(12) STANDARD PATENT (11) Application No. **AU 2007334323 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Naphthalenone compounds exhibiting prolyl hydroxylase inhibitory activity, compositions, and uses thereof

(51) International Patent Classification(s)

C07D 311/96 (2006.01)	***C07D 213/56*** (2006.01)
A61K 31/352 (2006.01)	***C07D 213/61*** (2006.01)
A61P 9/10 (2006.01)	***C07D 215/48*** (2006.01)
C07C 59/88 (2006.01)	***C07D 217/02*** (2006.01)
C07C 235/82 (2006.01)	***C07D 221/20*** (2006.01)
C07C 237/24 (2006.01)	***C07D 307/94*** (2006.01)

(21) Application No: **2007334323** (22) Date of Filing: **2007.12.17**

(87) WIPO No: **WO08/076427**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/963,152	**2007.08.01**	**US**
60/875,693	**2006.12.18**	**US**

(43) Publication Date: **2008.06.26**
(44) Accepted Journal Date: **2011.03.10**

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(56) Related Art
US 2005/0107364
BUCKLE, D.R. et al., Journal of Medicinal Chemistry. 1977, vol. 20, pages 1059-1064

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/076427 A2

(51) International Patent Classification:
C07D 311/96 (2006.01) *C07D 221/20* (2006.01)
C07C 235/82 (2006.01) *C07D 215/48* (2006.01)
C07D 213/56 (2006.01) *C07C 59/88* (2006.01)
C07D 213/61 (2006.01) *C07D 217/02* (2006.01)
C07D 307/94 (2006.01) *A61K 31/352* (2006.01)
C07C 237/24 (2006.01) *A61P 9/10* (2006.01)

(21) International Application Number:
PCT/US2007/025819

(22) International Filing Date:
17 December 2007 (17.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/875,693 18 December 2006 (18.12.2006) US
60/963,152 1 August 2007 (01.08.2007) US

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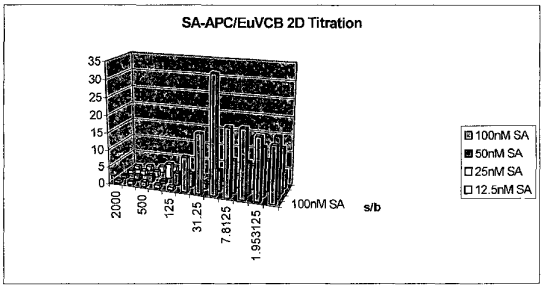
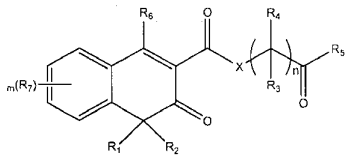
[Continued on next page]

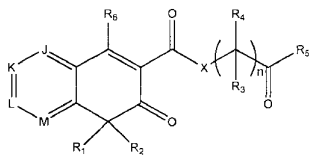
(54) **Title:** NAPHTHALENONE COMPOUNDS EXHIBITING PROLYL HYDROXYLASE INHIBITORY ACTIVITY, COMPOSITIONS, AND USES THEREOF

(57) **Abstract:** Compounds of Formula (I) and Formula (II) are useful as inhibitors of HIF prolyl hydroxylases. Compounds of Formula(I) and Formula (II) have the following structures, where the definitions of the variables are provided herein.





(I)



(II)

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report*

— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

2007334323 16 Dec 2010

NAPHTHALENONE COMPOUNDS EXHIBITING PROLYL HYDROXYLASE INHIBITORY ACTIVITY, COMPOSITIONS, AND USES THEREOF

CROSS REFERENCES TO RELATED APPLICATIONS

[001] This application claims the benefit of United States Provisional Application No. 60/875,693, filed on December 18, 2006, and United States Provisional Application No. 60/963,152, filed on August 1, 2007, which are both hereby incorporated by reference in their entireties and for all purposes as if fully set forth herein.

FIELD OF THE INVENTION

[002] The present invention relates to compounds capable of inhibiting prolyl hydroxylases such as HIF (Hypoxia Inducible Factor) prolyl hydroxylases, compounds that modulate HIF levels, compounds that stabilize HIF, compositions comprising the compounds, and methods for their use for controlling HIF levels. The compounds and compositions may be used to treat diseases or conditions modulated by HIF such as ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, and inflammatory disorders.

