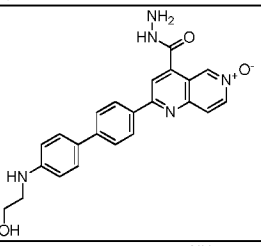
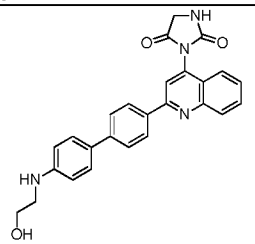
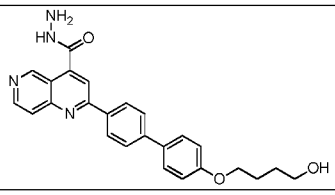
9	A	1.90	469		
10	A	2.88	569.5	Racemate	
11	A	2.06	483.6		
12	A	2.20	468.6		
13	A	1.40	412 (M-1)		
14	A	1.79	492.7		
15	A	1.65	456.7		

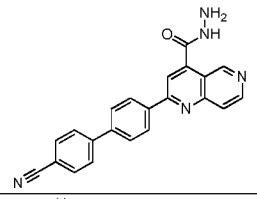
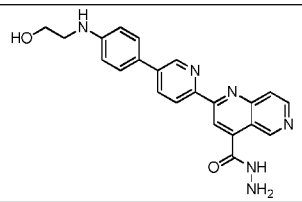
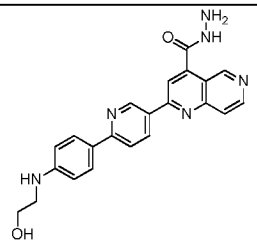
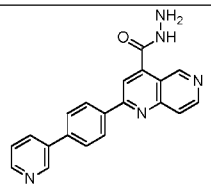
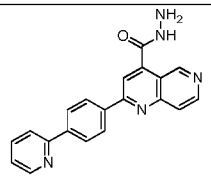
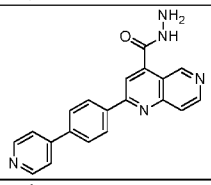
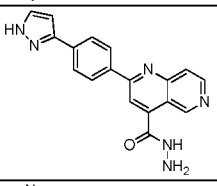
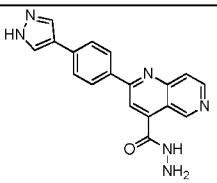
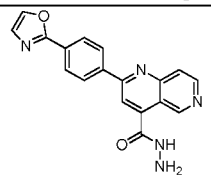
16	A	1.83	521		
17	A	1.53	477		
18	A	1.49	414		
19	A	2.01	385.7		
20	A	2.16	399.4		
21	C	10.64	384.4		
22	A	1.59	434		
23	C	8.07	432.5 (M-1)		

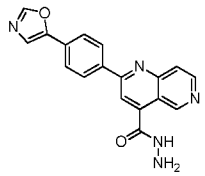
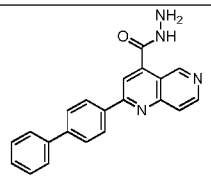
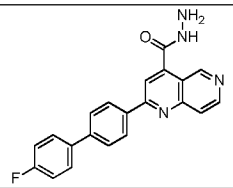
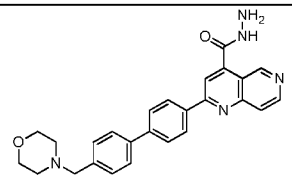
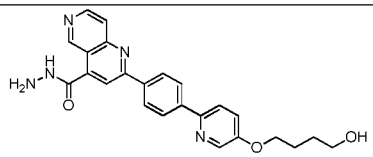
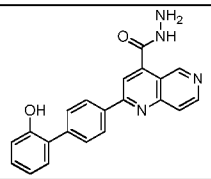
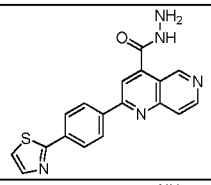
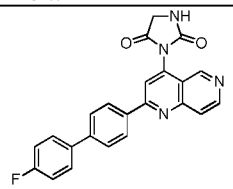
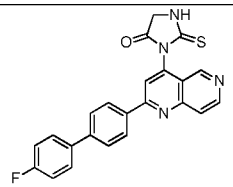
24	C	7.83	398		
25	A	1.47	398		
26	A	1.76	454	Racemate	
27	A	1.61	468.3		
28	A	1.68	484		
29	A	2.10	504		
30			452.3		

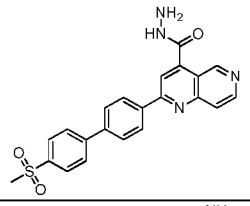
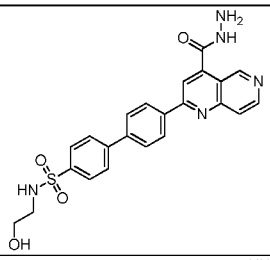
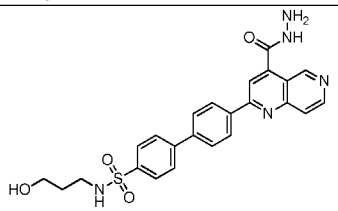
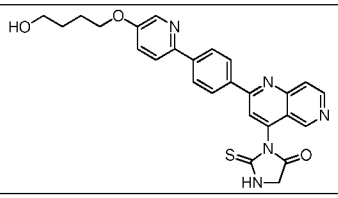
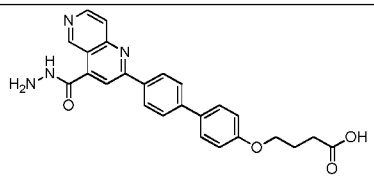
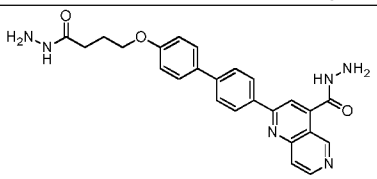
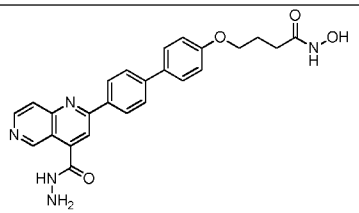
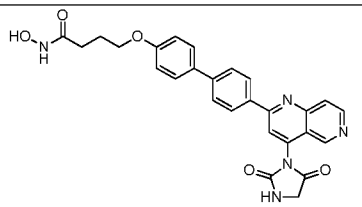
31	B	8.02	549.3	R	
32	A	1.81	495.2		
33	A	1.60	494.3		
34	A	1.60	479.3		
35	A	1.70	515.4		
36	A	1.85	562.4	R	
37	A	1.97	521		
38	D	9.83	365.0		

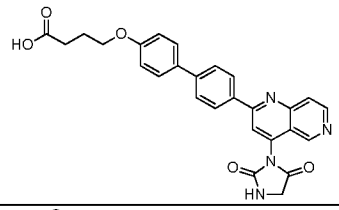
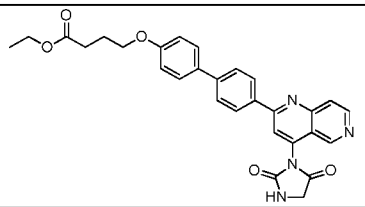
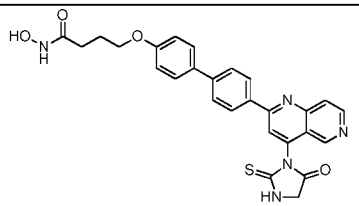
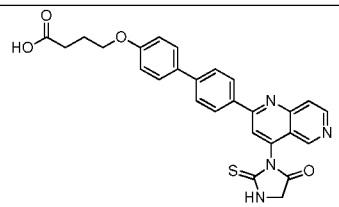
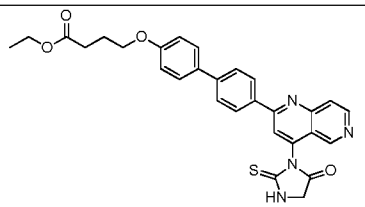
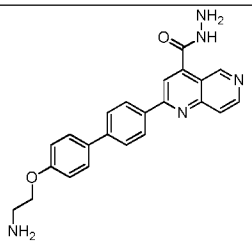
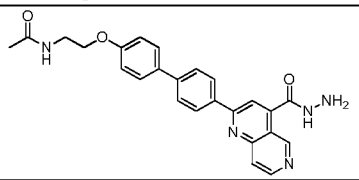
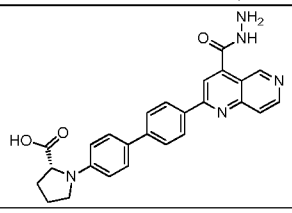
39	A	1.37	414		
40	A	1.45	492		
41	C	7.98	415		
42	A	1.89	385		
43	A	1.66	399.1		
44	A	1.32	430.1		
45	A	1.27	416		

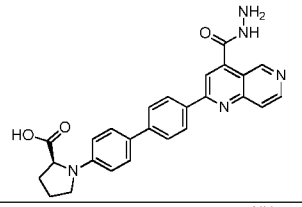
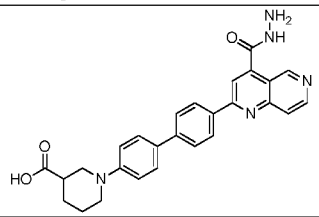
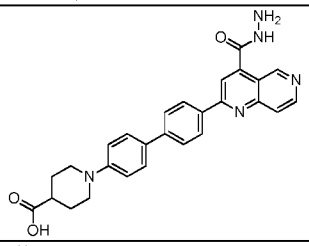
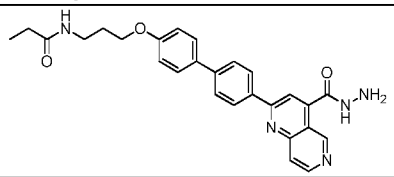
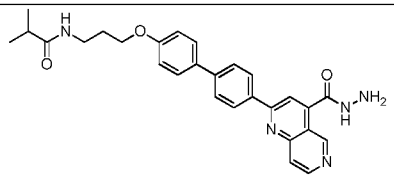
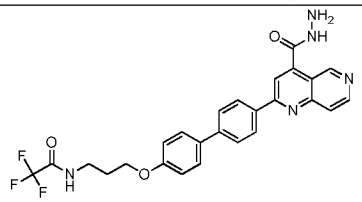
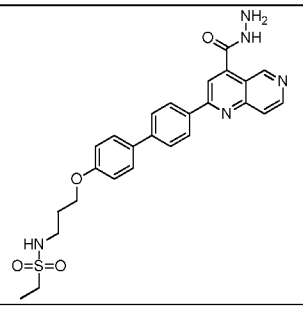
46	C	7.07	400.2		
47	A	2.67	351.1		
48	A	1.32	413		
49	A	1.53	415		
50	C	8.71	375		
51	A	1.34	416		
52	A	1.83	439		
53	A	1.70	429.6		

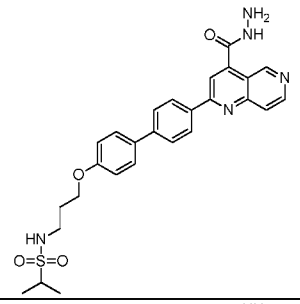
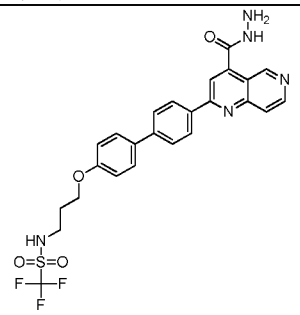
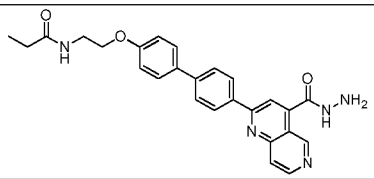
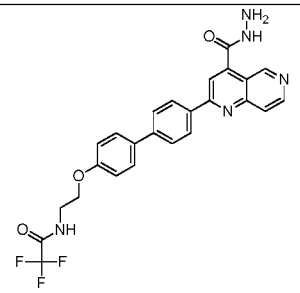
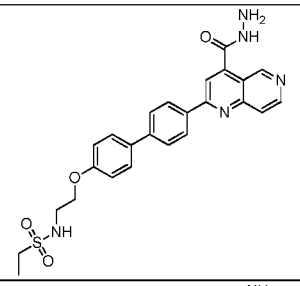
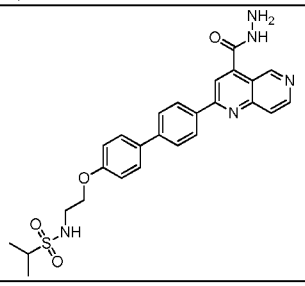
54	C	8.96	366.3		
55	A	1.36	401		
56	C	7.00	401		
57	A	3.03	342		
58	C	7.87	342		
59	E	10.52	342		
60	C	7.89	331.4		
61	A	1.24	331		
62	A	1.49	332		

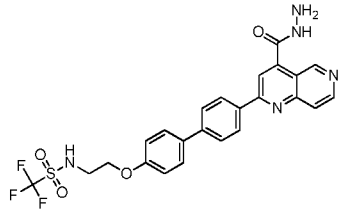
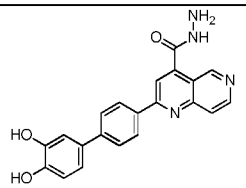
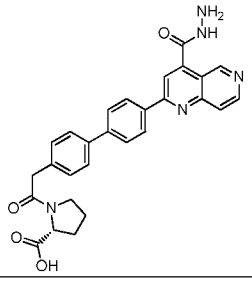
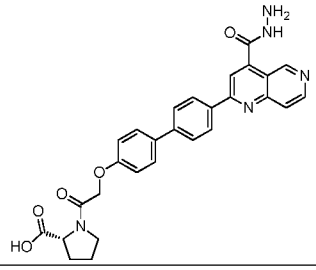
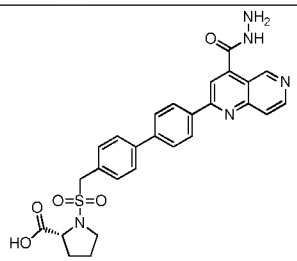
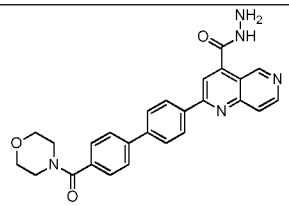
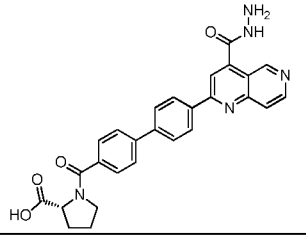
63	A	1.43	332		
64	A	1.95	341		
65	A	2.00	359		
66	C	8.73	440		
67	A	1.44	430		
68	C	8.35	357		
69	A	1.48	348.5		
70	A	2.28	397.3 (M-1)		
71	A	2.49	415.6		

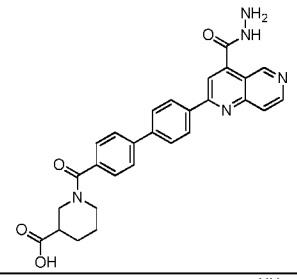
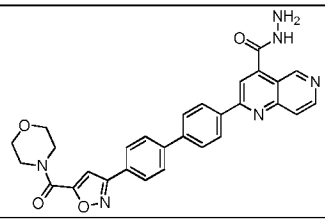
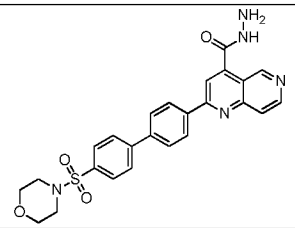
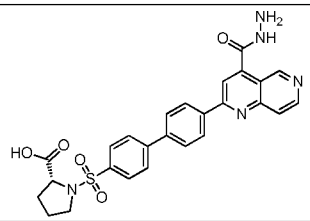
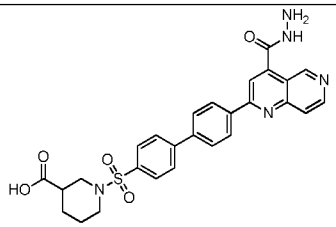
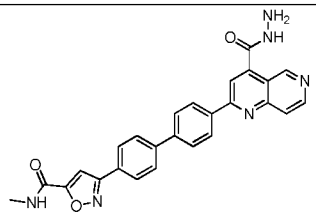
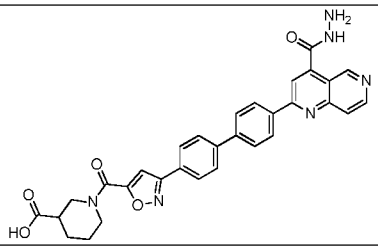
72	A	1.60	417.6 (M-1)		
73	C	7.48	464		
74	C	8.81	478		
75	A	1.73	486.8		
76	C	6.9	443		
77	C	7.56	457		
78	A	1.53	458		
79	A	1.69	496.2		

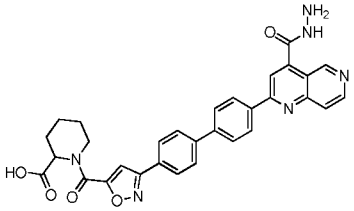
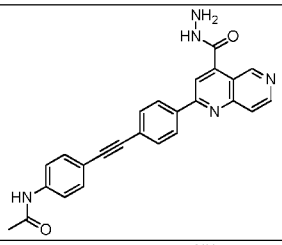
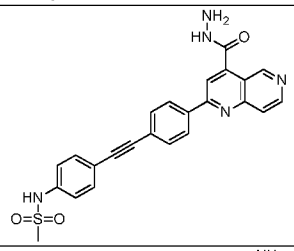
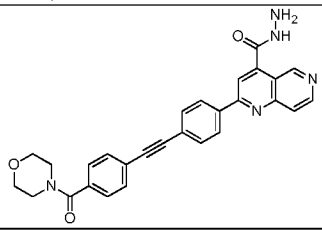
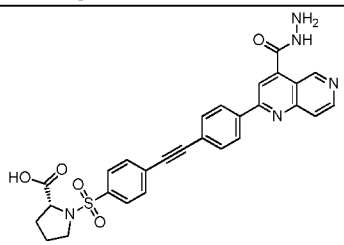
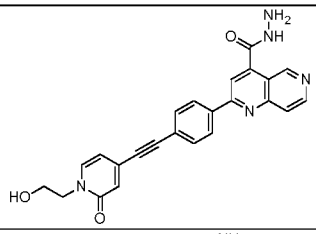
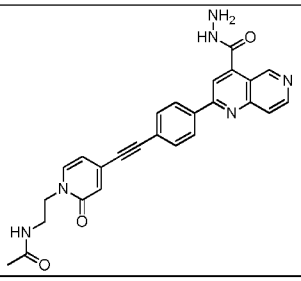
80	C	7.47	483		
81	F	4.07	512.0		
82	A	1.81	514.2		
83	A	2.10	499		
84	A	2.55	527		
85	A	1.33	400		
86	A	1.56	442		
87	A	1.89	454.3	R	

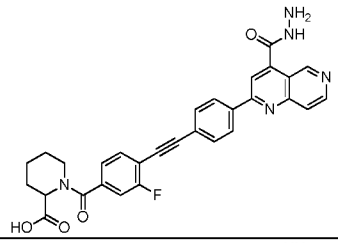
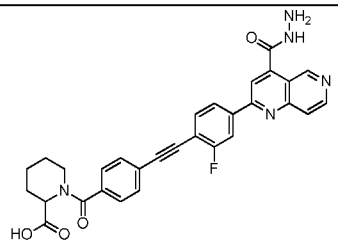
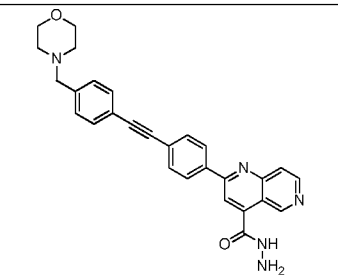
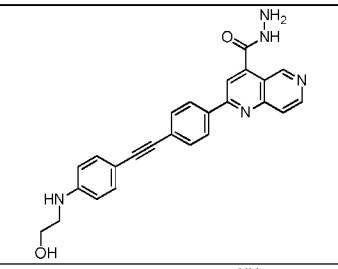
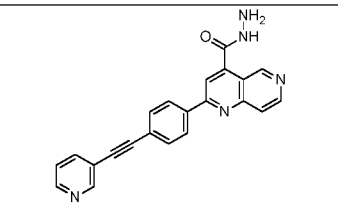
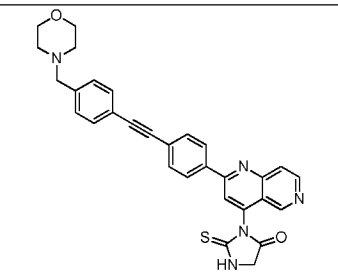
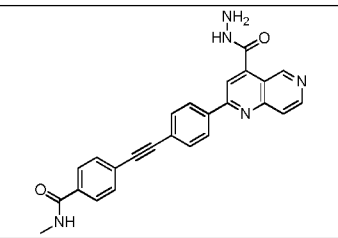
88	A	1.91	452.5 (M-1)	S	
89	A	1.61	468	Racemate	
90	A	1.44	468.4		
91	A	1.76	470.5		
92	A	1.84	484		
93	A	1.40	510		
94	A	1.85	506.3		

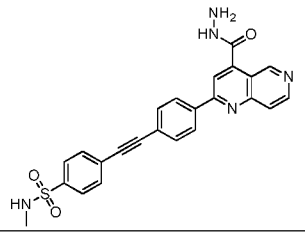
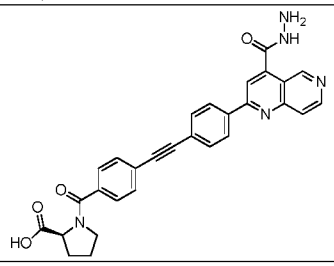
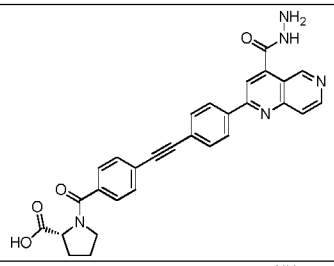
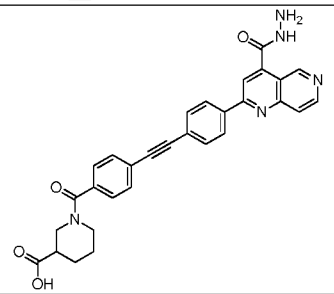
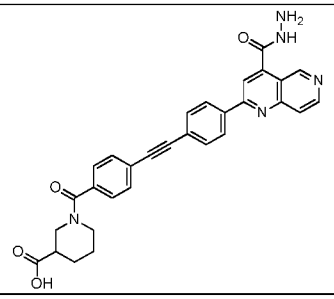
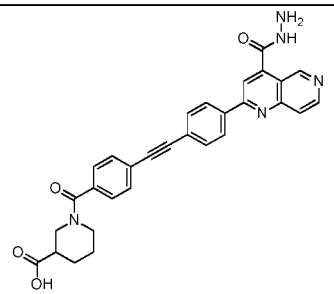
95	A	1.94	520.5		
96	A	2.25	544		
97	A	1.68	456.8		
98	A	1.32	496		
99	A	1.78	492.2		
100	A	1.88	506.5		

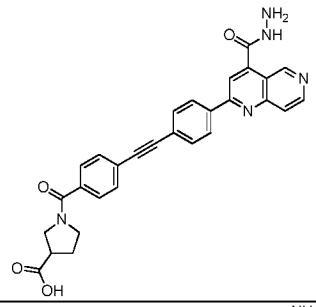
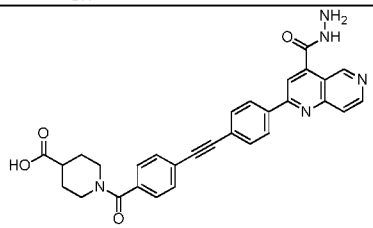
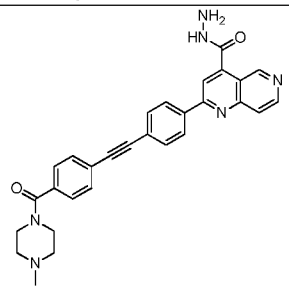
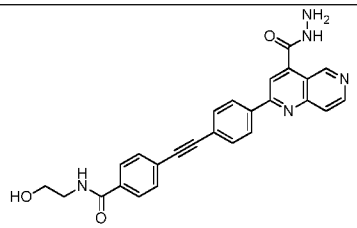
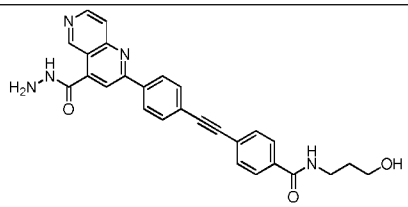
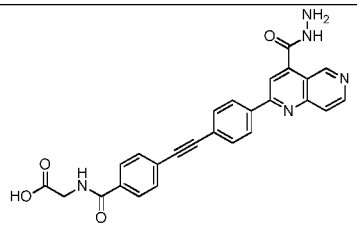
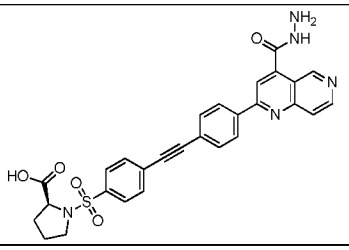
101	A	2.18	530.4 (M-1)		
102	A	1.48	371 (M-1)		
103	A	1.91	497.1	R	
104	A	1.68	512	R	
105	A	1.66	532	R	
106	A	1.54	454.4		
107	A	1.53	482	R	

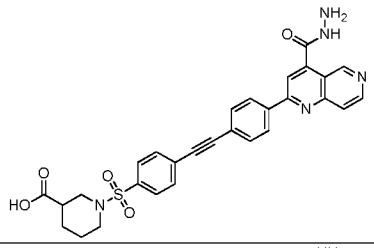
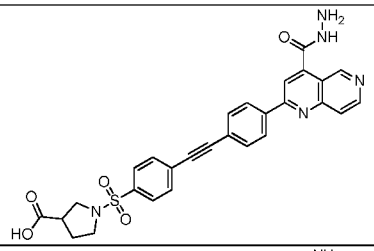
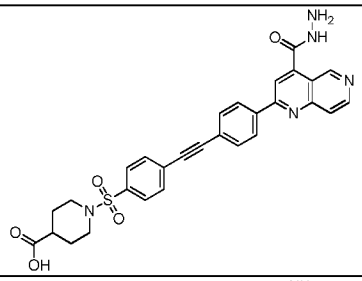
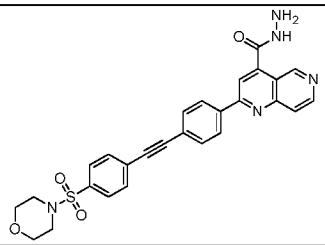
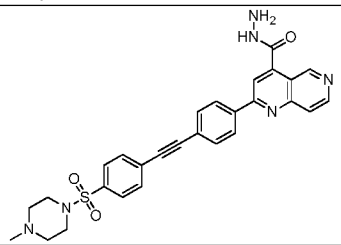
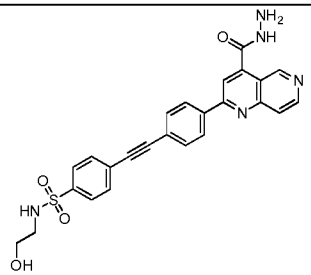
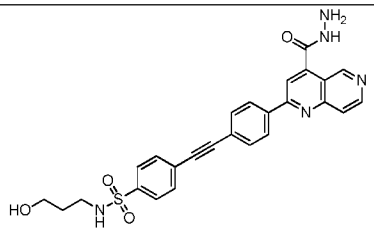
108	A	1.56	496	Racemate	
109	A	1.80	521.3		
110	A	1.78	488.3 (M-1)		
111	A	1.62	518	R	
112	A	1.78	532	Racemate	
113	A	1.69	465.7		
114	A	1.81	563.3	Racemate	

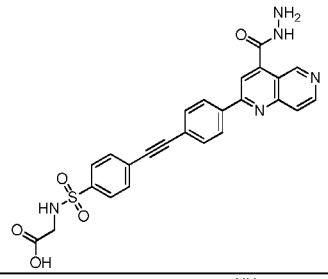
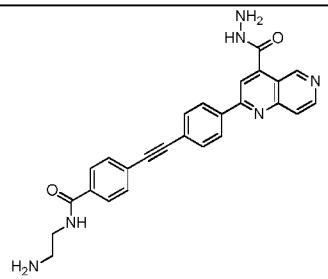
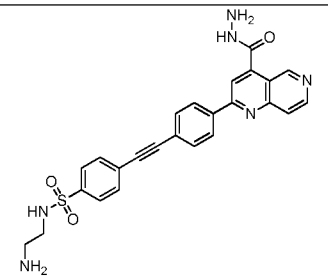
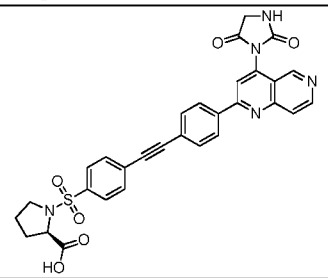
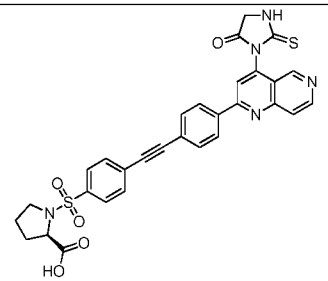
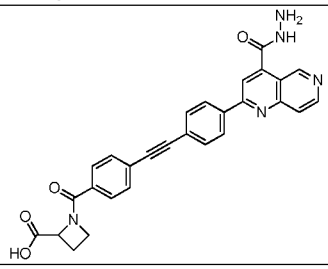
115	A	1.90	563.5	Racemate	
116	A	1.72	422		
117	A	1.77	458		
118	A	1.75	487		
119	A	1.85	542	R	
120	A	1.39	426		
121	A	1.38	467.4		

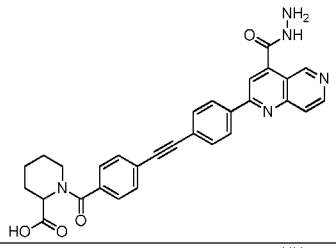
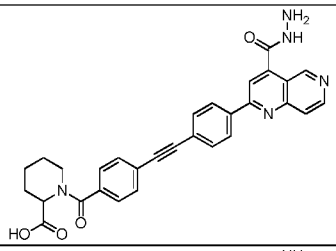
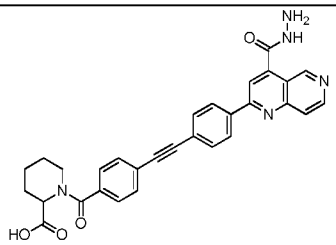
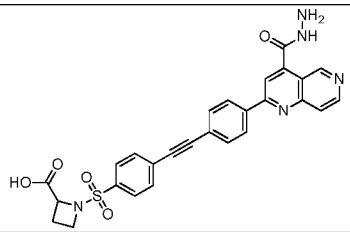
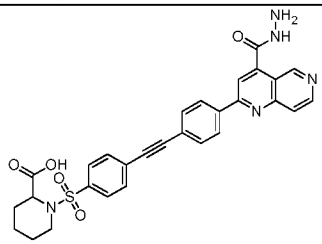
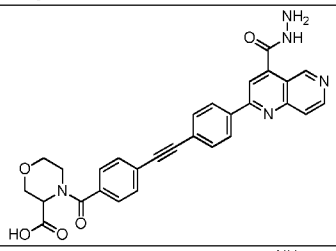
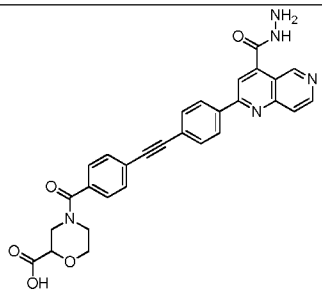
122	A	1.87	538.4	Racemate	
123	A	1.89	538.8	Racemate	
124	A	1.44	464.6		
125	A	1.66	424		
126	C	8.48	366.4		
127	C	11.21	520		
128	A	1.67	422		

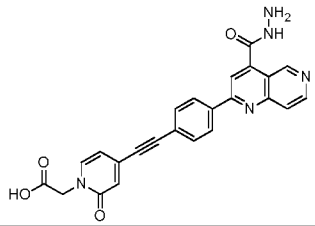
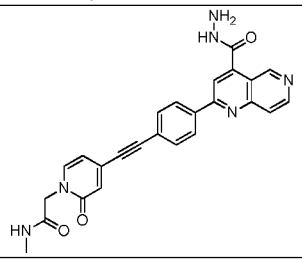
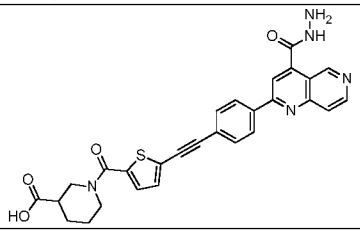
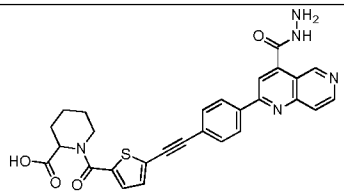
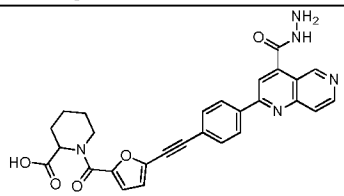
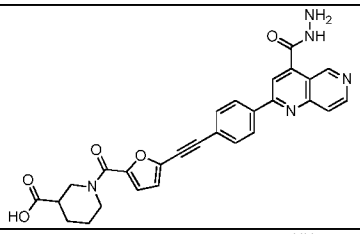
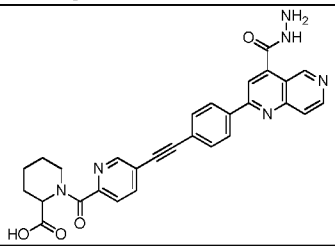
129	A	1.84	458		
130	A	1.77	506.4	S	
131	A	1.74	506.4	R	
132	A	1.82	520.5	Racemate	
133	A	1.73	520.6	(-)	
134	A	1.72	520.5	(+)	

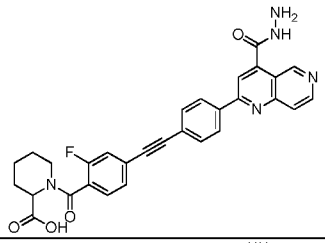
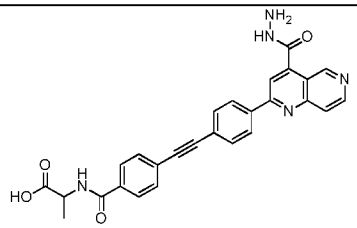
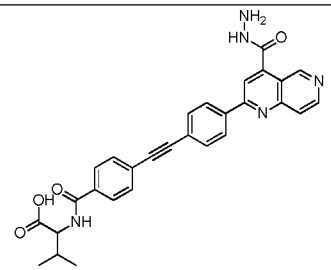
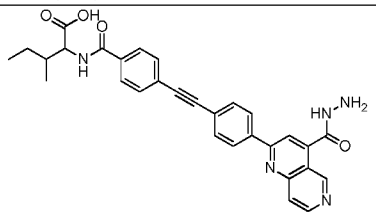
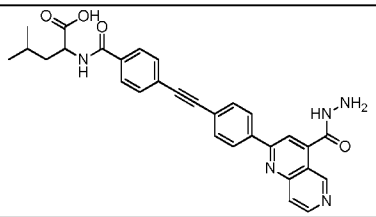
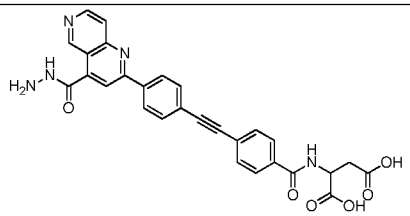
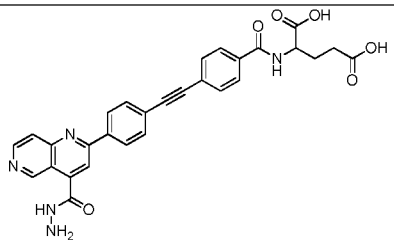
135	A	1.72	506	Racemate	
136	A	1.84	520		
137	A	1.42	491		
138	A	1.57	425		
139	A	1.61	466.4		
140	A	1.67	466		
141	A	1.87	542	S	

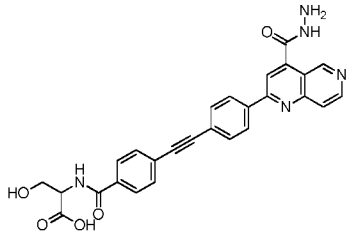
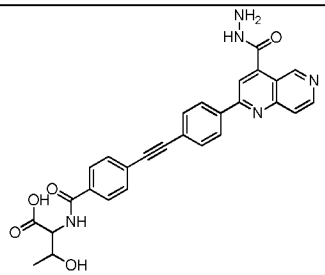
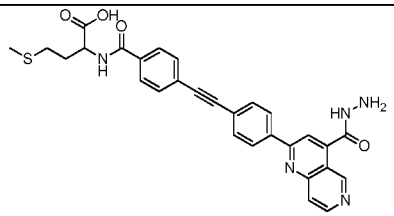
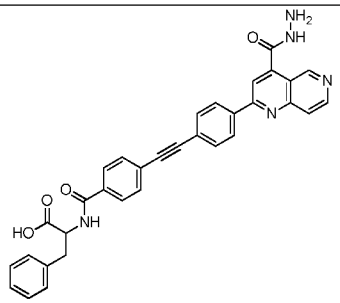
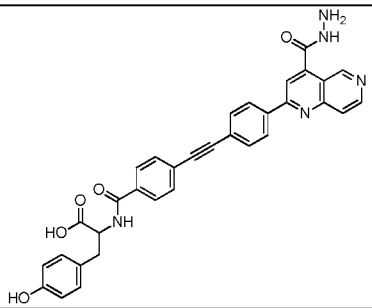
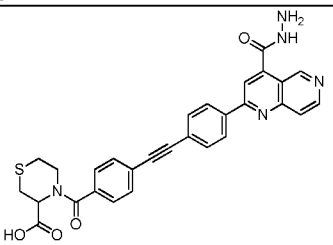
142	A	1.99	556	Racemate	
143	A	1.86	542.2	Racemate	
144	A	2.06	556.6		
145	A	2.02	514		
146	A	1.64	527.8		
147	A	1.70	486.6 (M-1)		
148	A	1.75	500.5 (M-1)		

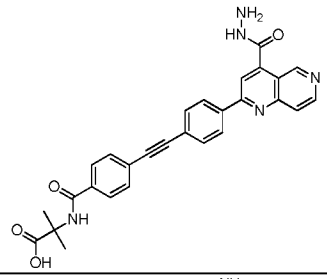
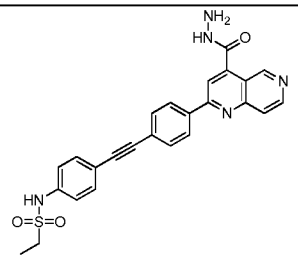
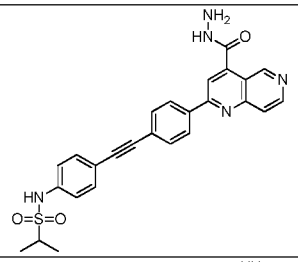
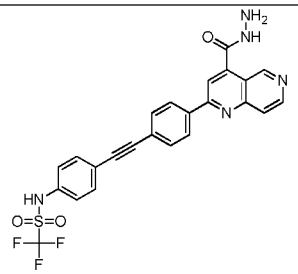
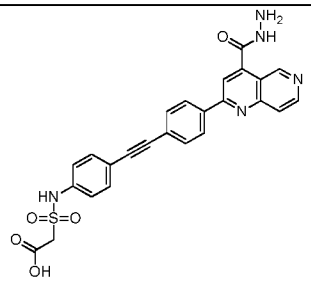
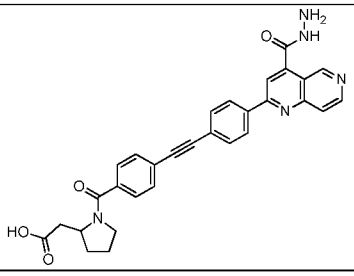
149	A	1.65	500.3		
150	A	1.59	451.4		
151	A	1.55	487		
152	A	2.08	581	R	
153	A	2.08	598.4	R	
154	A	1.69	492.5	Racemate	

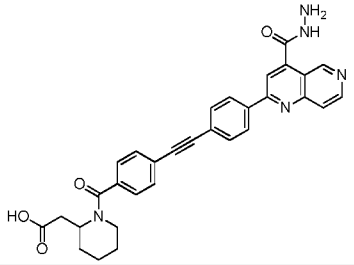
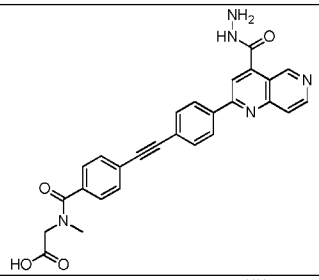
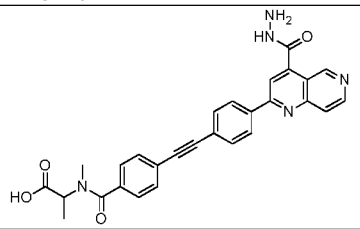
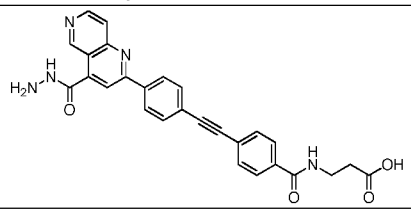
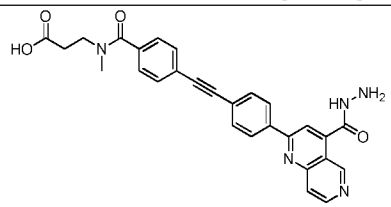
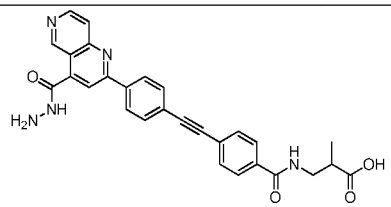
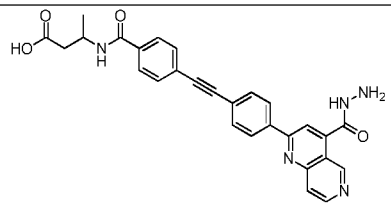
155	A	1.88	520.4	Racemate	
156	A	1.84	520.4	(-)	
157	A	1.83	518.4 (M-1)	(+)	
158	A	1.98	528.3	Racemate	
159	A	2.10	556	Racemate	
160	A	1.65	522.2	Racemate	
161	G	2.19	522	Racemate	

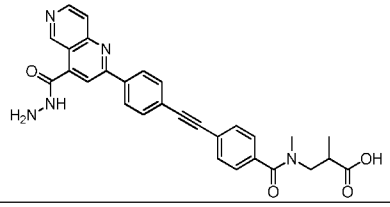
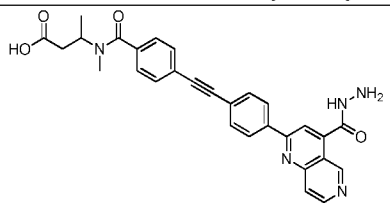
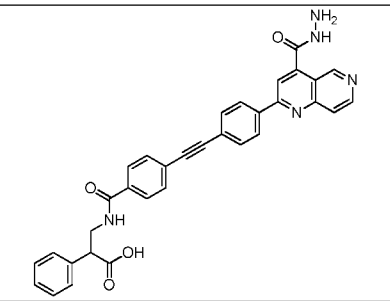
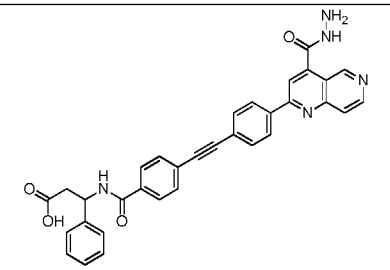
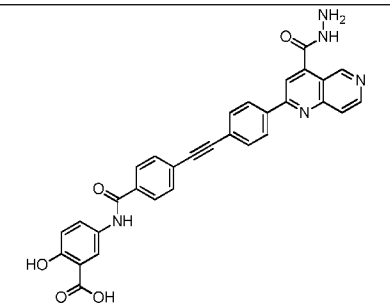
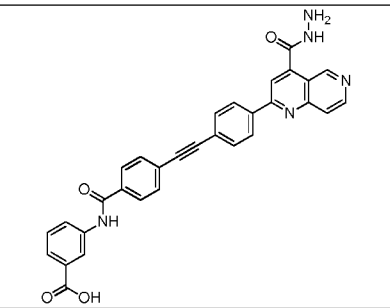
162	G	2.54	440.3		
163	A	1.45	453.2		
164	A	1.76	526	Racemate	
165	A	1.86	526.3	Racemate	
166	A	1.81	510.5	Racemate	
167	A	1.70	510	Racemate	
168	A	1.70	521	Racemate	