BACKGROUND OF THE INVENTION

[002a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[003] The cellular transcription factor HIF (Hypoxia Inducible Factor) occupies a central position in oxygen homeostasis in a wide range of organisms and is a key regulator of responses to hypoxia. The genes regulated by HIF transcriptional activity can play critical roles in angiogenesis, erythropoiesis, hemoglobin F production, energy metabolism, inflammation, vasomotor function, apoptosis and cellular proliferation. HIF can also play a role in cancer, in which it is commonly upregulated, and in the pathophysiological responses to ischemia and hypoxia.

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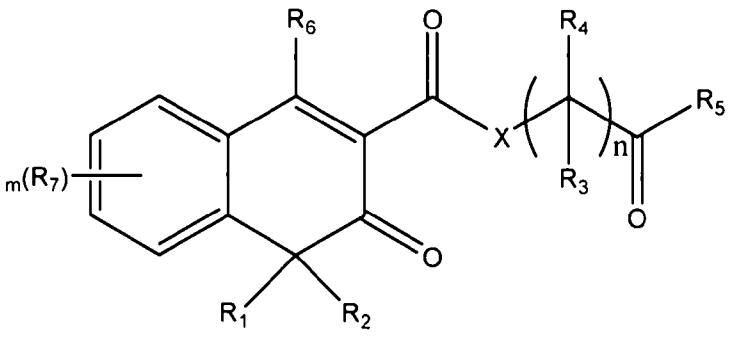
[004] The HIF transcriptional complex comprises an αβ heterodimer: HIF-β is a constitutive nuclear protein that dimerizes with oxygen-regulated HIF-α subunits. Oxygen regulation occurs through hydroxylation of the HIF-α subunits, which are then rapidly destroyed by the proteasome. In oxygenated cells, the von Hippel-Lindau tumor suppressor protein (pVHL) binds to hydroxylated HIF-α subunits, thereby promoting their ubiquitin dependent proteolysis. This process is suppressed under hypoxic conditions, stabilizing HIF-α and promoting transcriptional activation by the HIF αβ complex. *See, e.g.*, U.S. Patent 6,787,326.

[005] Hydroxylation of HIF-α subunits can occur on proline and asparagine residues and can be mediated by a family of 2-oxoglutarate dependent enzymes. This family includes the HIF prolyl hydroxylase isozymes (PHDs), which hydroxylate Pro 402 and Pro 564 of human HIF1α, as well as Factor Inhibiting HIF (FIH), which hydroxylates Asn 803 of human HIF1α. Inhibition of FIH or the PHDs leads to HIF stabilization and transcriptional activation. *See, e.g.*, Schofield and Ratcliffe, Nature Rev. Mol. Cell Biol., Vol 5, pages 343-354 (2004).

SUMMARY OF THE INVENTION

[005a] According to a first aspect, the present invention provides at least one compound of the Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

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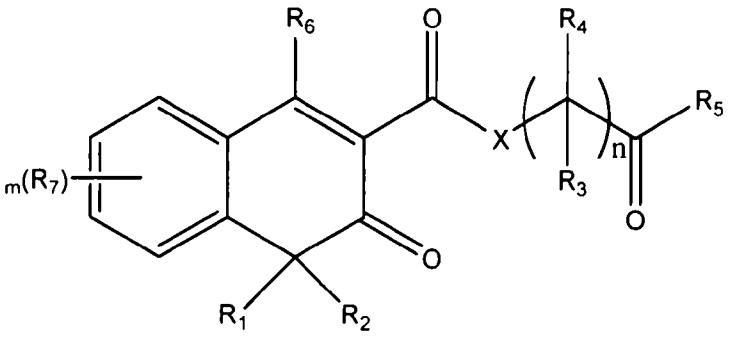
R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[005b] According to a second aspect, the present invention provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a therapeutically effective amount of at least one compound of Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_c, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

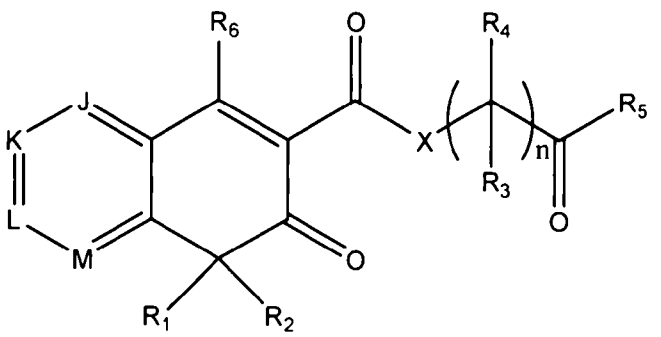
R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[005c] According to a third aspect, the present invention provides at least one compound of the Formula II:



II

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a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any one of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

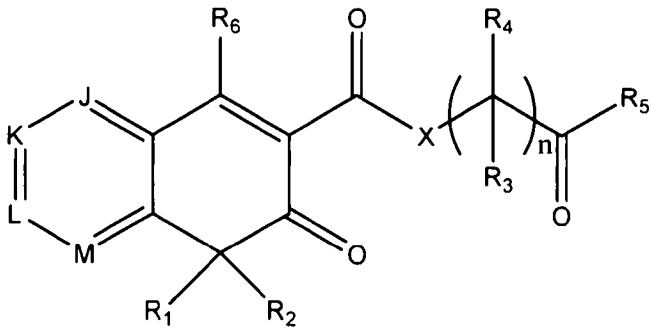
R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[005d] According to a fourth aspect, the present invention provides a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a therapeutically effective amount of at least one compound of Formula II:



II

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any one of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted

heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[005e] According to a fifth aspect, the present invention provides a method of increasing or stabilizing HIF levels or activity in a subject, comprising administering to the subject the at least one compound according to the first or the third aspect.

[005f] According to a sixth aspect, the present invention provides a method of treating a condition where it is desired to modulate HIF activity, comprising administering to a subject the at least one compound according to the first or the third aspect.

[005g] According to a seventh aspect, the present invention provides a method of treating a hypoxic or ischemic related disorder in a subject, comprising administering to a subject the at least one compound according to the first or the third aspect.

[005h] According to an eighth aspect, the present invention provides a method of modulating the amount of HIF in a cell, comprising contacting the cell with the at least one compound according to the first or the third aspect.

[005i] According to a ninth aspect, the present invention provides a method of inhibiting HIF hydroxylation in a subject, comprising administering to the subject the at least one compound according to the first or the third aspect.

[005j] According to a tenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament.

[005k] According to an eleventh aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament for increasing or stabilizing HIF levels or activity in a subject.

[005l] According to a twelfth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament for treating a condition where it is desired to modulate HIF activity.

[005m] According to a thirteenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament for treating a hypoxic or ischemic related disorder in a subject.

[005n] According to a fourteenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a composition for modulating the amount of HIF in a cell.

[005o] According to a fifteenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the modulation of the amount of HIF in a cell.

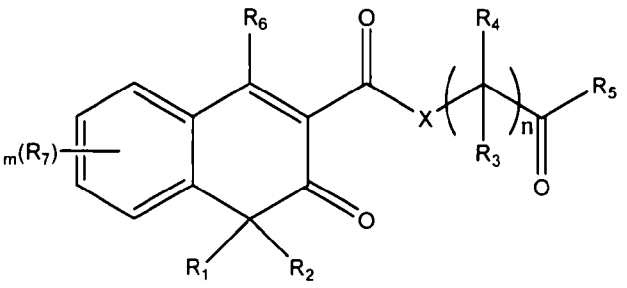
[005p] According to a sixteenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament for modulating angiogenesis in a subject.

[005q] According to a seventeenth aspect, the present invention provides the use of the at least one compound according to the first or the third aspect, in the preparation of a medicament for inhibiting HIF hydroxylation in a subject.

[005r] According to an eighteenth aspect, the present invention provides a method for modulating angiogenesis in a subject comprising administering the at least one compound according to the first or the third aspect to a subject.

[005s] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[006] In one or more preferred embodiments, the invention relates to at least one compound of Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[007] In some embodiments of the compound of Formula I, R_5 is OH

[008] In some embodiments of the compound of Formula I, R_6 is selected from OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl. In some such embodiments, R_6 is OH.

[009] In some embodiments of the compound of Formula I, m is 1 to 4 and at least one instance of R_7 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group. In some such embodiments, m is 1 to 4 and at least one instance of R_7 is a heterocyclyl group. In other such embodiments, m is 1 to 4 and at least one instance of R_7 is a heteroaryl group. In other such embodiments, m is 1 to 4 and at least one instance of R_7 is a phenyl or substituted phenyl group.

[010] In some embodiments of the compound of Formula I, m is 1 to 4 and at least one instance of R_7 is independently selected from halo or a moiety substituted with at least one halo.