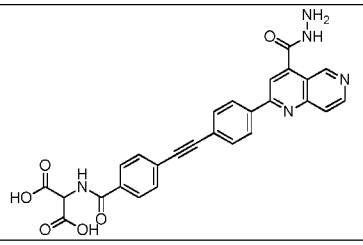
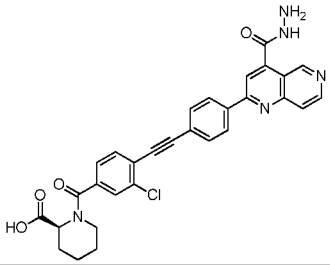
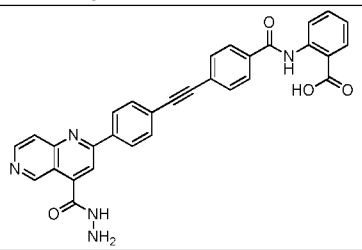
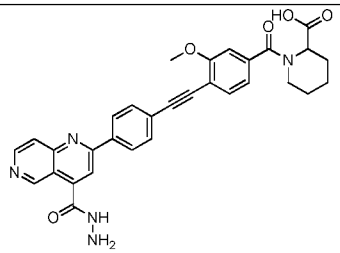
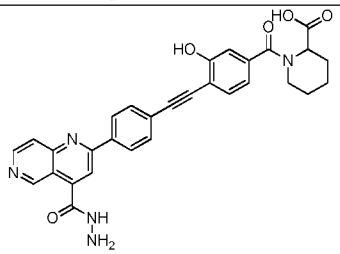
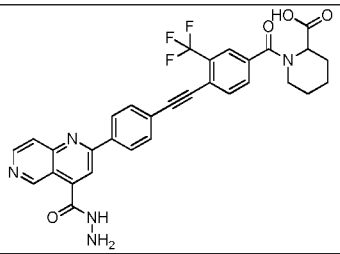
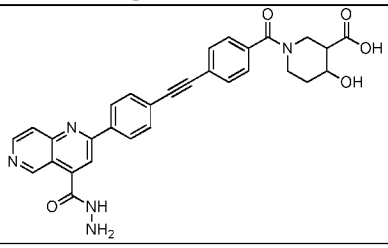
169	A	1.89	538.4	Racemate	
170	A	1.65	480.3	Racemate	
171	A	1.87	506.4	Racemate	
172	A	1.96	522.6	Racemate	
173	A	2.00	522.4	Racemate	
174	A	1.51	522.4	Racemate	
175	A	1.52	538	Racemate	

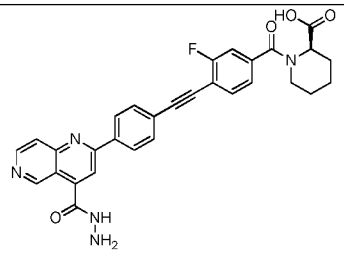
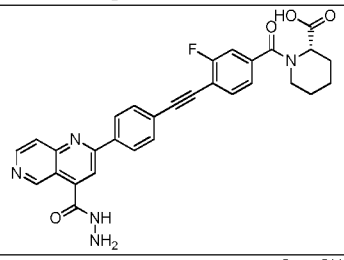
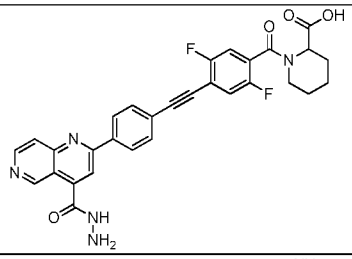
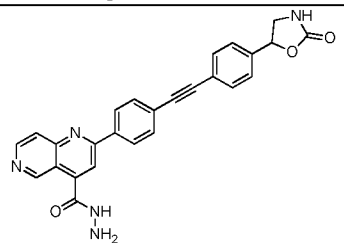
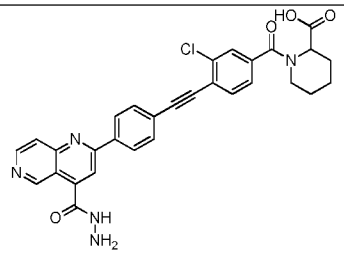
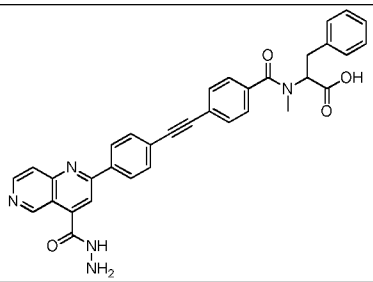
176	A	1.49	496.2	Racemate	
177	A	1.57	508.4	Racemate	
178	A	1.82	540	Racemate	
179	A	1.96	556.6	Racemate	
180	A	1.71	572	Racemate	
181	A	1.80	538.4	Racemate	

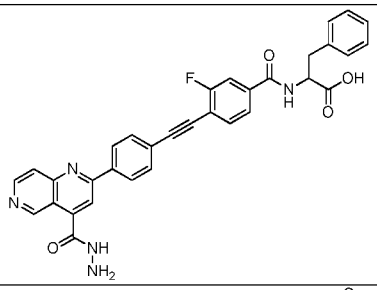
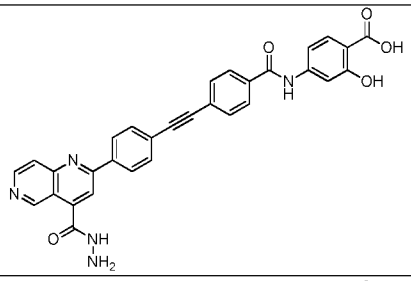
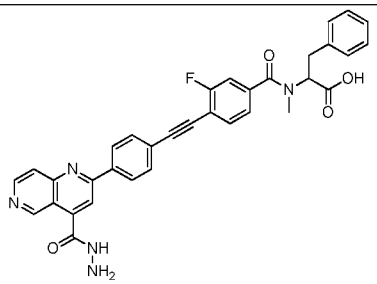
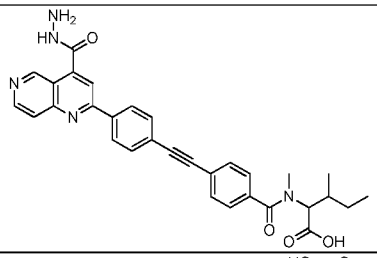
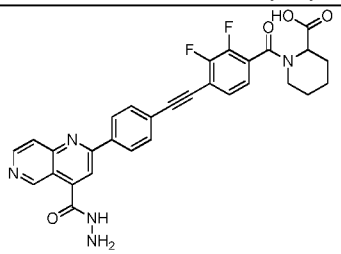
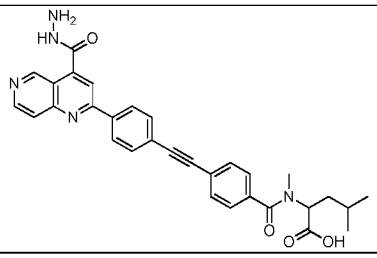
182	A	1.74	492.4		
183	A	1.84	470.4 (M-1)		
184	A	1.95	486.3		
185	A	2.18	512		
186	A	1.68	502.8		
187	A	1.74	520.4	Racemate	

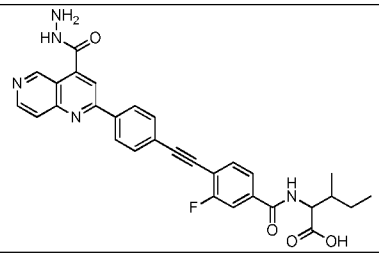
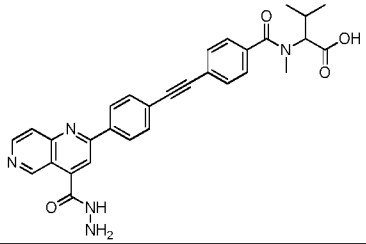
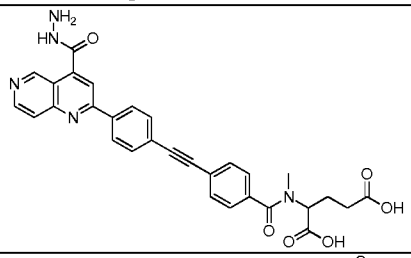
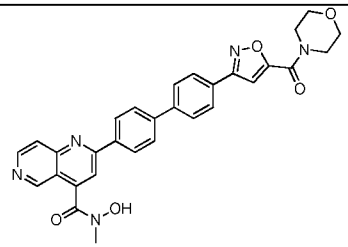
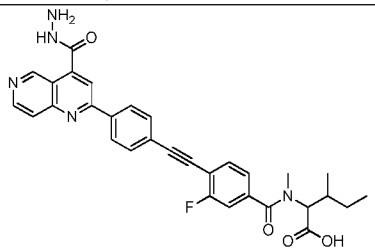
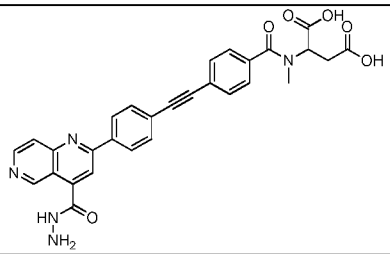
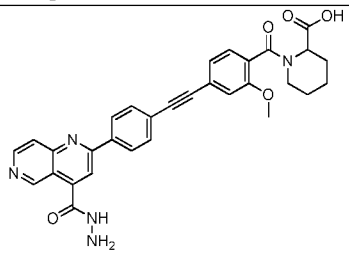
188	A	1.83	534.4	Racemate	
189	A	1.61	480.4		
190	A	1.70	494.7	Racemate	
191	A	1.59	480.4		
192	A	1.60	494.6		
193	A	1.67	494.4	Racemate	
194	A	1.65	494.4	Racemate	

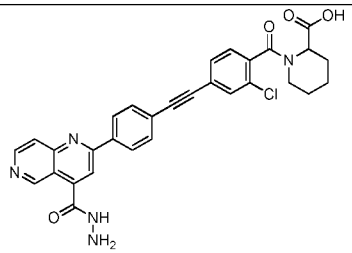
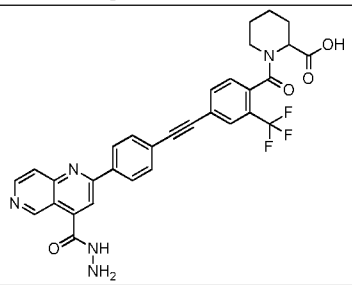
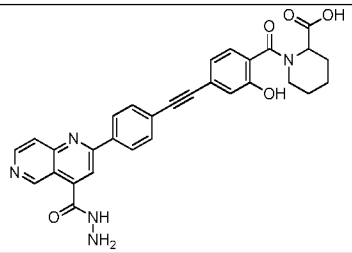
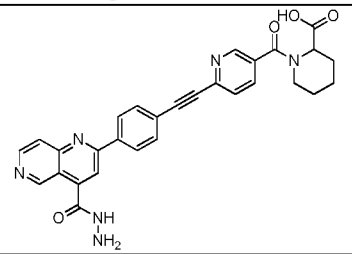
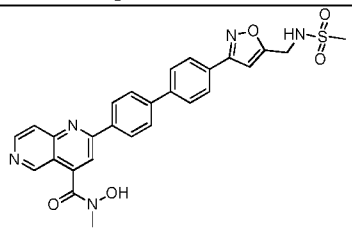
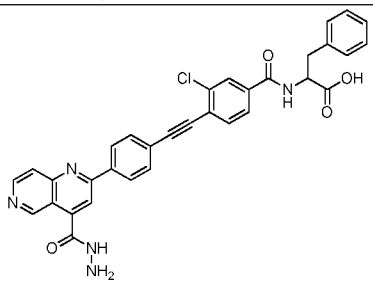
195	A	1.69	508.4	Racemate	
196	A	1.68	508.6	Racemate	
197	A	1.90	556.3	Racemate	
198	A	1.91	556.4	Racemate	
199	G	2.51	544.4		
200	F	2.88	528		

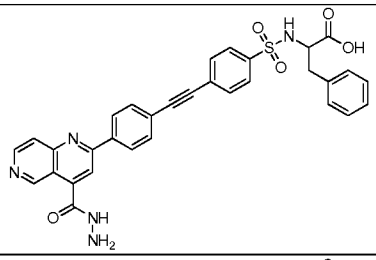
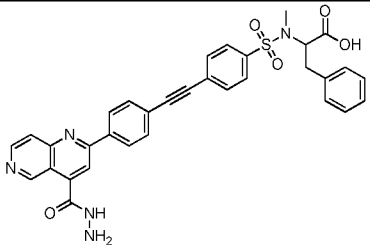
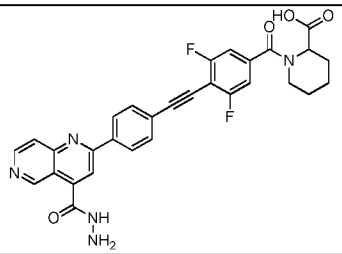
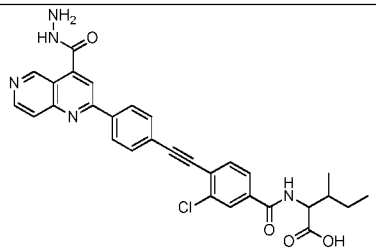
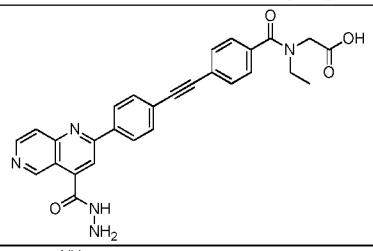
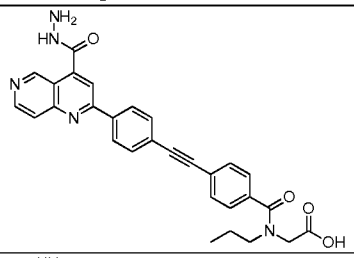
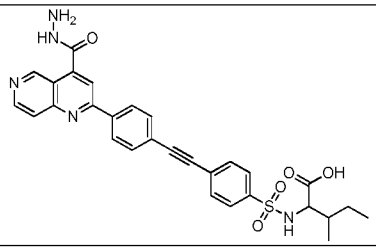
201	NA	NA	510		
202	A	1.93	554.5	S	
203	C	7.52	528.5		
204	C	6.91	548.4	Racemate	
205	C	6.85	536.4	Racemate	
206	G	2.65	588.8	Racemate	
207	A	1.53	536.6	Racemate	

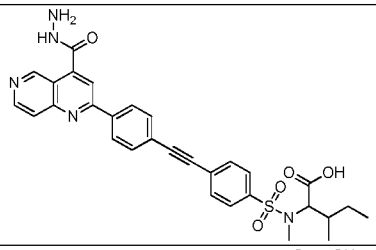
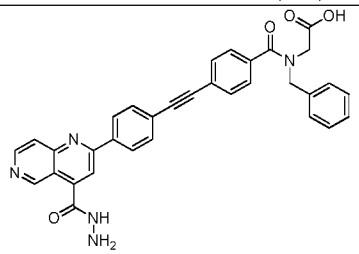
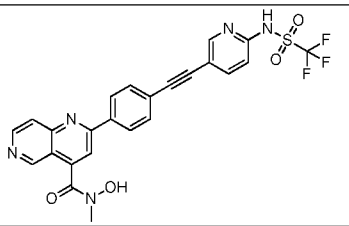
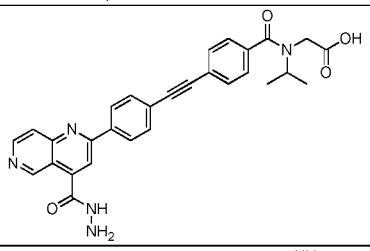
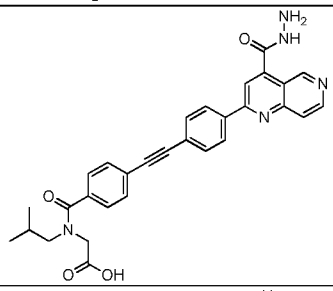
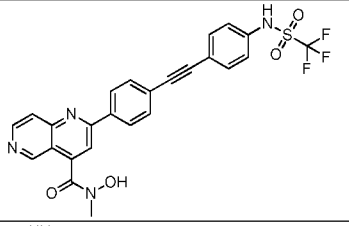
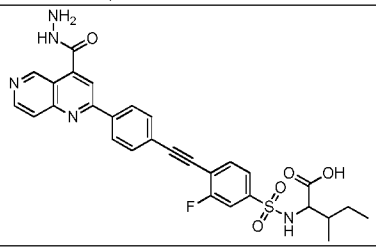
208	A	1.86	538.8	R	
209	A	1.85	538	S	
210	A	1.9	556.7	Racemate	
211	A	1.67	450.5	Racemate	
212	C	7.2	554.6	Racemate	
213	C	7.36	570.6	Racemate	

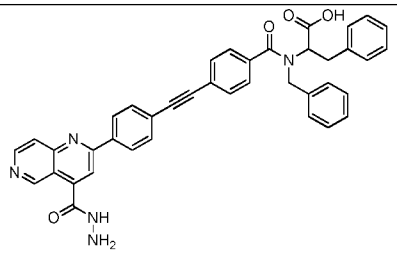
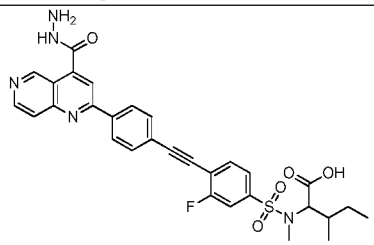
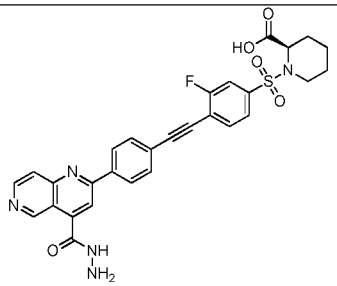
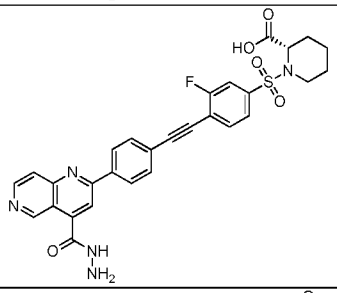
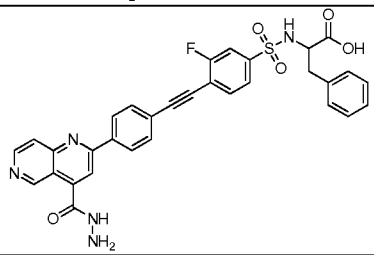
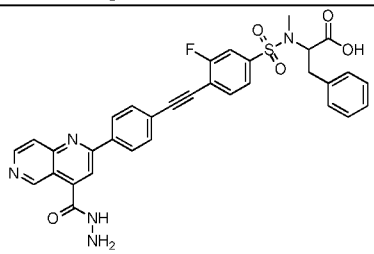
214	C	7.49	574.6	Racemate	
215	C	7.14	544		
216	A	2.01	588.6	Racemate	
217	A	1.99	536.5	Racemate	
218	A	1.96	556.6	Racemate	
219	A	1.98	536.6	Racemate	

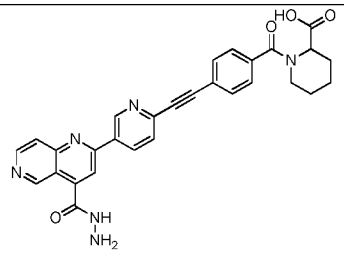
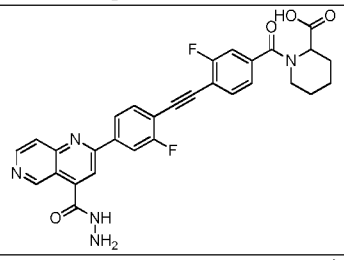
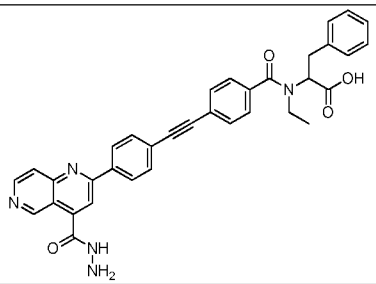
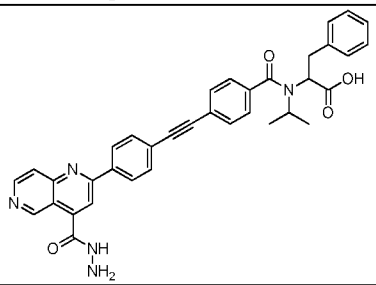
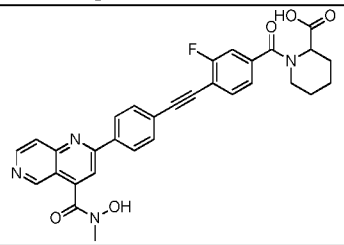
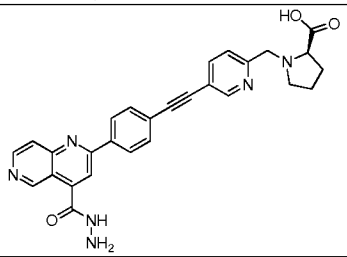
220	A	2.01	540.6	Racemate	
221	A	1.88	522.6	Racemate	
222	A	1.53	552.6		
223	A	1.92	536.5		
224	C	7.49	552.3 [M-1]	Racemate	
225	A	1.53	538.5	Racemate	
226	A	1.79	550	Racemate	

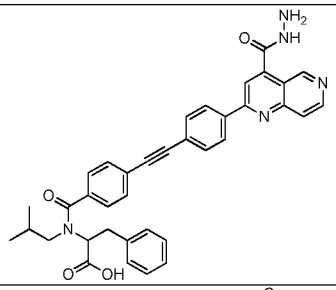
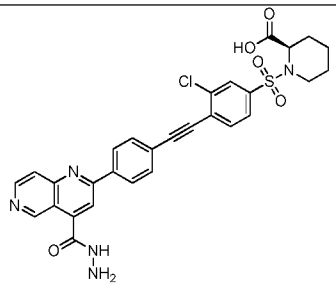
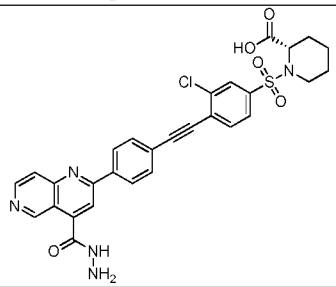
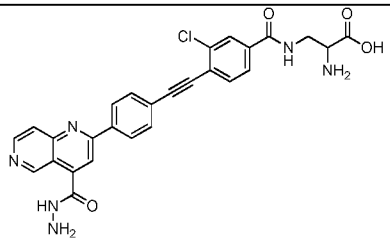
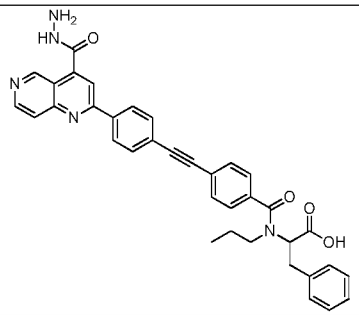
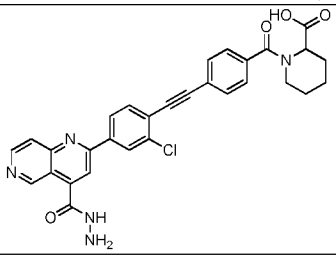
227	A	1.92	554.4	Racemate	
228	A	2.02	588	Racemate	
229	A	1.72	536.4	Racemate	
230	A	1.93	521.5	Racemate	
231	A	1.82	530.5		
232	A	2.04	590	Racemate	