[011] In some embodiments of the compound of Formula I, m is 0. In other embodiments, m is 1.

[012] In some embodiments of the compound of Formula I, n is 1. In some such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[013] In some embodiments of the compound of Formula I, R_1 and R_2 are independently selected from CN, lower alkyl, aryl, or substituted aryl. In some such embodiments, R_1 and R_2 are both lower alkyl. In some such

embodiments, R_1 and R_2 are both methyl groups. In other embodiments, R_1 and R_2 join to form a spirocyclic ring system. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered ring. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered cycloalkyl ring such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring. In some such embodiments, the cycloalkyl ring may be substituted. For example, the cycloalkyl ring may include an oxo (=O) group or other substituent. In some such embodiments, R_1 and R_2 join to form a heterocyclic spirocyclic ring system. In some such embodiments, the heterocyclic spirocyclic ring system includes one O, N, or S atom and in some cases includes one O atom. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring that comprises one N atom. In some such embodiments, R_1 and R_2 join to form a piperidine ring that is optionally substituted. In some embodiments, R_1 and R_2 join to form a 5 or 6 membered ring comprising one O atom. In still other such embodiments, R_1 and R_2 join to form a six membered ring comprising one O atom. In some such embodiments, R_1 and R_2 join to form a 6 membered ring. In some embodiments, R_1 and R_2 join to form a tetrahydrofuran ring whereas in other embodiments they join to form a pyran ring.

[014] In some embodiments of the compound of Formula I, R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$. In other embodiments, R_1 and R_2 join to form the group $-CH_2-O-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-CH_2-$.

[015] In some embodiments of the compound of Formula I, R_1 is CN. In some embodiments R_1 is CN and R_2 is a C_1-C_4 alkyl group. In some such embodiments, R_1 is CN and R_2 is a methyl group.

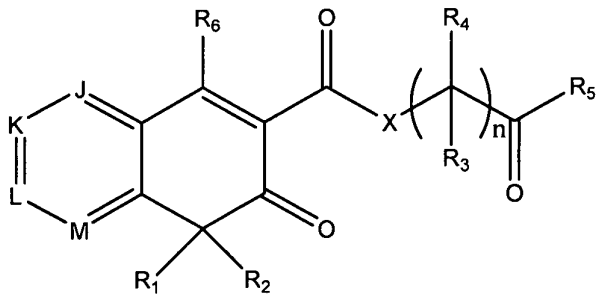
[016] In some embodiments of the compound of Formula I, X is NH, n is 1, R_3 and R_4 are independently selected from H, lower alkyl or substituted lower alkyl, and R_6 is OH. In some such embodiments R_5 is OH. In some such embodiments, one of R_3 and R_4 is a methyl group. In other such embodiments,

one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[017] In some embodiments of the compound of Formula I, R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring. In some such embodiments, one of R_3 or R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl. In some such embodiments, one of R_3 or R_4 is a methyl group. In some such embodiments, n is 1. In still other such embodiments, X is –NH-.

[018] In some embodiments of the compound of Formula I, X is $-(CR_bR_c)-$. In some such embodiments, X is $-CH_2-$. In other embodiments, X is –O-. In still other embodiments, X is $-NR_a-$. In some such embodiments, X is -NH-.

[019] In another aspect, the invention provides at least one compound of Formula II:



II

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, or a mixture of any of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[020] In some embodiments of the compound of Formula II, each of J, K, L, and M is CR_7.

[021] In some embodiments of the compound of Formula II, one of J, K, L, and M is N, and the other three of J, K, L, and M are CR_7. In some such embodiments, J is N and K, L, and M are CR_7. In other such embodiments, K is N and J, L, and M are CR_7. In still other such embodiments, L is N and J, K, and M are CR_7. In still further such embodiments, M is N and J, K, and L are CR_7.

[022] In some embodiments of any embodiments of the compound of Formula II, R_5 is OH.

[023] In some embodiments of any embodiments of the compound of Formula II, R_6 is OH.

[024] In some embodiments of the compound of Formula II, at least one instance of R_7 is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group. In some such embodiments, at least one instance of R_7 is a heterocyclyl group. In some embodiments, at least one instance of R_7 is a heteroaryl group. In some embodiments, at least one instance of R_7 is a phenyl or substituted phenyl group.

[025] In some embodiments of the compound of Formula II, at least one instance of R_7 is chosen from a halo or a moiety substituted with at least one halo.

[026] In some embodiments of the compound of Formula II, n is 1. In some such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[027] In some embodiments of the compound of Formula II, R_1 and R_2 are independently selected from CN, lower alkyl, aryl, or substituted aryl. In some such embodiments, R_1 and R_2 are both lower alkyl. In some such embodiments, R_1 and R_2 are both methyl groups. In other embodiments, R_1 and R_2 join to form a spirocyclic ring system. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered ring. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered cycloalkyl ring such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring. In some such embodiments, the cycloalkyl ring may be substituted. For example, the cycloalkyl ring may include an oxo (=O) group or other substituent. In some such embodiments, R_1 and R_2 join to form a heterocyclic spirocyclic ring system. In some such embodiments, the heterocyclic spirocyclic ring system includes one O, N, or S atom and in some cases includes one O atom. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring that comprises one N atom. In some such embodiments, R_1 and R_2 join to form a piperidine ring that is optionally substituted. In some embodiments, R_1 and R_2 join to form a 5 or 6 membered ring comprising one O atom. In still other such embodiments, R_1 and R_2 join to form a six membered ring comprising one O atom. In some such embodiments, R_1 and R_2 join to form a 6 membered ring. In some embodiments, R_1 and R_2 join to form a tetrahydrofuran ring whereas in other embodiments they join to form a pyran ring.

[028] In some embodiments of the compound of Formula II, R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$. In other embodiments, R_1 and

R_2 join to form the group $-CH_2-O-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-CH_2-$.

[029] In some embodiments of the compound of Formula II, R_1 is CN. In some embodiments R_1 is CN and R_2 is a C_1-C_4 alkyl group. In some such embodiments, R_1 is CN and R_2 is a methyl group.

[030] In some embodiments of the compound of Formula II, X is NH, n is 1, R_3 and R_4 are independently selected from H, lower alkyl or substituted lower alkyl, and R_6 is OH. In some such embodiments R_5 is OH. In some such embodiments, one of R_3 and R_4 is a methyl group. In other such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[031] In some embodiments of the compound of Formula II, R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring. In some such embodiments, one of R_3 or R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl. In some such embodiments, one of R_3 or R_4 is a methyl group. In some such embodiments, n is 1. In still other such embodiments, X is –NH-.

[032] In some embodiments of the compound of Formula II, X is $-(CR_bR_c)-$. In some such embodiments, X is $-CH_2-$. In other embodiments, X is –O-. In still other embodiments, X is $-NR_a-$. In some such embodiments, X is -NH-.

[033] In some embodiments, the at least one compound is a salt. Such salts may be anhydrous or associated with water as a hydrate.

[034] In some embodiments, the compound is a prodrug. In some such embodiments, the compound is a $(C_1$-$C_6)$alkyl ester such as a methyl, ethyl, propyl, butyl, pentyl, or hexyl ester.

[035] Also provided herein are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, and a therapeutically effective amount of at least one compound of any of the embodiments described

herein. In such embodiments, the at least one compound is present in an amount effective for the treatment of at least one disease selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[036] Further provided are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, and a therapeutically effective amount of at least one compound of any of the embodiments described herein in combination with at least one additional compound such as an erythropoiesis stimulating agent or a chemotherapeutic agent.

[037] Additionally provided is a method of increasing or stabilizing HIF levels or activity in a subject by administering to the subject at least one compound of any of the embodiments described herein.

[038] Further provided is a method of treating a condition where it is desired to modulate HIF activity comprising administering to a subject at least one compound of any of the embodiments described herein. In some such embodiments, the condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[039] Also provided is a method of treating a hypoxic or ischemic related disorder in a subject comprising administering to a subject at least one compound of any of the embodiments described herein.

[040] Also provided is a method of treating anemia in a subject comprising administering to a subject at least one compound of any of the embodiments described herein.

[041] Further provided is a method of modulating the amount of HIF in a cell. Such methods include contacting the cell with at least one compound of any of the embodiments described herein.

[042] Additionally provided is a method of increasing the amount of hemoglobin F in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[043] Also provided is a method of modulating angiogenesis in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[044] Additionally provided is a method of treating at least one disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of any of the embodiments described herein. In some such embodiments, the at least one disease is selected from ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[045] Also provided is a method of inhibiting HIF hydroxylation in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[046] In some embodiments, the HIF PHD inhibitory activity IC_{50} value of the compound is 40 μM or less. In other embodiments, the HIF PHD inhibitory activity IC_{50} value of the compound is 10 μM or less.