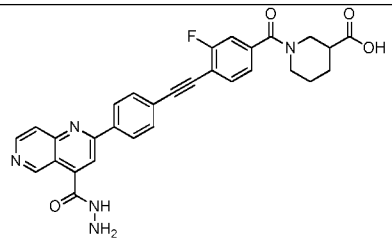
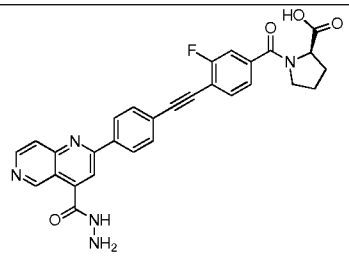
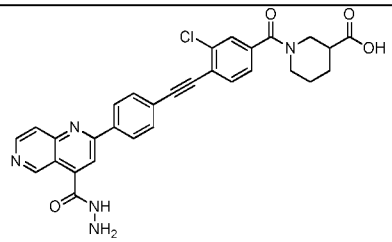
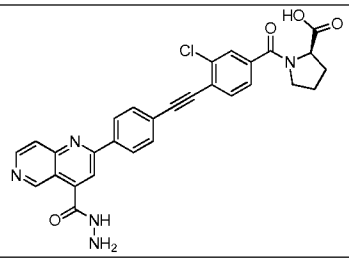
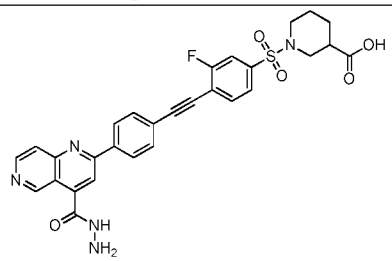
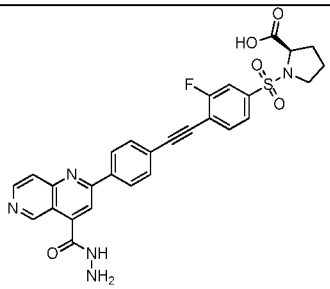
233	A	1.96	591	Racemate	
234	A	2.11	606	Racemate	
235	A	1.87	556	Racemate	
236	C	7.49	556.5	Racemate	
237	C	6.85	494.3		
238	C	6.98	508		
239	C	7.16	558.6	Racemate	

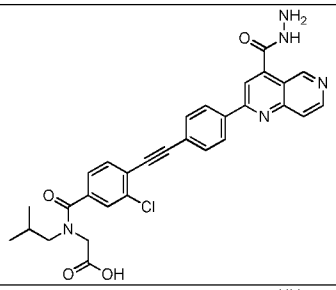
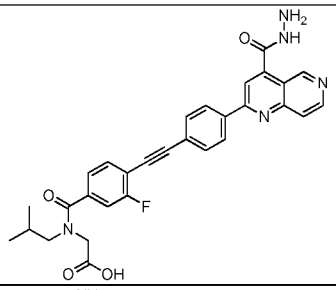
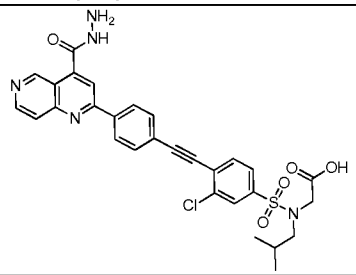
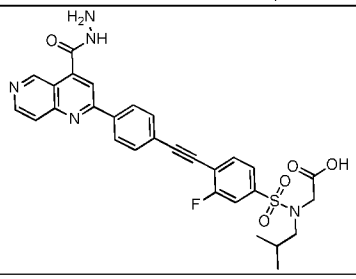
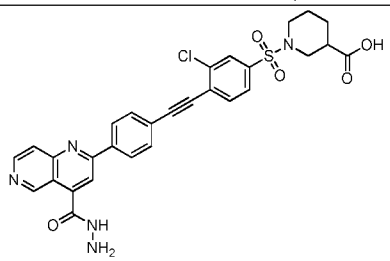
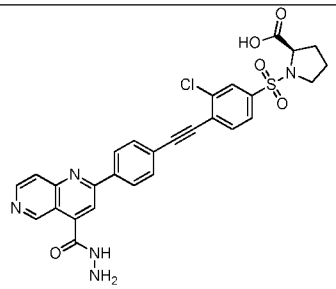
240	A	7.5	572.7	Racemate	
241	C	7.15	556.4		
242	NA	NA	528.4		
243	C	6.97	508		
244	C	7.15	522.6		
245	NA	NA	527.4		
246	C	7.37	576.5	Racemate	

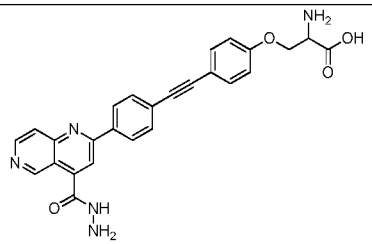
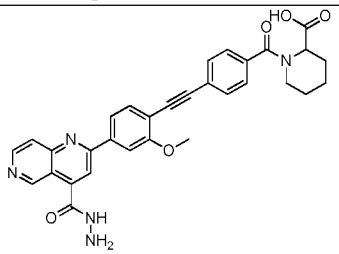
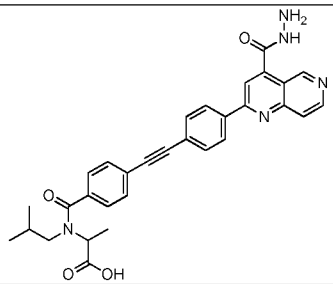
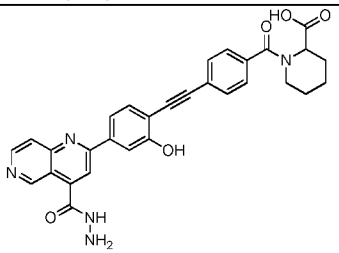
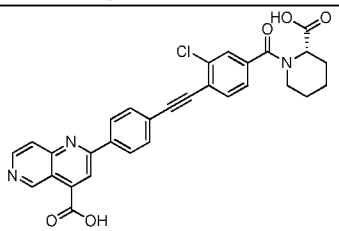
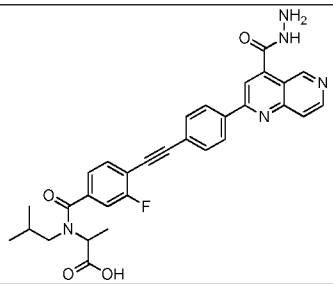
247	C	8.11	646.6	Racemate	
248	C	7.52	590.4	Racemate	
249	C	7.23	574.4	R	
250	C	7.42	574.3	S	
251	A	2	608.2 [M-1]	Racemate	
252	C	7.55	624.8	Racemate	

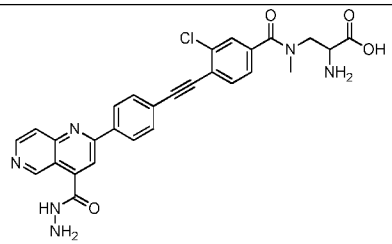
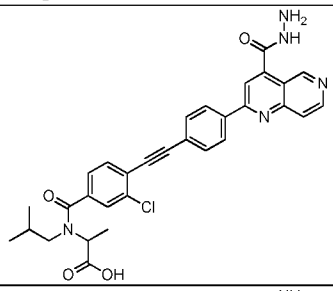
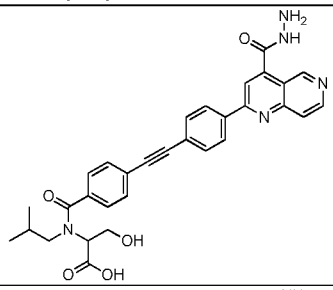
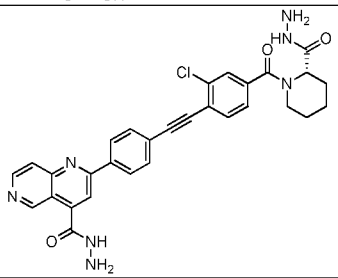
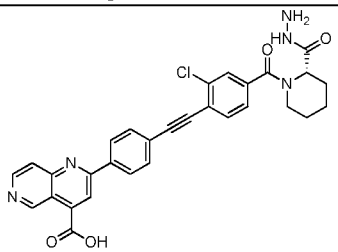
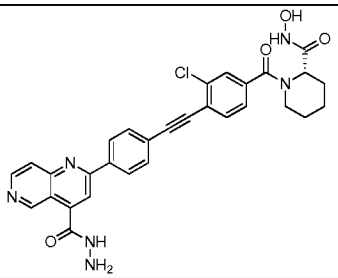
253	A	1.66	521.6	Racemate	
254	A	1.91	556.5	Racemate	
255	A	2.09	584.6	Racemate	
256	C	7.97	598.4	Racemate	
257	A	2.16	553.5	Racemate	
258	C	6.93	549.6	R	

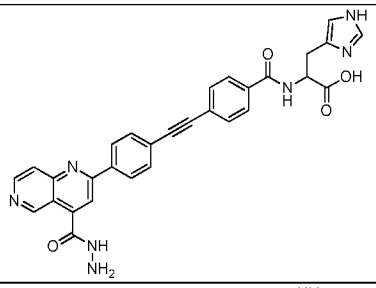
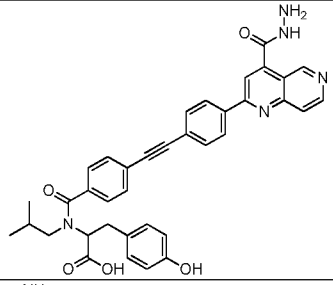
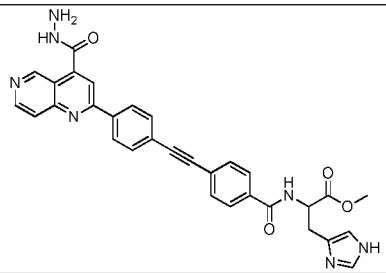
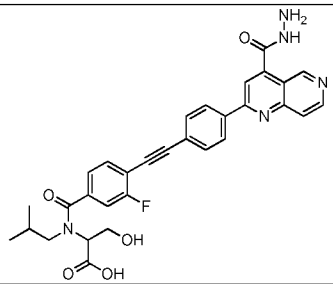
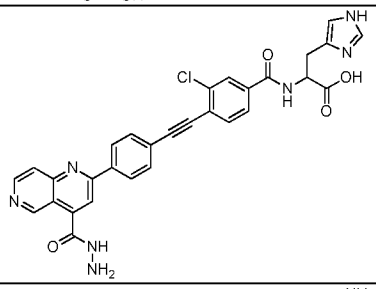
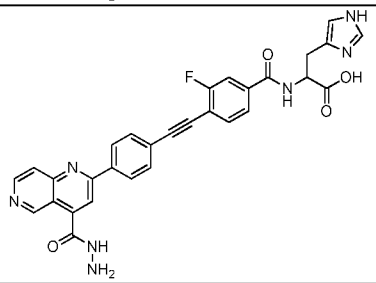
259	A	2.25	612.4	Racemate	
260	C	7.27	590.4	R	
261	C	7.26	590.5	S	
262	A	1.42	529.4	Racemate	
263	C	7.79	598.7	Racemate	
264	C	7.28	554.7	Racemate	

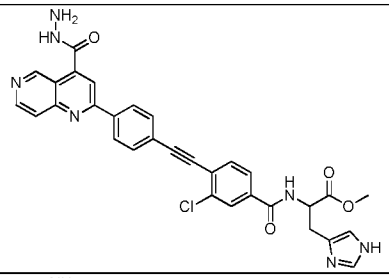
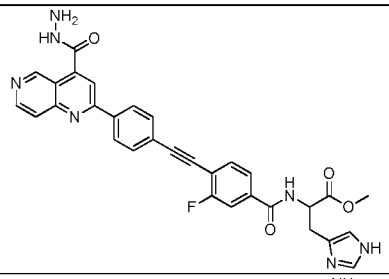
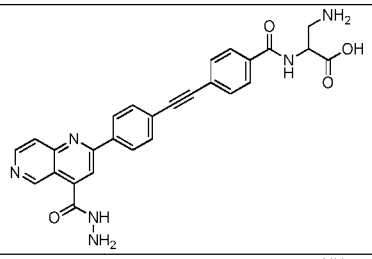
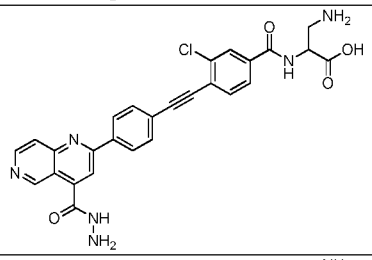
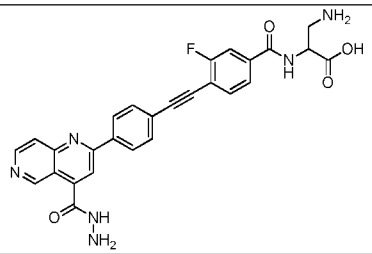
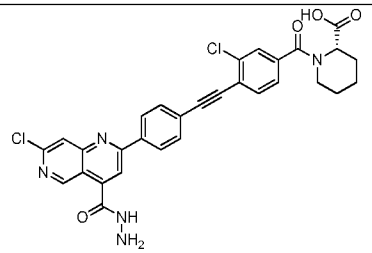
265	A	1.7	538.1	Racemate	
266	A	1.7	524.6	R	
267	C	7.16	554.5	Racemate	
268	A	6.94	540.5	R	
269	G	2.76	574.6	Racemate	
270	C	7.01	560.5	R	

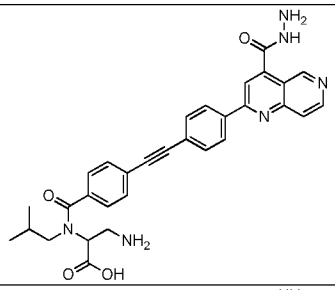
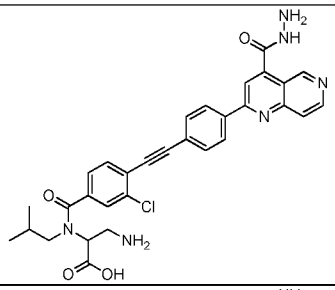
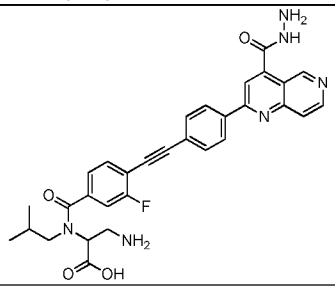
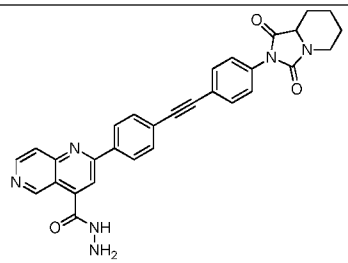
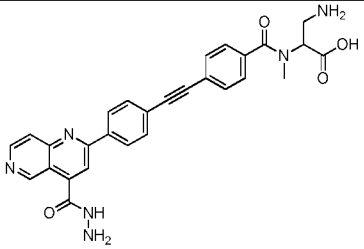
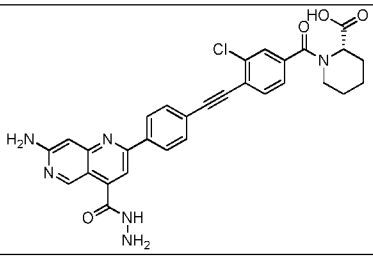
271	C	7.21	556.5		
272	C	7.09	540.6		
273	A	2.14	592.3		
274	A	2.08	576.3		
275	A	2.04	591.3	Racemate	
276	A	1.87	576.6	R	

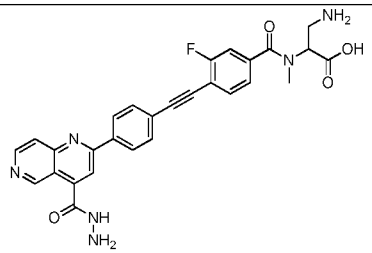
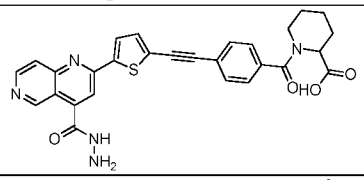
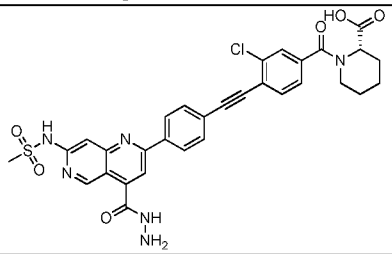
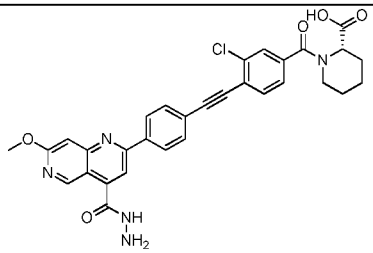
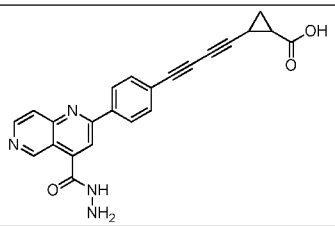
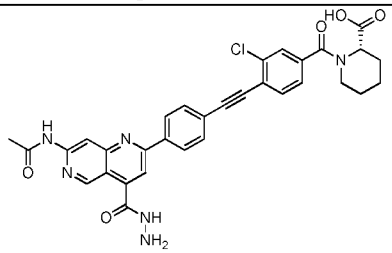
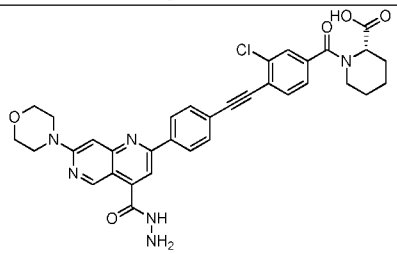
277	A	1.31	468.3	Racemate	
278	C	6.86	550.5	Racemate	
279	A	1.94	536.6	Racemate	
280	C	6.64	536.6	Racemate	
281	G	2.34	540.6	S	
282	A	1.93	554.6	Racemate	

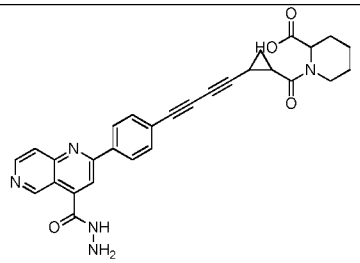
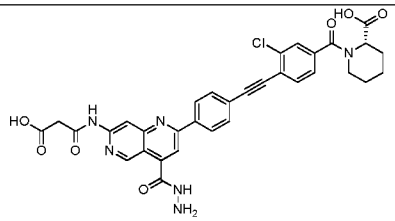
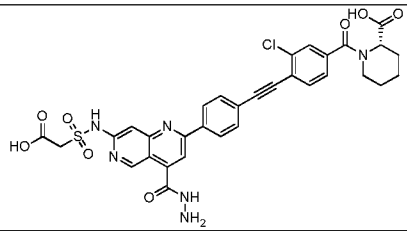
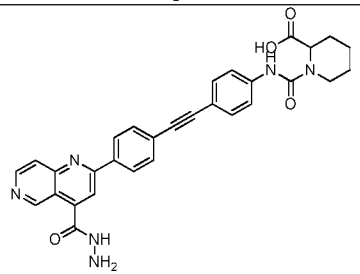
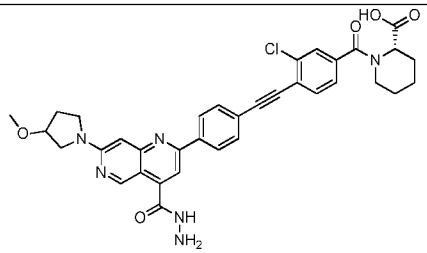
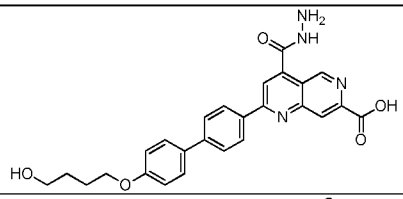
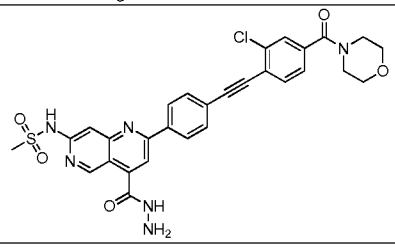
283	C	7.47	543.6	Racemate	
284	A	1.99	570.6	Racemate	
285	A	1.68	552.5	Racemate	
286	A	1.59	568.6	S	
287	A	1.69	554.6	S	
288	G	3.59	569.5	S	

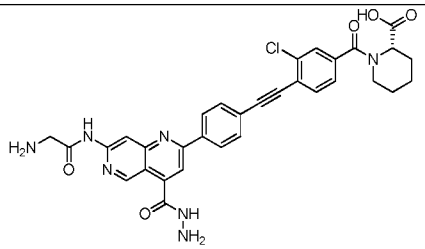
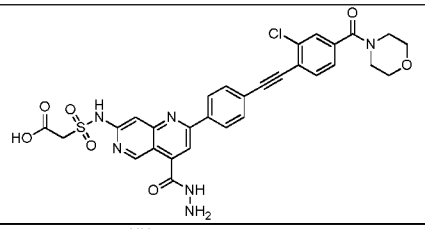
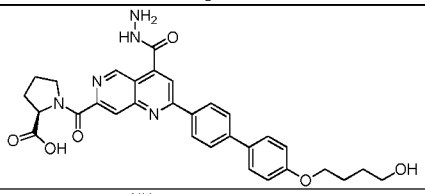
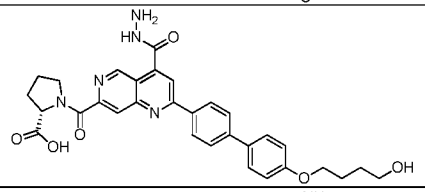
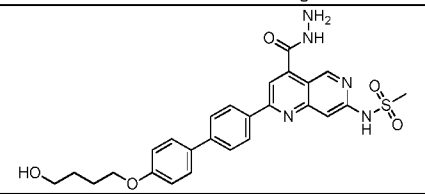
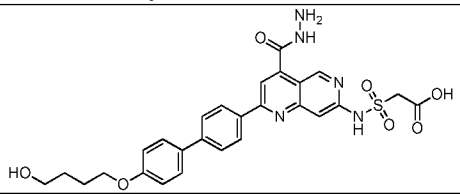
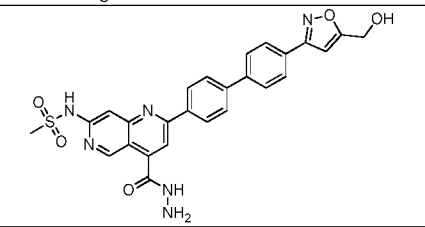
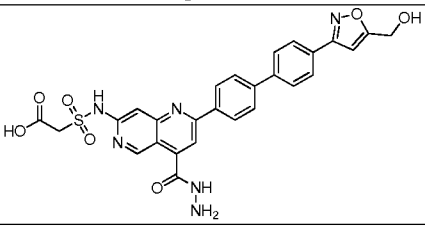
289	A	1.35	546.3	Racemate	
290	C	12.95	642.6	Racemate	
291	A	1.47	560.5	Racemate	
292	A	1.74	570.6	Racemate	
293	A	1.45	580.6	Racemate	
294	A	1.4	564.5	Racemate	

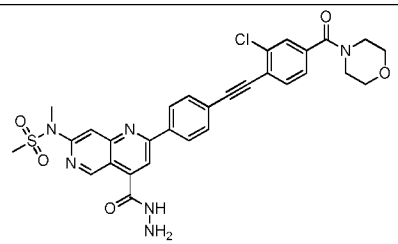
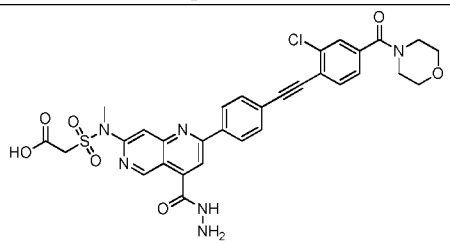
295	A	1.45	594.6	Racemate	
296	A	1.51	578.6	Racemate	
297	A	1.41	495.4	Racemate	
298	C	7.27	529.7	Racemate	
299	C	7.11		Racemate	
300	A	2.38	589.4	S	

301	A	1.53	551.8	Racemate	
302	G	2.7	585.6	Racemate	
303	A	1.55	569.8	Racemate	
304	A	1.89	517.5	Racemate	
305	G	2.51	509.6	Racemate	
306	A	1.79	569.6	S	

307	A	1.35	572.4	Racemate	
308	G	2.37	526.4	Racemate	
309	A	1.99	647.7	S	
310	C	7.35	584.8	S	
311	A	1.73	397.4	Racemate	
312	A	1.99	613.5	S	
313	F	3.31	639.7	S	

314	H	2.88	508.9	Racemate	
315	H	3.4	655.5	S	
316	I	8.31	691.5	S	
317	A	1.93	NA	Racemate	
318	C	7.19	653.7	S	
319	J	3.23	473.4		
320	C	8.3	605.3		

321	H	0.44	626.6	S	
322	I	8.19	649.4		
323	J	2.95	570.5	R	
324	NA	NA	568.4 [M-1]	S	
325	C	7.98	520.2 [M-1]		
326	I	7.9	566.7		
327	NA	NA	529.2 [M-1]		
328	J	3.01	575.5		

329	A	2.02	620.4		
330	A	1.9	663.5		

Example 331: Analytical Methods

Method A Specifications

Column: Aquity BEH C-18 (50x2.1 mm, 1.7 μ)

Mobile Phase: A) CH_3CN; B) 0.025% aq TFA

Flow Rate: 0.50 mL/min

Time (min)/%B: 0.01/90, 0.5/90, 3/10, 6/10

Method B Specifications:

Column: Eclipse XDB C-18 (150x4.6 mm, 5.0 μ)

Mobile Phase: A) CH_3CN; B) 5 millimolar (mM) acetic acid

Flow Rate: 1.0 mL/min

Time (min)/%B: 0.01/80, 2/80, 15/10, 15.01/stop

Method C Specifications:

Column: Eclipse XDB C-18 (150x4.6 mm, 5.0 μ)

Mobile Phase: A) CH_3CN; B) 5 mM ammonium acetate (NH_4OAc)

Flow Rate: 1.0 mL/min

Time (min)/%B: 0.01/80, 3/80, 10/10, 20/10

Method D Specifications:

Column: Eclipse XDB C-18 (150x4.6 mm, 5.0 μ)

Mobile Phase: A) CH_3CN; B) 5 mM ammonium formate

Flow Rate: 1.0 mL/min

Time (min)/%B: 0.01/80, 3/80, 10/10, 20/10

Method E Specifications:

Column: Zorbax SB C-18 (250x4.6 mm, 5 μ)

Mobile Phase: A) CH_3CN; B) 0.1% aq HClO4

Flow Rate: 1.00 mL/min

Time (min)/%B: 0.01/90, 5/90, 15/10, 25/10

Method F Specifications:

Column: XBridge C-18 (50x3.0 mm, 3.5 μ)

Mobile Phase: A) 0.1% aq TFA; B) CH_3CN

Flow Rate: 0.8 mL/min

Time (min)/%B: 0.01/10, 0.5/10, 4/90, 8/90

Method G Specifications:

Column: XBridge C-18 (50x3.0 mm, 3.5 μ)

Mobile Phase: A) 5.0mM NH4OAc; B) CH_3CN

Flow Rate: 0.8 mL/min

Time (min)/%B: 0.01/10, 0.5/10, 4/90, 8/90

Method H Specifications:

Column: XSelect C-18 (50x3.0 mm, 3.5 μ)

Mobile Phase: A) 5.0mM NH4OAc; B) CH_3CN

Flow Rate: 0.8 mL/min

Time (min)/%B: 0.01/10, 0.5/10, 4/90, 8/90

Method I Specifications:

Column: Eclipse XDB C-18 (150x4.6 mm, 5.0 μ)

Mobile Phase: A) CH_3CN; B) 0.05% aq TFA

Flow Rate: 1.0 mL/min

Time (min)/%B: 0.01/80, 3/80, 10/10, 20/10

Method J Specifications:

Column: XSelect CSH C-18 (50x3.0 mm, 3.5 μ)

Mobile Phase: A) 5.0mM NH4OAc; B) CH_3CN

Flow Rate: 0.8 mL/min

Time (min)/%B: 0.01/10, 0.5/10, 4/90, 8/90

EXAMPLE 332: Antibacterial activity

A. Minimum Inhibitory Concentration (MIC)

Minimum Inhibitory Concentrations (MICs) were determined for *Escherichia coli* (American Type Culture Collection (ATCC) 25922) and *Pseudomonas aeruginosa* (ATCC 27853) in accordance with the Clinical and Laboratory Standards Institute (CLSI). Serial, one-half dilutions of compounds were prepared in 96-well dilution blocks in cation-adjusted Mueller-Hinton Broth (MBH) +2% DMSO and transferred to 96-well assay plates in duplicate. Cell suspensions of *E. coli* and *P. aeruginosa* were prepared in MHB and added to each well at concentrations of approximately $1.2x10^6$ and $3.3x10^6$ colony-forming-units per milliliter (cfu/mL), respectively. The inoculated plates were incubated at 35±1°C for 18±2 h. At the completion of incubation the wells of each plate were evaluated visually for the presence of growth. The MIC was the concentration which completely inhibited growth (per CLSI, M2-A7). In addition to visual evaluation, optical densities were determined using a Tecan Infinite M200 microplate reader measuring absorbance at 600 nm. Example 202 exhibited an MIC of 128 μg/mL for *Pseudomonas aeruginosa* (ATCC 27853).

EXAMPLE 333: Metalloenzyme activity

A. Inhibition of LpxC Enzyme

Test compounds were dissolved in 100% DMSO @ 10mM. Then a series of dilutions were done with 100% DMSO, these were the first intermediate dilutions. Individual 100% DMSO dilutions were diluted independently to another intermediate dilution using assay buffer (bringing the DMSO concentration to 5%). Finally, 10μl of all these 5% intermediate dilutions were used directly in the 50μl reaction, making the final DMSO testing concentration at 1%. The enzymatic reactions were conducted in duplicate at room temperature for 1 hour in a 50μL mixture containing MMP-2 assay buffer, 1μM Mca-PLGLDpaAR, 10 uL MPP-2 enzyme (1.8ng) and 10μL of a test compound. All the reactions were conducted using 10μl MMP-2 assay buffer in place of enzyme, to detect just the background fluorescence from the compound. After enzymatic reactions, fluorescence intensity was measured at an excitation of 328 nm and an emission of 393 nm using a Tecan Infinite M1000™ microplate reader.

Results

Example	LpxC IC50*
31	0.004
35	0.002
83	0.004
101	0.006
115	0.008
172	0.018
185	0.005
202	0.002
309	0.002
327	0.005
328	0.002
BB-78485	0.020

* IC50s are in uM; LpxC enzyme is pseudomonas construct.

Select compounds of the invention exhibit growth arrest of *P. aeruginosa* and/or *E. coli*.

Incorporation by Reference

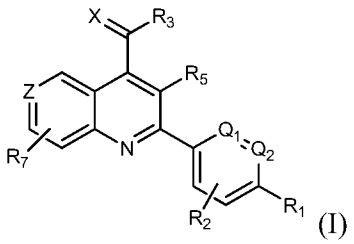
The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference.

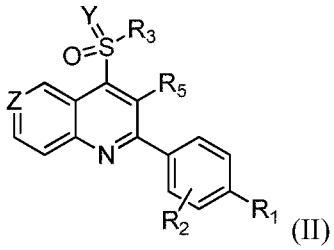
Equivalents

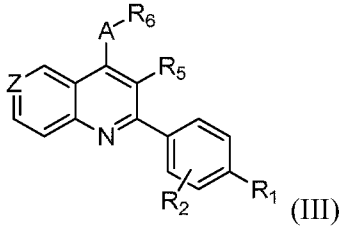
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended with be encompassed by the following claims.

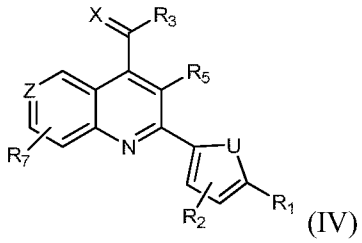
The claims defining the invention are as follows:

1. A compound of formula (I), (II), (III), (IV), or salt or N-oxide thereof, wherein:


(I)


(II)

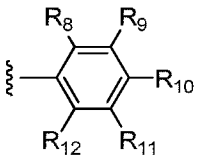

(III)


(IV)

U is O or S;

each X is independently O; S; NR_4; or H and R_4;

each R_1 is independently selected from:


a) ; b) heteroaryl optionally substituted with alkoxy wherein alkoxy is optionally substituted with 1, 2, or 3 OR_4; c) C≡C-R_{13}; d) C(=O)NR_4R_7; e) N(R_7)C(=O)R_4; f) $SO_2NR_4R_7$; g) N(R_7)SO_2R_4; i) hydroxy; j) optionally substituted alkoxy; k) SO_2NHR_4; l) optionally substituted alkenyl; m) optionally substituted arylalkyl; or n) C≡C-C≡C-R_{13};

each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) H; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent heterocycloalkoxy, heterocycloalkylcarbonyl, hydroxy, amino, $NHSO_2R_4$, $NHC(=O)R_4$, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) SO_2NHR_{18}; f) $NHSO_2R_4$; g) $NHC(=O)R_4$; h) $C(=O)NHR_4$; i) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; j) heteroaryl containing 5 to 6 ring atoms optionally substituted with 1, 2, or 3 independent:

(1) $C(=O)OR_{17}$;

(2) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

(3) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$; or

(4) $C(=O)NHR_4$;

k) cyano; l) hydroxy; m) SO_2R_4; n) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; o) heterocycloalkylsulfonyl optionally substituted with 1, 2, or, 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; p)  ; q) mercapto; r) thioalkoxy; s) alkylamino; t) alkyl optionally substituted with 1, 2, or 3 independent heterocycloalkylcarbonyl, heterocycloalkyl, or heterocycloalkylsulfonyl, each optionally substituted with independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; u) dialkylamino; or v) $–O-(CH_2)_n-C(=O)$-heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

R_2 is H, alkyl, fluoroalkyl, alkoxy, fluoroalkoxy, halogen, aryl, or heteroaryl;

R_3 is $CH(R_4)NHR_4$, $CH(R_4)NHSO_2R_4$, $CH(R_4)SH$, $CH(R_4)OH$, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NHNHR_4$, $C\equiv N$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $N(OH)C(=O)R_4$, $NHNHR_4$, $NHC(=O)R_4$, $N(R_4)NHC(=O)R_4$, $NHC(=O)NHR_4$, $NHC(=S)NHR_4$, $NHSO_2R_4$, $NHSO_2NHR_4$; $NHNHSO_2R_4$, NO_2, SO_2NHR_4 (only in the case of formula I), SO_2NHOH (only in the case of formula I), SO_3H (only in the case of formula I), OSO_2R_4, OSO_2NHR_4, SR_4, $B(OR_4)_2$, $CH_2B(OR_4)_2$, $P(=O)OH$, $P(=O)_2OH$, $Se(=O)OH$, $Se(=O)_2OH$, a heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms, or a 5-membered heterocycle that is connected through a CH_2;

Y is O or null;

Z is N;

each R_4 is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_{27}$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; e) optionally substituted heteroaryl; or f) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{27}$, $C(=O)NR_{27}R_{27}$, or $SO_2NR_{27}R_{27}$;

each R_5 is independently H, alkyl, fluoroalkyl, halogen, alkoxy, fluoroalkoxy, substituted amino, aryl, or heteroaryl;

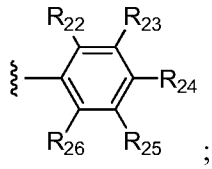
A is O, S, CH_2 or $N(R_4)$;

A may also be the following when R_6 is null: an optionally substituted heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms, $B(OR_4)_2$, P(=O)OH, $P(=O)_2OH$, Se(=O)OH, $Se(=O)_2OH$;

R_6 is null, $CH(R_4)CO_2R_4$, $CH(R_4)CONHR_4$; $CH(R_4)CONHOH$; $CH(R_4)CONHNHR_4$; $C(=O)R_4$, CO_2R_4, $C(=O)NHR_4$, $C(=O)NR_4OH$, $C(=O)NHNHR_4$, $C(=S)NHR_4$, $C(=S)NR_4OH$, $C(=S)NHNHR_4$, C≡N, $C(=NH)NH_2$, SO_2NHNR_4 (with the proviso that A cannot be S), SO_2NHR_4 (with the proviso that A cannot be S), SO_2NHOH (with the proviso that A cannot be S); a heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms, or a (preferably 5-membered) heterocycle that is connected through a CH_2; and

each R_7 is independently H; alkyl; alkoxy; hydroxy; $C(=O)OR_4$; $NHSO_2R_4$; $N(alkyl)SO_2R_4$; NHR_4; $NHC(=O)R_4$; $N(alkyl)C(=O)R_4$; $C(=O)NR_{27}R_4$; $SO_2NR_{27}R_4$; $C(=O)NR_{27}NHR_4$; $C(=O)NR_{27}OR_4$; halogen; optionally substituted aryl; optionally substituted heteroaryl; heterocycloalkyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$; or heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$;

each R_{13} is independently selected from:

a) 

;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$;

c) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) $NR_{27}SO_2R_4$, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, 4) (heterocycloalkyl)alkyl; or 5) $NR_{27}C(=O)R_4$; or

d) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, hydroxyalkyl, or $SO_2NR_4R_7$;

each R_{14} is independently selected from heterocycloalkylcarbonyl, heterocycloalkylsulfonyl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

each R_{15} is independently H; alkyl; fluoroalkyl; aryl; arylalkyl; or heteroaryl;

each R_{16} is independently hydrogen; alkyl; alkoxy; hydroxy; NHR_4; $NHC(=O)R_4$; halogen; optionally substituted aryl; optionally substituted heteroaryl; heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or $NHSO_2R_4$;

each R_{17} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{18} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{19} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{20} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, optionally substituted heteroaryl, or optionally substituted aryl; c) fluoroalkyl; d) aryl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$ or OR_4; or e) heteroaryl;

each R_{21} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) aryl; or e) heteroaryl;

each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from

i) hydrogen; ii) $NHC(=O)R_4$; iii) $NHSO_2R_4$; iv) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent alkyl, $CH_2C(=O)OR_{19}$, $CH_2C(=O)NR_4R_7$, OR_4, $CH_2SO_2NR_4R_7$, $C(=O)OR_{19}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; v) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or alkyl; vi) halogen; vii) alkyl optionally substituted with heterocycloalkyl wherein heterocycloalkyl is optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; viii) hydroxyalkylamino; ix) $C(=O)NR_{15}R_{20}$; x) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, halogen, $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, amino, alkylthio, or optionally substituted aryl; xi) haloalkoxy; xii) haloalkyl; xiii)

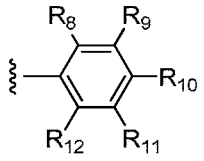
hydroxy; xiv) $SO_2NR_4R_{21}$; or xv) heterocycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, $SO_2NR_4R_7$, or $CH_2C(=O)OR_4$;

each R_{27} is independently a) H; b) alkyl optionally substituted with 1, 2, or 3 independent hydroxy, halogen, amino, alkylthio, or optionally substituted aryl; c) fluoroalkyl; d) optionally substituted aryl; or e) optionally substituted heteroaryl;

each n is independently 0, 1, 2, 3, or 4; and

Q_1 and Q_2 are each independently CH or N;

wherein "substituted" in all instances refers to alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, halogen, haloalkyl, cyano, nitro, alkoxy, aryloxy, hydroxyl, hydroxylalkyl, oxo (i.e., carbonyl), carboxyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, heteroaryloxy, heteroaryloxycarbonyl, thio, mercapto, mercaptoalkyl, arylsulfonyl, amino, aminoalkyl, dialkylamino, hydroxyalkylamino, alkylcarbonylamino, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino, arylamino, diarylamino, alkylcarbonyl, or arylamino-substituted aryl; arylalkylamino, aralkylaminocarbonyl, amido, alkylaminosulfonyl, arylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, imino, carboxamido, carbamido, carbamyl, thioureido, thiocyanato, sulfoamido, sulfonylalkyl, sulfonylaryl, mercaptoalkoxy, N-hydroxyamidinyl, or N'-aryl, N''-hydroxyamidinyl.



2. A compound according to claim 1 or salt or N-oxide thereof, wherein R_1 is and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

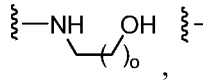
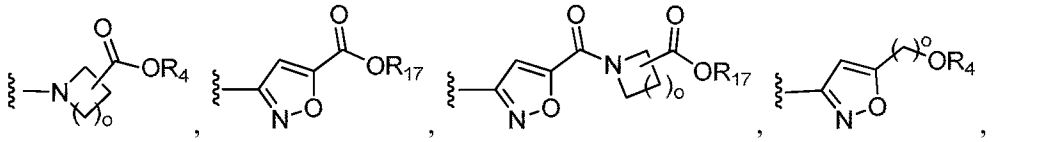
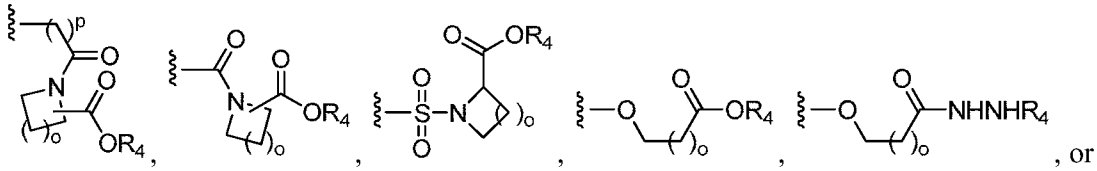
a) hydrogen; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; f) heteroaryl optionally substituted with 1, 2, or 3 independent:

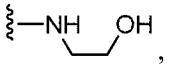
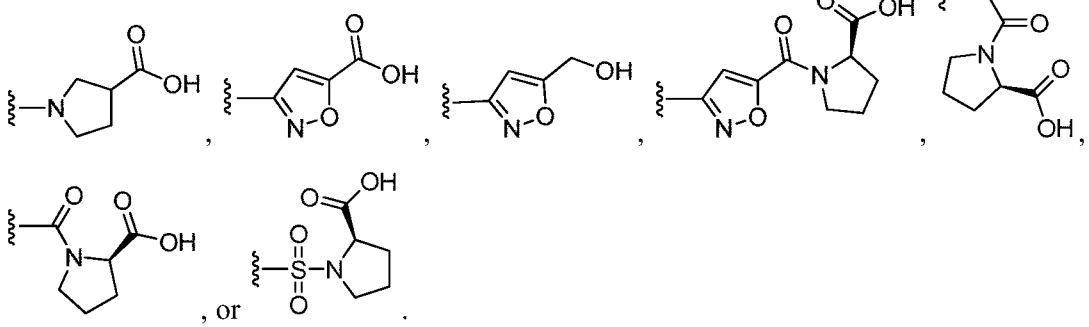
i) $C(=O)OR_{17}$; or

ii) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or

iii) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$;

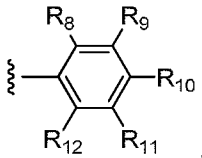
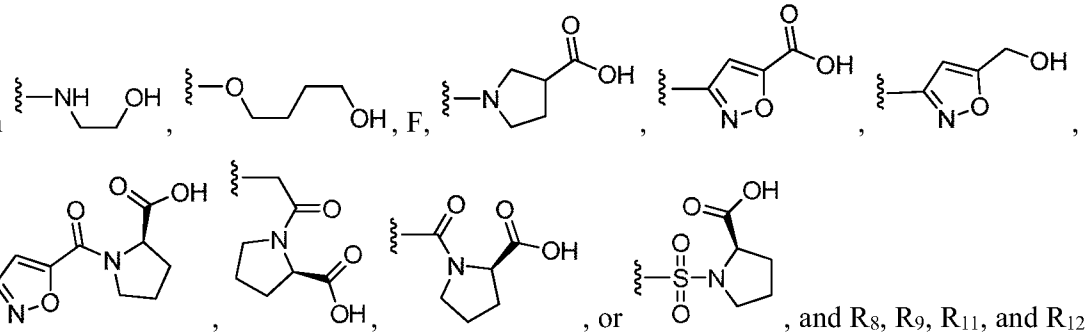
g) alkyl optionally substituted with 1, 2, or 3 heterocycloalkylcarbonyl substituted with $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; h) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or i) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

3. A compound according to claim 2 or salt or N-oxide thereof, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from halogen, hydrogen,  ,  ,  ; each o is independently 1, 2, 3, or 4; and each p is independently 1, 2, 3, or 4.

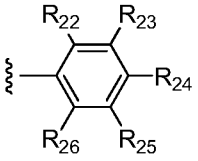
4. A compound according to claim 3 or salt or N-oxide thereof, wherein each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from hydrogen,  ,  .

5. A compound according to formulae (I) or (IV) in claim 1 or salt or N-oxide thereof, wherein X is O and R_3 is selected from $NHNHR_4$, $NHNHSO_2R_4$, $C(=O)NR_4OH$, or $C(=O)OR_4$.

6. A compound according to claim 5 or salt or N-oxide thereof, wherein R_3 is $NHNH_2$.

7. The compound of claim 6, wherein R_3 is $NHNH_2$, R_1 is  , R_{10} is selected from  , and R_8, R_9, R_{11}, and R_{12} are each H.

8. A compound according to claim 1 or salt or N-oxide thereof, wherein R_1 is $C\equiv C\text{-}R_{13}$ and R_{13} is independently selected from:

a)  ;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

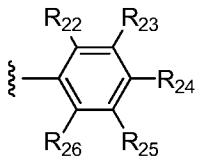
iii) $C(=O)OR_4$; or

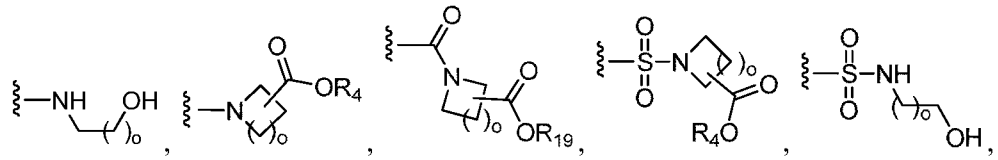
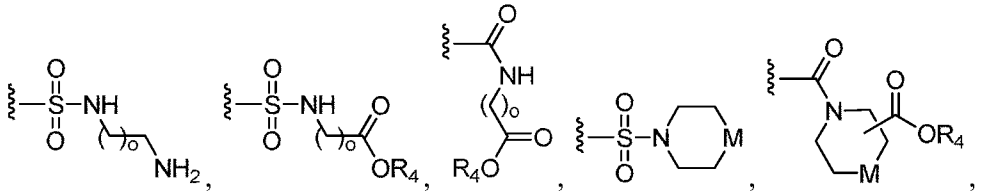
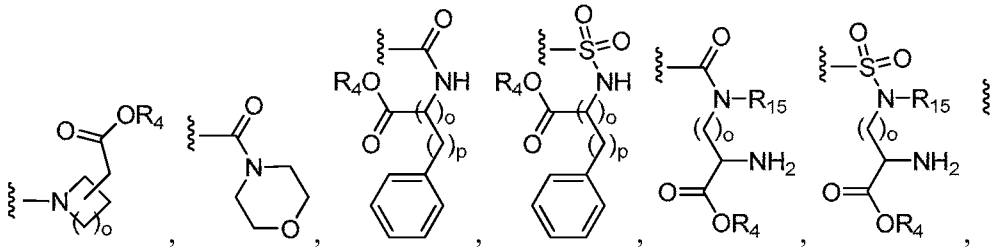
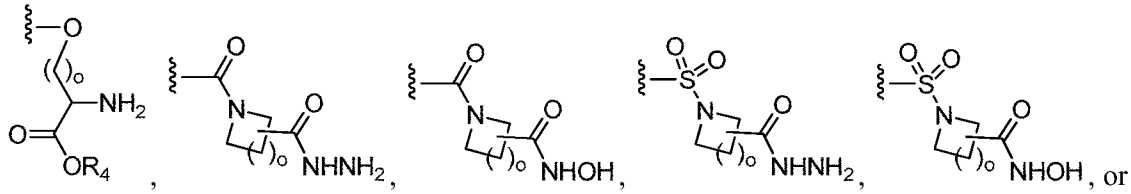
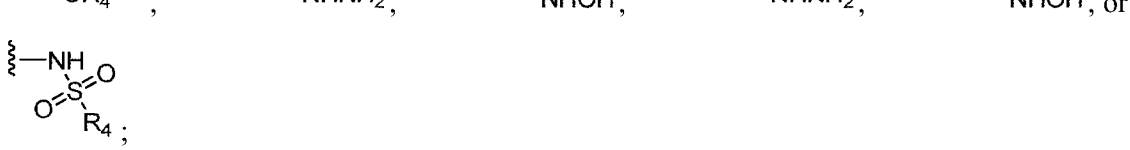
iv) $C(=O)NHR_4$;

c) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) NH_2SO_4, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or 4) (heterocycloalkyl)alkyl; or

d) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

9. A compound according to claim 8 or salt or N-oxide thereof, wherein R_{13} is

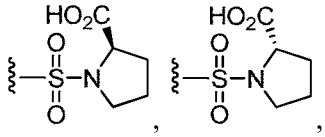


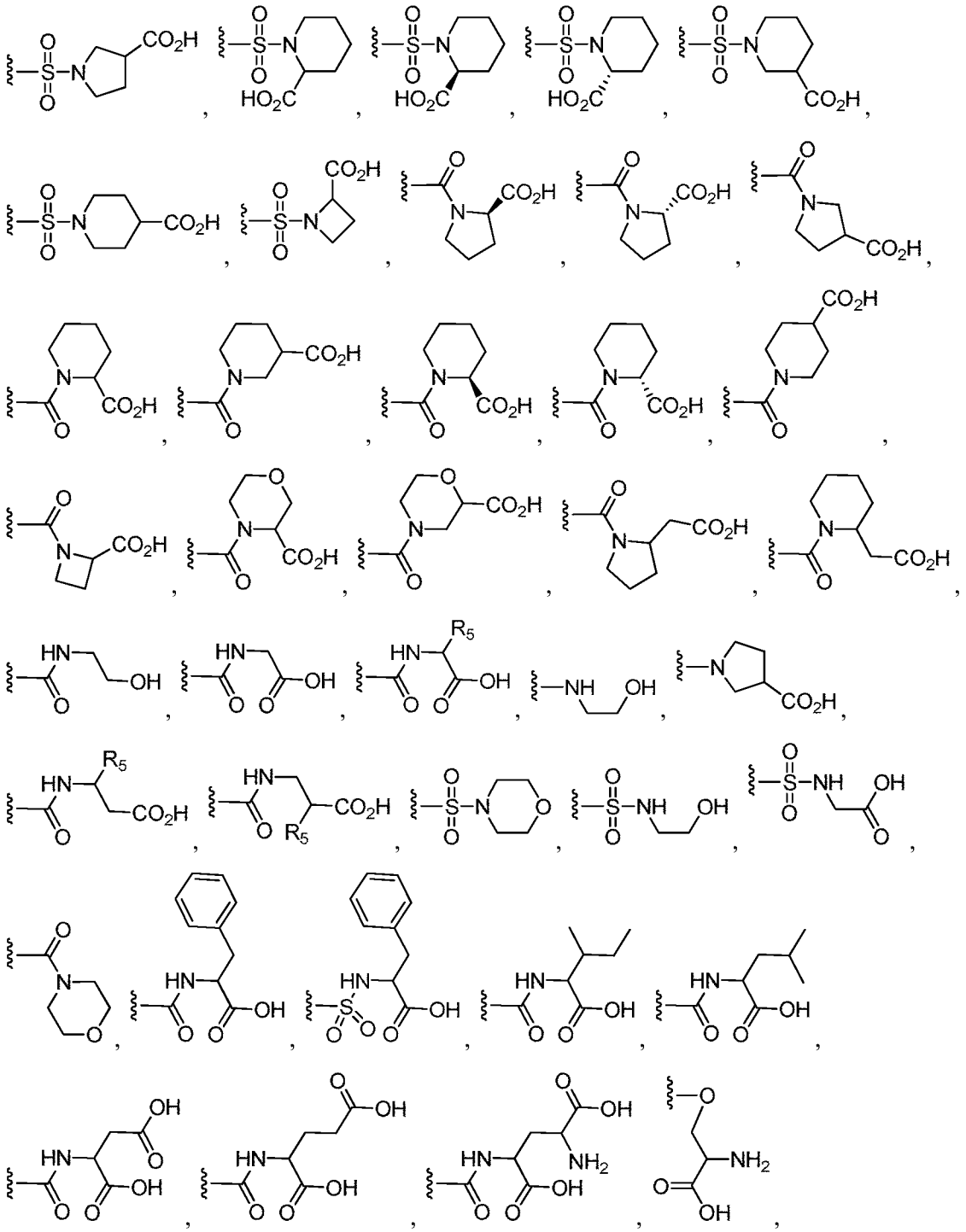
and each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from halogen, hydrogen,  ,  ,  ,  ,  ;

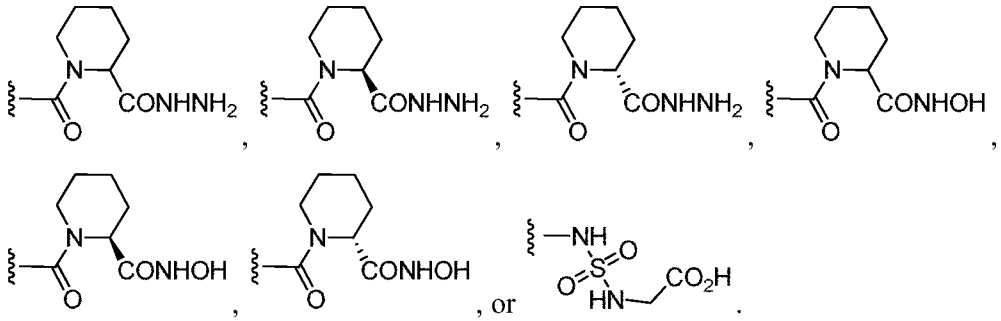
each M is independently O, CH_2, or S;

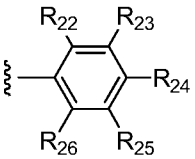
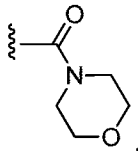
each o is independently 1, 2, 3, or 4; and

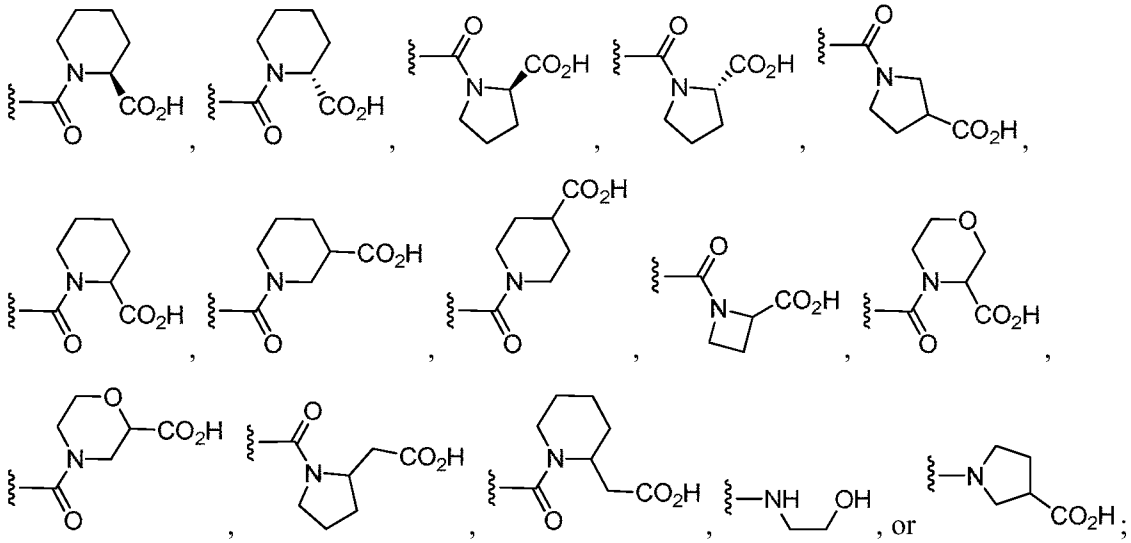
each p is independently 1, 2, 3, or 4.

10. A compound according to claim 9 or salt or N-oxide thereof, wherein each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from hydrogen,  ,





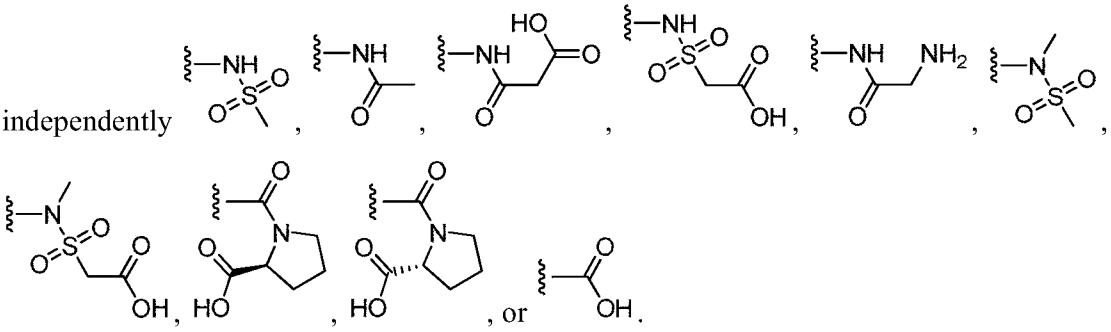
11. A compound according to claim 6 or salt or N-oxide thereof, wherein R_3 is $NHNH_2$, R_1 is $C\equiv C\text{-}R_{13}$, R_{13} is  , R_{24} is independently selected from hydrogen,  ,



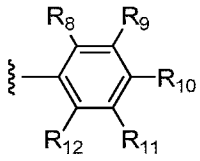
and

R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

12. A compound of formula (I) according to claim 1 or salt or N-oxide thereof, wherein each R_7 is independently $C(=O)OR_4$; $NHSO_2R_4$; $N(alkyl)SO_2R_4$; $NHC(=O)R_4$; $N(alkyl)C(=O)R_4$; $C(=O)NR_{27}R_4$; $SO_2NR_{27}R_4$; $C(=O)NR_{27}NHR_4$; $C(=O)NR_{27}OR_4$; or heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent OR_4, $C(=O)OR_4$, or $NHSO_2R_4$.

13. A compound according to claim 12 or salt or N-oxide thereof, wherein each R_7 is independently  .

14. A compound according to claim 12 or salt or N-oxide thereof, wherein R_1 is



and each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from:

a) hydrogen; b) hydroxyalkylamino; c) alkoxy optionally substituted with 1, 2, or 3 independent hydroxy, $C(=O)OR_4$, $C(=O)NHNHR_4$, or $C(=O)NR_4OH$; d) halogen; e) heterocycloalkyl containing 5 to 6 ring atoms, optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; f) heteroaryl optionally substituted with 1, 2, or 3 independent:

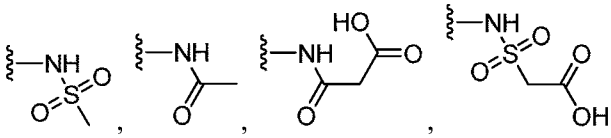
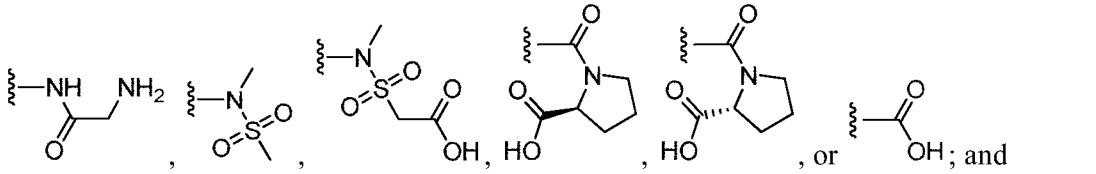
i) $C(=O)OR_{17}$; or

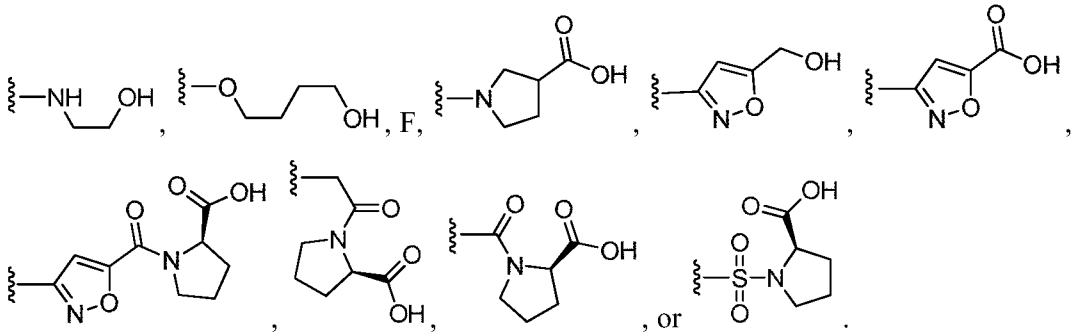
ii) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_{17}$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$;

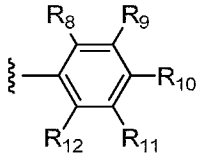
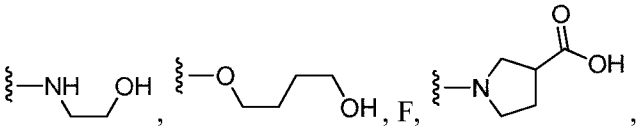
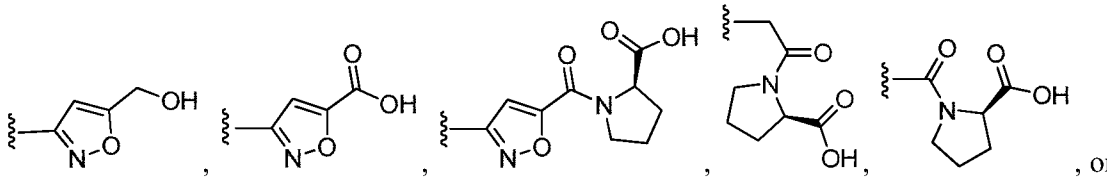
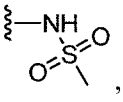
iii) alkyl optionally substituted with 1, 2, or 3 independent $OC(=O)NHR_4$, $NHC(=O)NHR_4$, $NHSO_2R_4$, hydroxy, or $C(=O)NHR_4$;

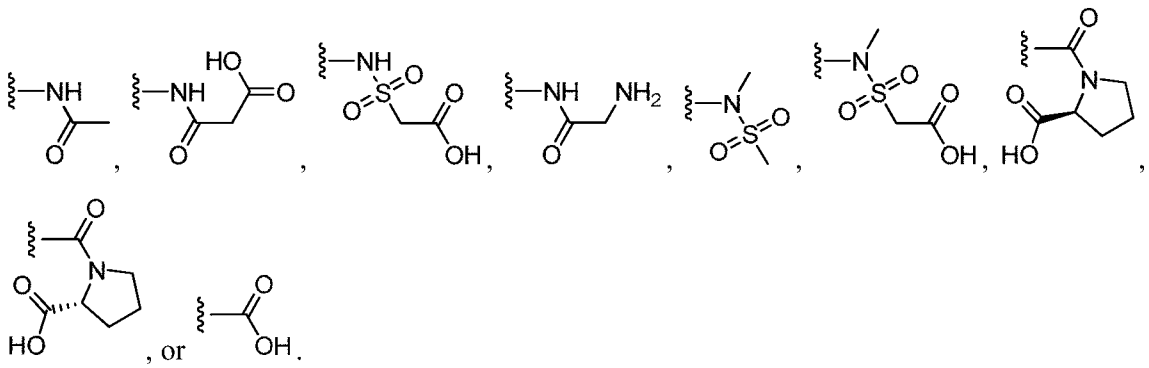
g) alkyl optionally substituted with 1, 2, or 3 heterocycloalkylcarbonyl substituted with $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; h) heterocycloalkylcarbonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$; or i) heterocycloalkylsulfonyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

15. A compound according to claim 14 or salt or N-oxide thereof, wherein:

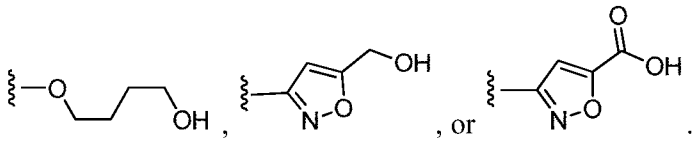
each R_7 is independently  ,  , or ; and

each R_8, R_9, R_{10}, R_{11}, and R_{12} is independently selected from hydrogen,  , or .

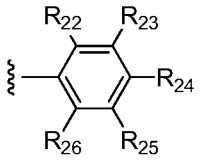
16. A compound according to claim 12 or salt or N-oxide thereof, wherein R_3 is $NHNH_2$, R_1 is  , R_{10} is selected from  ,  , or , R_8, R_9, R_{11}, and R_{12} are each H; and each R_7 is independently  ,



17. A compound according to claim 16 or salt or N-oxide thereof, wherein R_{10} is selected from



18. A compound according to claim 12 or salt or N-oxide thereof, wherein R_1 is C≡C-R_{13} and R_{13} is independently selected from:

a)  ;

b) heterocycloalkyl optionally substituted with 1, 2, or 3 independent alkyl wherein alkyl is optionally substituted with independent:

i) OR_4;

ii) $NHC(=O)R_4$;

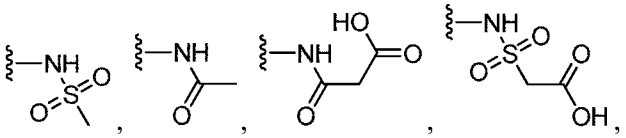
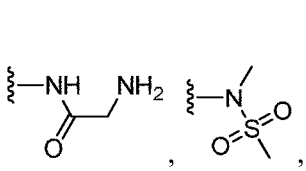
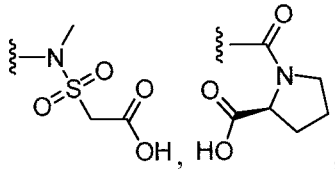
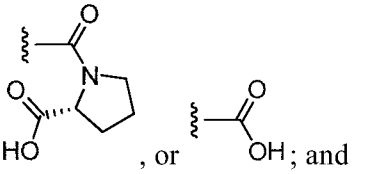
iii) $C(=O)OR_4$; or

iv) $C(=O)NHR_4$;

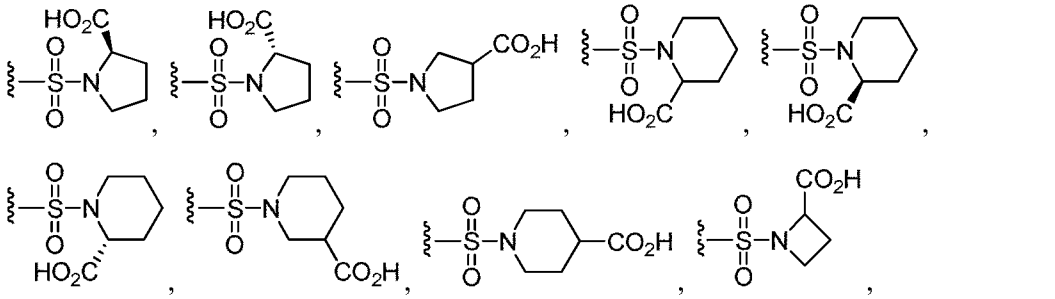
c) heteroaryl optionally substituted with 1, 2, or 3 independent 1) heterocycloalkylcarbonyl, 2) NH_2SO_4, 3) alkylaminocarbonyl, each optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$, or 4) (heterocycloalkyl)alkyl; or

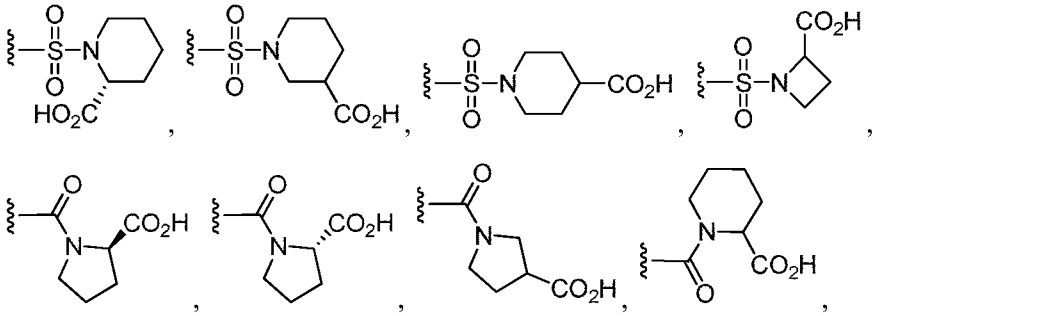
d) cycloalkyl optionally substituted with 1, 2, or 3 independent $C(=O)OR_4$, $C(=O)NR_4R_7$, or $SO_2NR_4R_7$.

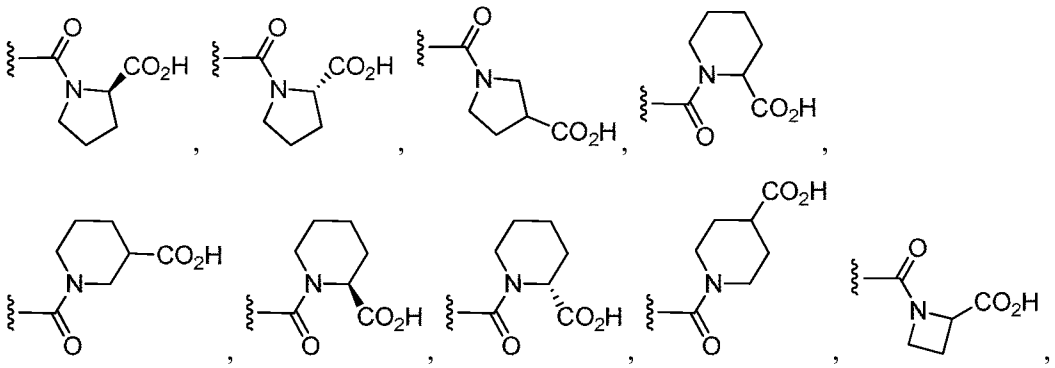
19. A compound according to claim 18 or salt or N-oxide thereof, wherein:

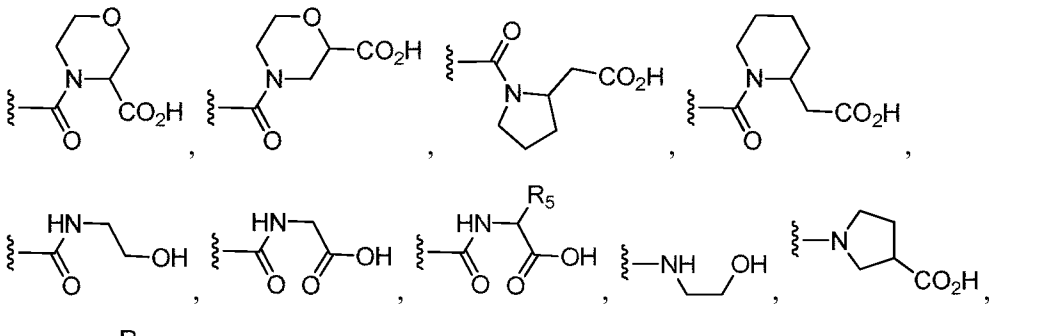
each R_7 is independently  ,  ,  ,  , or ; and

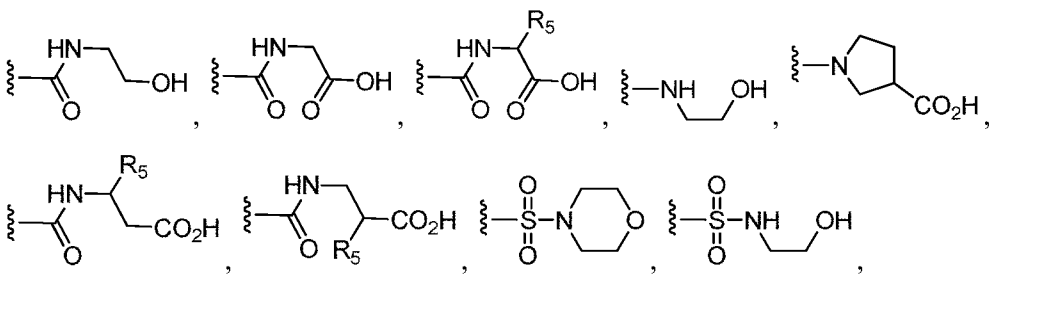
each R_{22}, R_{23}, R_{24}, R_{25}, and R_{26} is independently selected from hydrogen, halo,

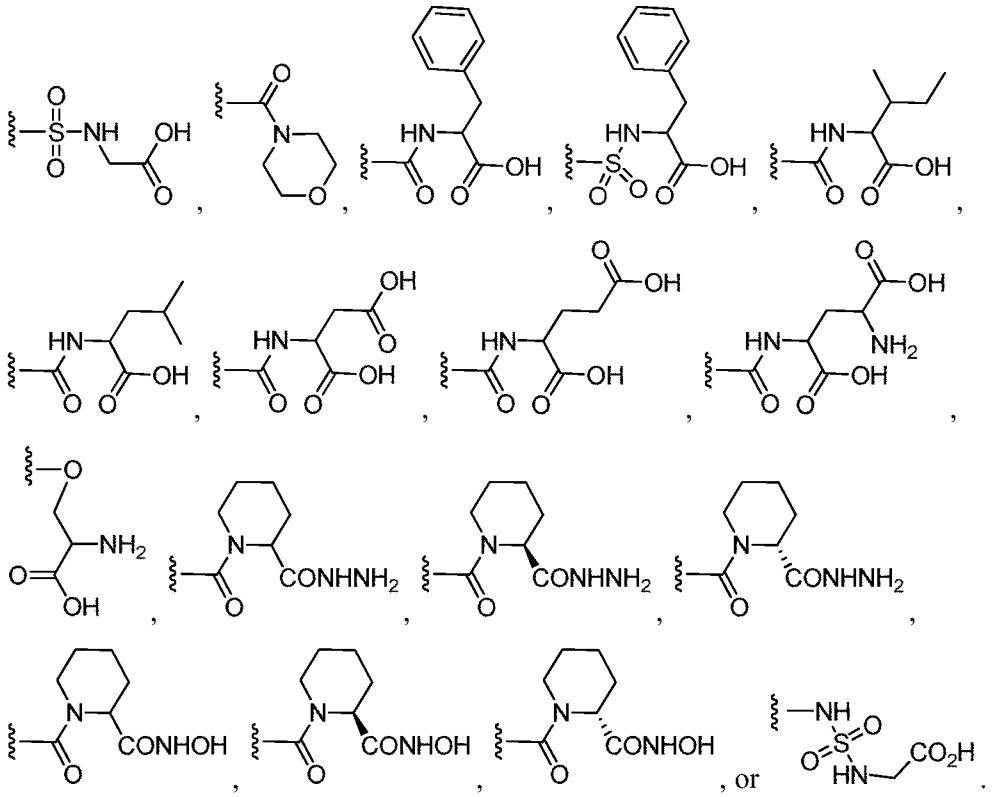


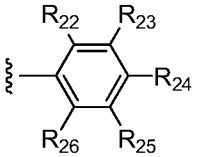
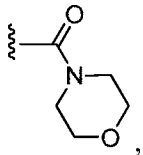
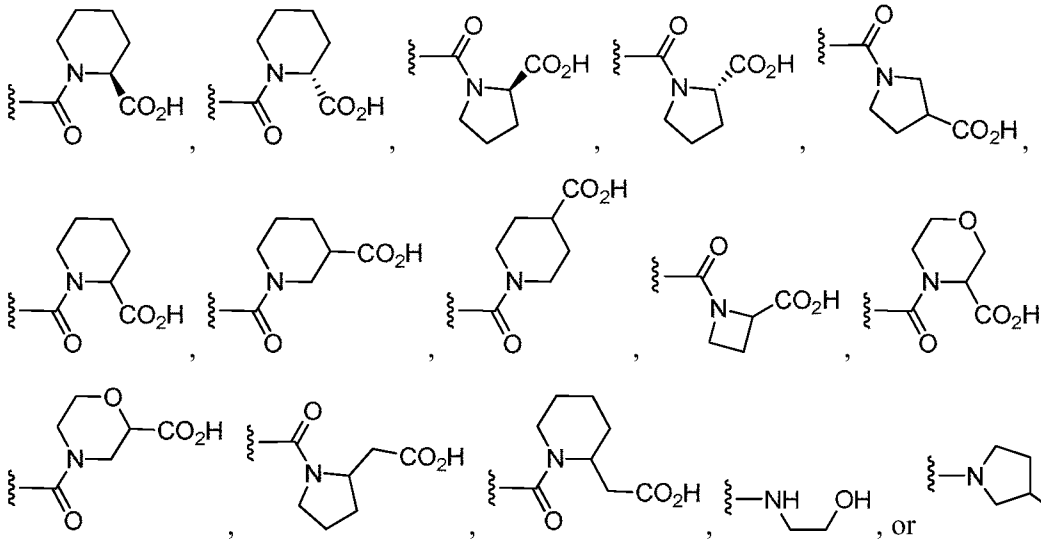


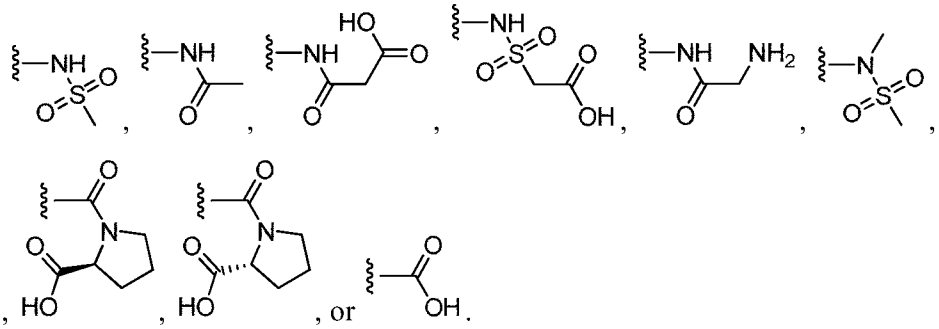


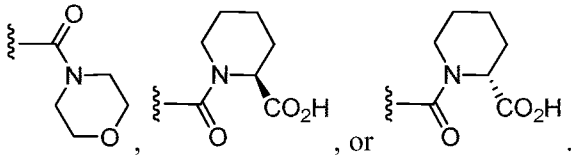






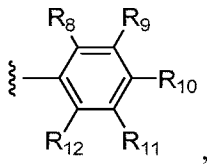
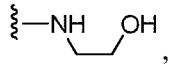
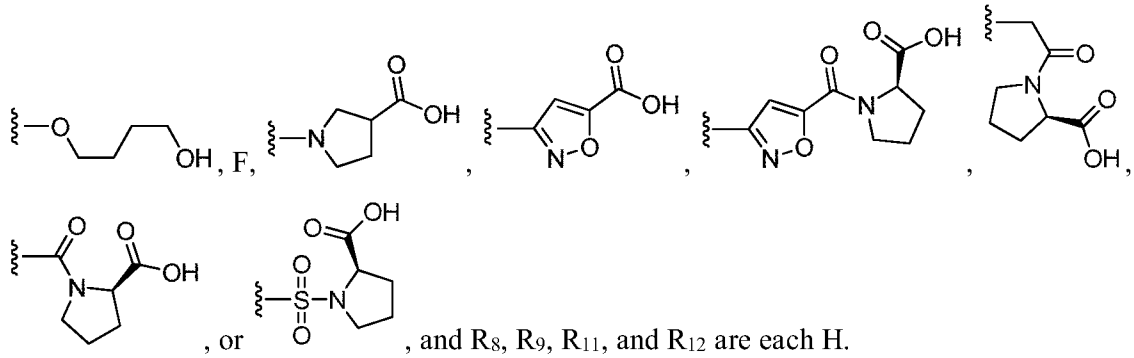
20. A compound according to claim 12 or salt or N-oxide thereof, wherein R_3 is $NHNH_2$, R_1 is $C\equiv C\text{-}R_{13}$; R_{13} is  ; R_{24} is independently selected from hydrogen,  ,  ; R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen; and each R_7 is

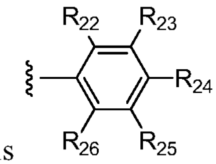
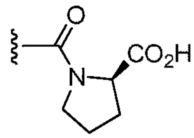
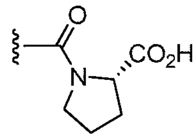
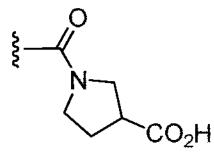
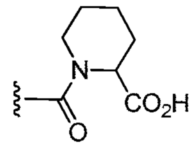
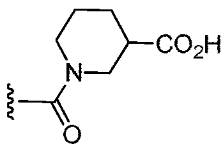
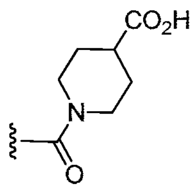
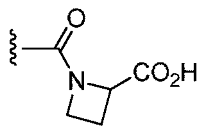
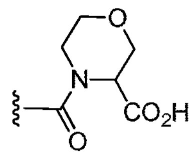
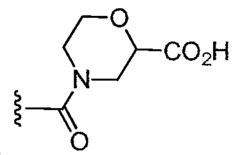
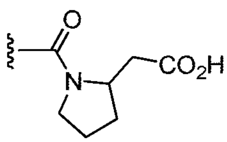
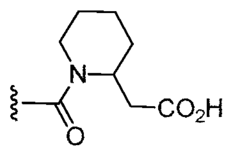
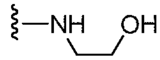
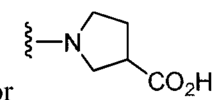
independently 

21. A compound according to claim 20 or salt or N-oxide thereof, wherein R_{24} is independently selected from 

22. A compound of formula (III) according to claim 1 or salt or N-oxide thereof, wherein A is an optionally substituted heterocycle that is preferably a 5-membered ring with 1-4 heteroatoms and R_6 is null.

23. A compound according to claim 22 or salt or N-oxide thereof, wherein A is 5-methylimidazolidinyl-2,4-dione, 2-thioxoimidazolidin-4-one, or imidazolidine-2,4-dione.

24. A compound according to claim 23 or salt or N-oxide thereof, wherein A is 2-thioxoimidazolidin-4-one, R_1 is  , R_{10} is selected from  ,  , and R_8, R_9, R_{11}, and R_{12} are each H.

25. A compound according to claim 23 or salt or N-oxide thereof, wherein A is 2-thioxoimidazolidin-4-one, R_1 is C≡C-R_{13}, R_{13} is  , R_{24} is independently selected from hydrogen,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; and R_{22}, R_{23}, R_{25}, and R_{26} are each independently hydrogen or halogen.

26. A compound according to claim 1, which is:

5-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-5-methylimidazolidine-2,4-dione (**1**);

1-hydroxy-3-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)urea (**2**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**4**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)isobutyramide (**5**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)methanesulfonamide (**6**);

2-(4'-(5-(hydroxymethyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**7**);

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**8**);

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**9**);

3-(2-(4'-(4-((tetrahydro-2H-pyran-2-yl)oxy)butoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**10**);

3-(2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**11**);

2-(4'-(3-aminopropoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**13**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)methanesulfonamide (**14**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)acetamide (**15**);

N'-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbonyl)methanesulfonohydrazide (**17**);

1-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidin-2-one (**19**);

1-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**20**);

5-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-1,3,4-oxadiazol-2-amine (**21**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-methyl-[1,1'-biphenyl]-4-sulfonamide (**22**);

N-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)methanesulfonamide (**23**);

N-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)acetamide (**24**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-methyl-[1,1'-biphenyl]-4-carboxamide (**25**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-3-carboxylic acid (**26**);

2-(4'-(2-morpholino-2-oxoethyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**27**);

2-(4'-(2-morpholino-2-oxoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**28**);

2-(4'-((morpholinosulfonyl)methyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**29**);

3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carboxylic acid (**30**);

(R)-1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)pyrrolidine-2-carboxylic acid (**31**);

(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl methylcarbamate (**32**);

1-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)-3-methylurea (**33**);

N-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)acetamide (**34**);

N-((3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazol-5-yl)methyl)methanesulfonamide (**35**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methyl-1,6-naphthyridine-4-carbohydrazide (**39**);

N'-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methyl-1,6-naphthyridine-4-carbonyl)methanesulfonohydrazide (**40**);

N-(2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)hydrazinecarboxamide (**41**);

2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-3-methoxy-1,6-naphthyridine-4-carbohydrazide (**44**);

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-4-(hydrazinecarbonyl)-1,6-naphthyridine 6-oxide (**50**);

4-(hydrazinecarbonyl)-2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine 6-oxide (**51**);

2-(4'-(4-hydroxybutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**53**);

2-(4'-cyano-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**54**);

2-(5-(4-((2-hydroxyethyl)amino)phenyl)pyridin-2-yl)-1,6-naphthyridine-4-carbohydrazide (**55**);

2-(6-(4-((2-hydroxyethyl)amino)phenyl)pyridin-3-yl)-1,6-naphthyridine-4-carbohydrazide (**56**);

2-(4-(pyridin-3-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**57**);

2-(4-(pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**58**);

2-(4-(pyridin-4-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**59**);

2-(4-(1H-pyrazol-3-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**60**);

2-(4-(1H-pyrazol-4-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**61**);

2-(4-(oxazol-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**62**);

2-(4-(oxazol-5-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**63**);

2-([1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**64**);

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**65**);

2-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**66**);

2-(4-(5-(4-hydroxybutoxy)pyridin-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**67**);

2-(2'-hydroxy-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**68**);

2-(4-(thiazol-2-yl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**69**);

3-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)imidazolidine-2,4-dione (**70**);

3-(2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**71**);

2-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**72**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-(2-hydroxyethyl)-[1,1'-biphenyl]-4-sulfonamide (**73**);

4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-N-(3-hydroxypropyl)-[1,1'-biphenyl]-4-sulfonamide (**74**);

3-(2-(4-(5-(4-hydroxybutoxy)pyridin-2-yl)phenyl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**75**);

4-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**76**);

2-(4'-(4-hydrazinyl-4-oxobutoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**77**);

4-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)-N-hydroxybutanamide (**78**);

4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)-N-hydroxybutanamide (**79**);

4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**80**);

ethyl 4-((4'-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoate (**81**);

N-hydroxy-4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanamide (**82**);

4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoic acid (**83**);

ethyl 4-((4'-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)butanoate (**84**);

2-(4'-(2-aminoethoxy)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**85**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)acetamide (**86**);

(R)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-2-carboxylic acid (**87**);

(S)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)pyrrolidine-2-carboxylic acid (**88**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)piperidine-3-carboxylic acid (**89**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)piperidine-4-carboxylic acid (**90**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)propionamide (**91**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)isobutyramide (**92**);

2,2,2-trifluoro-N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)acetamide (**93**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)ethanesulfonamide (**94**);

N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)propane-2-sulfonamide (**95**);

1,1,1-trifluoro-N-(3-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)propyl)methanesulfonamide (**96**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)propionamide (**97**);

2,2,2-trifluoro-N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)acetamide (**98**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)ethanesulfonamide (**99**);

N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)propane-2-sulfonamide (**100**);

1,1,1-trifluoro-N-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)ethyl)methanesulfonamide (**101**);

2-(3',4'-dihydroxy-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**102**);

(R)-1-(2-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)acetyl)pyrrolidine-2-carboxylic acid (**103**);

(R)-1-(2-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)oxy)acetyl)pyrrolidine-2-carboxylic acid (**104**);

(R)-1-(((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)methyl)sulfonyl)pyrrolidine-2-carboxylic acid (**105**);

2-(4'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**106**);

(R)-1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-carbonyl)pyrrolidine-2-carboxylic acid (**107**);

1-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-carbonyl)piperidine-3-carboxylic acid (**108**);

2-(4'-(5-(morpholine-4-carbonyl)isoxazol-3-yl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**109**);

2-(4'-(morpholinosulfonyl)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine-4-carbohydrazide (**110**);

(R)-1-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)sulfonyl)pyrrolidine-2-carboxylic acid (**111**);

1-((4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)sulfonyl)piperidine-3-carboxylic acid (**112**);

3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)-N-methylisoxazole-5-carboxamide (**113**);

1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)piperidine-3-carboxylic acid (**114**);

1-(3-(4'-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)-[1,1'-biphenyl]-4-yl)isoxazole-5-carbonyl)piperidine-2-carboxylic acid (**115**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)acetamide (**116**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)methanesulfonamide (**117**);

2-(4-((4-(morpholine-4-carbonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**118**);

(R)-1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**119**);

2-(4-((1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**120**);

N-(2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)ethyl)acetamide (**121**);

1-(3-fluoro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**122**);

1-(4-((2-fluoro-4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**123**);

2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**124**);

2-(4-((4-((2-hydroxyethyl)amino)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**125**);

2-(4-(pyridin-3-ylethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**126**);

3-(2-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-1,6-naphthyridin-4-yl)-2-thioxoimidazolidin-4-one (**127**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamide (**128**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzenesulfonamide (**129**);

(S)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid (**130**);

(R)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-2-carboxylic acid (**131**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**132**);

(-)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**133**);

(+)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-3-carboxylic acid (**134**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidine-3-carboxylic acid (**135**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-4-carboxylic acid (**136**);

2-(4-((4-(4-methylpiperazine-1-carbonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**137**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(2-hydroxyethyl)benzamide (**138**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(3-hydroxypropyl)benzamide (**139**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)acetic acid (**140**);

(S)-1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**141**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-3-carboxylic acid (**142**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-3-carboxylic acid (**143**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-4-carboxylic acid (**144**);

2-(4-((4-(morpholinosulfonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**145**);

2-(4-((4-((4-methylpiperazin-1-yl)sulfonyl)phenyl)ethynyl)phenyl)-1,6-naphthyridine-4-carbohydrazide (**146**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(2-hydroxyethyl)benzenesulfonamide (**147**);

4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-(3-hydroxypropyl)benzenesulfonamide (**148**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenylsulfonamido)acetic acid (**149**);

N-(2-aminoethyl)-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamide (**150**);

N-(2-aminoethyl)-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzenesulfonamide (**151**);

(R)-1-((4-((4-(4-(5-oxo-2-thioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**152**);

(R)-1-((4-((4-(4-(2,5-dioxoimidazolidin-1-yl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)pyrrolidine-2-carboxylic acid (**153**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)azetidine-2-carboxylic acid (**154**);

1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**155**);

(-)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**156**);

(+)-1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**157**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)azetidine-2-carboxylic acid (**158**);

1-((4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfonyl)piperidine-2-carboxylic acid (**159**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)morpholine-3-carboxylic acid (**160**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)morpholine-2-carboxylic acid (**161**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)acetic acid (**162**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-2-oxopyridin-1(2H)-yl)-N-methylacetamide (**163**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)thiophene-2-carbonyl)piperidine-3-carboxylic acid (**164**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)thiophene-2-carbonyl)piperidine-2-carboxylic acid (**165**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)furan-2-carbonyl)piperidine-2-carboxylic acid (**166**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)furan-2-carbonyl)piperidine-3-carboxylic acid (**167**);

1-(5-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)picolinoyl)piperidine-2-carboxylic acid (**168**);

1-(2-fluoro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**169**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)propanoic acid (**170**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-methylbutanoic acid (**171**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-methylpentanoic acid (**172**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-4-methylpentanoic acid (**173**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)succinic acid (**174**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)pentanedioic acid (**175**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-hydroxypropanoic acid (**176**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-hydroxybutanoic acid (**177**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-4-(methylthio)butanoic acid (**178**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-phenylpropanoic acid (**179**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-(4-hydroxyphenyl)propanoic acid (**180**);

4-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)thiomorpholine-3-carboxylic acid (**181**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-methylpropanoic acid (**182**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)ethanesulfonamide (**183**);

N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)propane-2-sulfonamide (**184**);

1,1,1-trifluoro-N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)methanesulfonamide (**185**);

2-(N-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)phenyl)sulfamoyl)acetic acid (**186**);

2-(1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)pyrrolidin-2-yl)acetic acid (**187**);

2-(1-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidin-2-yl)acetic acid (**188**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)acetic acid (**189**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)propanoic acid (**190**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)propanoic acid (**191**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)propanoic acid (**192**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-methylpropanoic acid (**193**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)butanoic acid (**194**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)-2-methylpropanoic acid (**195**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)-N-methylbenzamido)butanoic acid (**196**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-phenylpropanoic acid (**197**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-3-phenylpropanoic acid (**198**);

5-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)-2-hydroxybenzoic acid (**199**);

3-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)benzoic acid (**200**);

2-(4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzamido)malonic acid (**201**); or

(S)-1-(3-chloro-4-((4-(4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl)phenyl)ethynyl)benzoyl)piperidine-2-carboxylic acid (**202**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzamido]benzoic acid (**203**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-methoxybenzoyl]piperidine-2-carboxylic acid (**204**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-hydroxybenzoyl]piperidine-2-carboxylic acid (**205**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-(trifluoromethyl)benzoyl]piperidine-2-carboxylic acid (**206**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]-4-hydroxypiperidine-3-carboxylic acid (**207**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**208**);

(2S)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**209**);

1-[2,5-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**210**);

2-(4-{2-[4-(2-oxo-1,3-oxazolidin-5-yl)phenyl]ethynyl}phenyl)-1,6-naphthyridine-4-carbohydrazide (**211**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**212**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-phenylpropanoic acid (**213**);

2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**214**);

4-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzamido]-2-hydroxybenzoic acid (**215**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-phenylpropanoic acid (**216**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylpentanoic acid (**217**);

1-[2,3-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**218**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-4-methylpentanoic acid (**219**);

2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-methylpentanoic acid (**220**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylbutanoic acid (**221**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}pentanedioic acid (**222**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}-3-methylpentanoic acid (**224**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}butanedioic acid (**225**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-methoxybenzoyl]piperidine-2-carboxylic acid (**226**);

1-[2-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**227**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-(trifluoromethyl)benzoyl]piperidine-2-carboxylic acid (**228**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-2-hydroxybenzoyl]piperidine-2-carboxylic acid (**229**);

1-[6-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)pyridine-3-carbonyl]piperidine-2-carboxylic acid (**230**);

2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**232**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**233**);

2-[N-methyl4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**234**);

1-[3,5-difluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**235**);

2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-methylpentanoic acid (**236**);

2-{N-ethyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}acetic acid (**237**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-propylformamido}acetic acid (**238**);

2-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-methylpentanoic acid (**239**);

3-methyl-2-[N-methyl4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]pentanoic acid (**240**);

2-{N-benzyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}acetic acid (**241**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(propan-2-yl)formamido}acetic acid (**243**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**244**);

2-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-methylpentanoic acid (**246**);

2-{N-benzyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**247**);

3-methyl-2-[N-methyl3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]pentanoic acid (**248**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**249**);

(2S)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**250**);

2-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**251**);

2-[N-methyl3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]-3-phenylpropanoic acid (**252**);

1-[4-(2-{5-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]pyridin-2-yl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**253**);

1-[3-fluoro-4-(2-{2-fluoro-4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**254**);

2-{N-ethyl-1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-phenylpropanoic acid (**255**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(propan-2-yl)formamido}-3-phenylpropanoic acid (**256**);

(2R)-1-{[5-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)pyridin-2-yl]methyl}pyrrolidine-2-carboxylic acid (**258**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-phenylpropanoic acid (**259**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**260**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-2-carboxylic acid (**261**);

2-amino-3-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**262**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-propylformamido}-3-phenylpropanoic acid (**263**);

1-[4-(2-{2-chloro-4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**264**);

1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-3-carboxylic acid (**265**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]pyrrolidine-2-carboxylic acid (**266**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-3-carboxylic acid (**267**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]pyrrolidine-2-carboxylic acid (**268**);

1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-3-carboxylic acid (**269**);

(2R)-1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]pyrrolidine-2-carboxylic acid (**270**);

2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**271**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}acetic acid (**272**);

2-[N-(2-methylpropyl)3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]acetic acid (**273**);

2-[N-(2-methylpropyl)3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonamido]acetic acid (**274**);

1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]piperidine-3-carboxylic acid (**275**);

(2R)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzenesulfonyl]pyrrolidine-2-carboxylic acid (**276**);

2-amino-3-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenoxy]propanoic acid (**277**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]-2-methoxyphenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**278**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**279**);

1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]-2-hydroxyphenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**280**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**282**);

2-amino-3-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**283**);

2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**284**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**285**);

2-[4-(2-{2-chloro-4-[(2S)-2-(hydrazinecarbonyl)piperidine-1-carbonyl]phenyl}ethynyl)phenyl]-1,6-naphthyridine-4-carbohydrazide (**286**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]-N-hydroxypiperidine-2-carboxamide (**288**);

2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoic acid (**289**);

2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-(4-hydroxyphenyl)propanoic acid (**290**);

methyl 2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**291**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**292**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**293**);

2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}-3-hydroxypropanoic acid (**294**);

methyl 2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**295**);

methyl 2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}-3-(1H-imidazol-4-yl)propanoate (**296**);

3-amino-2-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**297**);

3-amino-2-{[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**298**);

3-amino-2-{[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]formamido}propanoic acid (**299**);

(2S)-1-[3-chloro-4-(2-{4-[7-chloro-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**300**);

3-amino-2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**301**);

3-amino-2-{1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**302**);

3-amino-2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-(2-methylpropyl)formamido}propanoic acid (**303**);

2-{4-[2-(4-{1,3-dioxo-octahydroimidazolidino[1,5-a]pyridin-2-yl}phenyl)ethynyl]phenyl}-1,6-naphthyridine-4-carbohydrazide (**304**);

3-amino-2-{1-[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**305**);

(2S)-1-[4-(2-{4-[7-amino-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**306**);

3-amino-2-{1-[3-fluoro-4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]-N-methylformamido}propanoic acid (**307**);

1-[4-(2-{5-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]thiophen-2-yl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**308**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-methanesulfonamido-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**309**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-methoxy-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**310**);

2-(4-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}buta-1,3-diyn-1-yl)cyclopropane-1-carboxylic acid (**311**);

(2S)-1-[3-chloro-4-(2-{4-[7-acetamido-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**312**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-(morpholin-4-yl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**313**);

1-[2-(4-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}buta-1,3-diyn-1-yl)cyclopropanecarbonyl]piperidine-2-carboxylic acid (**314**);

(2S)-1-[4-(2-{4-[7-(2-carboxyacetamido)-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**315**);

(2S)-1-[4-(2-{4-[7-carboxymethanesulfonamido-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**316**);

1-{[4-(2-{4-[4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)phenyl]carbamoyl}piperidine-2-carboxylic acid (**317**);

(2S)-1-[3-chloro-4-(2-{4-[4-(hydrazinecarbonyl)-7-(3-methoxypyrrolidin-1-yl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)benzoyl]piperidine-2-carboxylic acid (**318**);

4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carboxylic acid (**319**);

N-[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]methanesulfonamide (**320**);

(2S)-1-[4-(2-{4-[7-(2-aminoacetamido)-4-(hydrazinecarbonyl)-1,6-naphthyridin-2-yl]phenyl}ethynyl)-3-chlorobenzoyl]piperidine-2-carboxylic acid (**321**);

2-{[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**322**);

(2R)-1-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carbonyl]pyrrolidine-2-carboxylic acid (**323**);

(2S)-1-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridine-7-carbonyl]pyrrolidine-2-carboxylic acid (**324**);

N-[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridin-7-yl]methanesulfonamide (**325**);

2-{[4-(hydrazinecarbonyl)-2-{4-[4-(4-hydroxybutoxy)phenyl]phenyl}-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**326**);

N-[4-(hydrazinecarbonyl)-2-(4-{4-[5-(hydroxymethyl)-1,2-oxazol-3-yl]phenyl}phenyl)-1,6-naphthyridin-7-yl]methanesulfonamide (**327**);

2-{[4-(hydrazinecarbonyl)-2-(4-{4-[5-(hydroxymethyl)-1,2-oxazol-3-yl]phenyl}phenyl)-1,6-naphthyridin-7-yl]sulfamoyl}acetic acid (**328**);

N-[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl]-N-methylmethanesulfonamide (**329**); or

2-{[2-(4-{2-[2-chloro-4-(morpholine-4-carbonyl)phenyl]ethynyl}phenyl)-4-(hydrazinecarbonyl)-1,6-naphthyridin-7-yl](methyl)sulfamoyl}acetic acid (**330**) or salt or N-oxide thereof.

27. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound attains affinity for a metalloenzyme by formation of one or more of the following types of chemical interactions or bonds to a metal: sigma bonds, covalent bonds, coordinate-covalent bonds, ionic bonds, pi bonds, delta bonds, or backbonding interactions.

28. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound binds to a metal.

29. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound binds to iron, zinc, heme iron, manganese, magnesium, iron sulfide cluster, nickel, molybdenum, or copper.

30. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound inhibits an enzyme class selected from cytochrome P450 family, histone deacetylases, matrix metalloproteinases, phosphodiesterases, cyclooxygenases, carbonic anhydrases, nitric oxide synthases, and LpxC.

31. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound inhibits an enzyme selected from 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR), 17-alpha hydroxylase/17,20-lyase (CYP17), aldosterone synthase

(CYP11B2), aminopeptidase p, anthrax lethal factor, arginase, beta-lactamase, cytochrome P450 2A6, d-ala d-ala ligase, dopamine beta-hydroxylase, endothelin converting enzyme-1, glutamate carboxypeptidase II, glutaminyl cyclase, glyoxalase, heme oxygenase, HPV/HSV E1 helicase, indoleamine 2,3-dioxygenase, leukotriene A4 hydrolase, methionine aminopeptidase 2, peptide deformylase, phosphodiesterase VII, relaxase, retinoic acid hydroxylase (CYP26), TNF-alpha converting enzyme (TACE), UDP-(3-O-(R-3-hydroxymyristoyl))-N-acetylglucosamine deacetylase (LpxC), vascular adhesion protein-1 (VAP-1), and vitamin D hydroxylase (CYP24).

32. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound inhibits an enzyme selected from 4-hydroxyphenyl pyruvate dioxygenase, 5-lipoxygenase, adenosine deaminase, alcohol dehydrogenase, aminopeptidase n, angiotensin converting enzyme, aromatase (CYP19), calcineurin, carbamoyl phosphate synthetase, carbonic anhydrase family, catechol o-methyl transferase, cyclooxygenase family, dihydropyrimidine dehydrogenase-1, DNA polymerase, farnesyl diphosphate synthase, farnesyl transferase, fumarate reductase, GABA aminotransferase, HIF-prolyl hydroxylase, histone deacetylase family, HIV integrase, HIV-1 reverse transcriptase, isoleucine tRNA ligase, lanosterol demethylase (CYP51), matrix metalloprotease family, methionine aminopeptidase, neutral endopeptidase, nitric oxide synthase family, phosphodiesterase III, phosphodiesteraseIV, phosphodiesterase V, pyruvate ferredoxin oxidoreductase, renal peptidase, ribonucleoside diphosphate reductase, thromboxane synthase (CYP5a), thyroid peroxidase, tyrosinase, urease, and xanthine oxidase.

33. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as binding to a metal.

34. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as binding to iron, zinc, heme-iron, manganese, magnesium, iron-sulfide cluster, nickel, molybdenum, or copper.

35. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as inhibiting an enzyme class selected from cytochrome P450 family, histone deacetylases, matrix metalloproteinases, phsophodiesterases, cyclooxygenases, carbonic anhydrases, and nitric oxide synthases.

36. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as inhibiting an enzyme selected from 4-hydroxyphenyl pyruvate dioxygenase, 5-lipoxygenase, adenosine deaminase, alcohol dehydrogenase, aminopeptidase n, angiotensin converting enzyme, aromatase (CYP19), calcineurin, carbamoyl phosphate synthetase, carbonic anhydrase family, catechol o-methyl transferase, cyclooxygenase family, dihydropyrimidine dehydrogenase-1, DNA polymerase, farnesyl diphosphate synthase, farnesyl transferase, fumarate reductase, GABA aminotransferase, HIF-prolyl hydroxylase, histone deacetylase family, HIV integrase, HIV-1 reverse transcriptase, isoleucine tRNA ligase, lanosterol demethylase (CYP51), matrix metalloprotease family, methionine aminopeptidase, neutral endopeptidase, nitric oxide synthase family, phosphodiesterase III, phosphodiesteraseIV, phosphodiesteraseV, pyruvate ferredoxin oxidoreductase, renal peptidase, ribonucleoside diphosphate reductase, thromboxane synthase (CYP5a), thyroid peroxidase, tyrosinase, urease, and xanthine oxidase.

37. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as an inhibitor of LpxC.

38. A compound according to any one of claims 1 to 26 or salt or N-oxide thereof, wherein the compound is identified as having an activity range against a target enzyme and an activity range against an off-target enzyme (e.g., LpxC IC50<1.0 μM and IC50>3.0 μM for CYP3A4; LpxC IC50<0.5 μM and IC50>1.0 μM for CYP3A4; LpxC IC50<0.24 μM and IC50>3.5 μM for CYP3A4; LpxC IC50<XX μM and IC50>YY μM for CYP3A4, in each instance XX is an independent number; in each instance YY is an independent number; in certain aspects XX is a number less than YY). In certain aspects, for example, XX is 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, or 1000-fold less than YY.

39. A method of inhibiting metalloenzyme activity comprising contacting a compound according to any one of claims 1 to 26 or salt or N-oxide thereof with a metalloenzyme.

40. A method according to claim 39, wherein the contacting is in vivo.

41. A method according to claim 39, wherein the contacting is in vitro.

42. A method according to any one of claims 39 to 41, wherein the metalloenzyme comprises a metal atom that is iron, zinc, heme iron, manganese, magnesium, iron sulfide cluster, nickel, molybdenum, or copper;

43. A method according to any one of claims 39 to 42, wherein the metalloenzyme is a member of an enzyme class selected from cytochrome cytochrome P450 family, histone deacetylases, matrix metalloproteinases, phsophodiesterases, cyclooxygenases, carbonic anhydrases, and nitric oxide synthases; the metalloenzyme is aromatase (CYP19), a cyclooxygenase, lanosterol demethylase (CYP51), a nitric oxide synthase, thromboxane synthase (CYP5a), thyroid peroxidase, 17-alpha hydroxylase/17,20-lyase (CYP17), aldosterone synthase (CYP11B2), cytochrome P450 2A6, heme oxygenase, indoleamine 2,3-dioxygenase, retinoic acid hydroxylase (CYP26), or vitamin D hydroxylase (CYP24).

44. A method according to any one of claims 39 to 43, wherein the metalloenzyme is LpxC.

45. A method according to any one of claims 39 to 43, wherein the metalloenzyme is 4-hydroxyphenyl pyruvate dioxygenase, 5-lipoxygenase, adenosine deaminase, alcohol dehydrogenase, aminopeptidase n, angiotensin converting enzyme, aromatase (CYP19), calcineurin, carbamoyl phosphate synthetase, carbonic anhydrase family, catechol o-methyl transferase, cyclooxygenase family, dihydropyrimidine dehydrogenase-1, DNA polymerase, farnesyl diphosphate synthase, farnesyl transferase, fumarate reductase, GABA aminotransferase, HIF-prolyl hydroxylase, histone deacetylase family, HIV integrase, HIV-1 reverse transcriptase, isoleucine tRNA ligase, lanosterol demethylase (CYP51), matrix metalloprotease family, methionine aminopeptidase, neutral endopeptidase, nitric oxide synthase family, phosphodiesterase III, phosphodiesteraseIV, phosphodiesteraseV, pyruvate ferredoxin oxidoreductase, renal peptidase, ribonucleoside diphosphate reductase, thromboxane synthase (CYP5a), thyroid peroxidase, tyrosinase, urease, and xanthine oxidase.

46. A method according to any one of claims 39 to 43, wherein the metalloenzyme is 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR), 17-alpha hydroxylase/17,20-lyase (CYP17), aldosterone synthase (CYP11B2), aminopeptidase p, anthrax lethal factor, arginase, beta-lactamase, cytochrome P450 2A6, d-ala d-ala ligase, dopamine beta-hydroxylase, endothelin converting enzyme-1, glutamate carboxypeptidase II, glutaminyl cyclase, glyoxalase, heme oxygenase, HPV/HSV E1 helicase, indoleamine 2,3-dioxygenase, leukotriene A4 hydrolase,

methionine aminopeptidase 2, peptide deformylase, phosphodiesteraseVII, relaxase, retinoic acid hydroxylase (CYP26), TNF-alpha converting enzyme (TACE), UDP-(3-O-(R-3-hydroxymyristoyl))-N-acetylglucosamine deacetylase (LpxC), vascular adhesion protein-1 (VAP-1), or vitamin D hydroxylase (CYP24).

47. A method according to any one of claims 39 to 46, further comprising administering the compound to a subject.

48. A method of modulating metalloenzyme activity in a subject, comprising contacting the subject with a compound according to any one of claims 1 to 38 or salt or N-oxide thereof, in an amount and under conditions sufficient to modulate metalloenzyme activity.

49. A method of treating a subject suffering from or susceptible to a metalloenzyme-related disorder or disease, comprising administering to the subject an effective amount of a compound according to any one of claims 1 to 38 or salt or N-oxide thereof.

50. A method of treating a subject suffering from or susceptible to a metalloenzyme-related disorder or disease, wherein the subject has been identified as in need of treatment for a metalloenzyme-related disorder or disease, comprising administering to said subject in need thereof, an effective amount of a compound according to any one of claims 1 to 38 or salt or N-oxide thereof, such that said subject is treated for said disorder.

51. A method of treating a subject suffering from or susceptible to a metalloenzyme-mediated disorder or disease, wherein the subject has been identified as in need of treatment for a metalloenzyme-mediated disorder or disease, comprising administering to said subject in need thereof, an effective amount of a compound according to any one of claims 1 or 38 or salt or N-oxide thereof, such that metalloenzyme activity in said subject is modulated (e.g., down regulated, inhibited).

52. The method of claim 51, wherein the disease or disorder is mediated by any of 4-hydroxyphenyl pyruvate dioxygenase, 5-lipoxygenase, adenosine deaminase, alcohol dehydrogenase, aminopeptidase n, angiotensin converting enzyme, aromatase (CYP19), calcineurin, carbamoyl phosphate synthetase, carbonic anhydrase family, catechol o-methyl transferase, cyclooxygenase family, dihydropyrimidine dehydrogenase-1, DNA polymerase,

farnesyl diphosphate synthase, farnesyl transferase, fumarate reductase, GABA aminotransferase, HIF-prolyl hydroxylase, histone deacetylase family, HIV integrase, HIV-1 reverse transcriptase, isoleucine tRNA ligase, lanosterol demethylase (CYP51), matrix metalloprotease family, methionine aminopeptidase, neutral endopeptidase, nitric oxide synthase family, phosphodiesterase III, phosphodiesteraseIV, phosphodiesteraseV, pyruvate ferredoxin oxidoreductase, renal peptidase, ribonucleoside diphosphate reductase, thromboxane synthase (CYP5a), thyroid peroxidase, tyrosinase, urease, or xanthine oxidase.

53. A method according to claim 51, wherein the disease or disorder is mediated by any of 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR), 17-alpha hydroxylase/17,20-lyase (CYP17), aldosterone synthase (CYP11B2), aminopeptidase p, anthrax lethal factor, arginase, beta-lactamase, cytochrome P450 2A6, d-ala d-ala ligase, dopamine beta-hydroxylase, endothelin converting enzyme-1, glutamate carboxypeptidase II, glutaminyl cyclase, glyoxalase, heme oxygenase, HPV/HSV E1 helicase, indoleamine 2,3-dioxygenase, leukotriene A4 hydrolase, methionine aminopeptidase 2, peptide deformylase, phosphodiesteraseVII, relaxase, retinoic acid hydroxylase (CYP26), TNF-alpha converting enzyme (TACE), UDP-(3-O-(R-3-hydroxymyristoyl))-N-acetylglucosamine deacetylase (LpxC), vascular adhesion protein-1 (VAP-1), or vitamin D hydroxylase (CYP24).

54. A method according to claim 51, wherein the disease or disorder is cancer, cardiovascular disease, endocrinologic disease, inflammatory disease, infectious disease, gynelogic disease, metabolic disease, opthalmologic disease, central nervous system (CNS) disease, urologic disease, or gastrointestinal disease.

55. A method according to claim 51, wherein the disease or disorder is prostate cancer, breast cancer, androgen-dependent cancers, estrogen-dependent cancers, adrenal hyperplasia, prostatic hypertrophy, virilism, hirsutism, male pattern alopecia, precocious puberty, endometriosis, uterus myoma, uterine cancer, mastopathy, polycystic ovary syndrome, infertility, acne, functional ovarian hyperandrogenism, hyperandrogenism with chronic anovulation, hyperandrogenemia, premature adrenarche, adrenal or androgen excess, uterine fibroids, inflammatory bowel disease, psoriasis, systemic fungal infection, onychomycosis, systemic bacterial infection, skin structure bacterial infection, gram-negative bacterial infection, or cardiovascular disease.

56. A composition comprising a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, and an agriculturally acceptable carrier.

57. A method of treating or preventing a metalloenzyme-mediated disease or disorder in or on a plant comprising contacting a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, with the plant or seeds.

58. A method of inhibiting metalloenzyme activity in a microorganism on a plant comprising contacting a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, with the plant or seeds.

59. A method of treating or preventing a fungal disease or disorder in or on a plant comprising contacting a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, with the plant or seeds.

60. A method of treating or preventing fungal growth in or on a plant comprising contacting a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, with the plant or seeds.

61. A method of inhibiting microorganisms in or on a plant comprising contacting a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, with the plant or seeds.

62. A composition according to claim 56, further comprising an azole fungicide selected from epoxyconazole, tebuconazole, fluquinconazole, flutriafol, metconazole, myclobutanil, cycproconazole, prothioconazole and propiconazole.

63. A composition according to claim 56 or 62, further comprising a strobilurin fungicide from the group trifloxystrobin, pyraclostrobin, orysastrobin, fluoxastrobin and azoxystrobin.

64. A composition comprising a compound according to any one of claims 1 to 38, or salt or N-oxide thereof, and a pharmaceutically acceptable carrier.

65. A composition according to claim 64 further comprising an additional therapeutic agent.

66. A composition according to claim 64 further comprising an additional therapeutic agent that is an anti-cancer agent, antifungal agent, cardiovascular agent, antiinflammatory agent, chemotherapeutic agent, an anti-angiogenesis agent, cytotoxic agent, an anti-proliferation agent, metabolic disease agent, opthalmologic disease agent, central nervous system (CNS) disease agent, urologic disease agent, or gastrointestinal disease agent.

67. A compound that is:

2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-4-(hydrazinecarbonyl)-1,6-naphthyridine 6-oxide (**50**);

4-(hydrazinecarbonyl)-2-(4'-((2-hydroxyethyl)amino)-[1,1'-biphenyl]-4-yl)-1,6-naphthyridine 6-oxide (**51**);

or salt thereof.