[047] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament.

[048] In some such embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for increasing or stabilizing HIF levels or activity in a subject.

[049] In some such embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating a condition where it is desired to modulate HIF activity. In some such embodiments, the condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[050] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating a hypoxic or ischemic related disorder in a subject.

[051] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for modulating the amount if HIF in a cell. In some embodiments, the at least one compound according to any of the embodiments is used to modulate the amount of HIF in a cell.

[052] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for modulating angiogenesis in a subject.

[053] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for inhibiting HIF hydroxylation in a subject.

[054] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating anemia.

[055] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[056] Figure 1 is a graph illustrating the ratio of fluorescence signal to background generated by the interaction of Eu-VCB with streptavidin-APC-hydroxyprolyl HIF1α peptide.

[057] Figures 2A and 2B are graphs illustrating the ratio of TR-FRET signal generated by the interaction of Eu-VCB with streptavidin-APC-hydroxyprolyl HIF1α peptide over background signal generated by the interaction of Eu-VCB with streptavidin-APC-HIF1α peptide (nonhydroxylated). Figure 2A illustrates a 0-125 nM peptide range and Figure 2B illustrates a 0-10 nM peptide range.

[058] Figures 3A and 3B are graphs illustrating VCB binding and TR-FRET detection for determining HIF PHD2 hydroxylation of a HIF1α peptide. Figure 3A illustrates a time course for the hydroxylation of the HIF1α peptide with increasing amounts of HIF PHD2 enzyme. Figure 3B illustrates initial rates with increasing enzyme concentrations.

DETAILED DESCRIPTION OF THE INVENTION

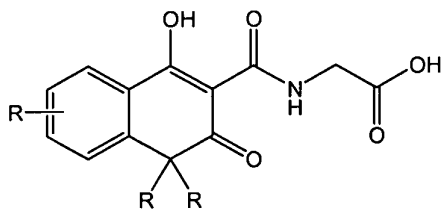
[059] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the standard deviation found in their respective testing measurements.

[060] As used herein, if any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. If the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the present disclosure may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers or diastereomers. Accordingly, any chemical structures within the scope of the specification depicted, in whole or in part, with a relative configuration encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into the component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan.

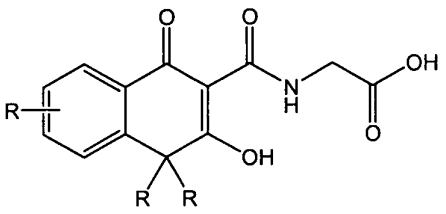
[061] Compounds of Formula I and Formula II include, but are not limited to, optical isomers of compounds of Formula I and Formula II,

racemates, and other mixtures thereof. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. In addition, compounds of Formula I and Formula II include Z- and E- forms (or *cis-* and *trans-* forms) of compounds with double bonds.

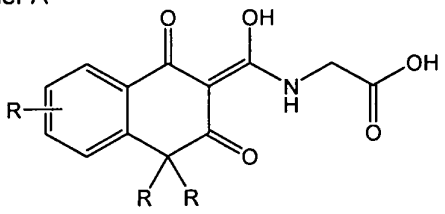
[062] Compounds of the invention may exist in multiple tautomeric forms. These forms are illustrated below as "Tautomer A", "Tautomer B", and "Tautomer C":



Tautomer A



Tautomer B



Tautomer C

Compounds of the invention are depicted structurally and named as compounds in the "Tautomer A" form. However, it is specifically contemplated that the compounds may also exist in "Tautomer B" or "Tautomer C" form and compounds in "Tautomer B" form or "Tautomer C" form or another tautomeric form are expressly considered to be part of the invention.

[063] Compounds of the present disclosure include, but are not limited to, compounds of Formula I and Formula II and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, solvates, crystal forms

(including polymorphs and clathrates), chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. As used herein, the term "compound" encompasses not only the compound itself, but also a pharmaceutically acceptable salt thereof, a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, and mixtures of any of the foregoing.

[064] As noted above, prodrugs also fall within the scope of chemical entities, for example, ester or amide derivatives of the compounds of Formula I or Formula II. The term "prodrugs" includes any compounds that become compounds of Formula I or Formula II when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, benzoate, carbomethoxy, carboethoxy and like derivatives of functional groups (such as alcohol, carboxylic acid, ether, ester, or amine groups) in the compounds of Formula I or Formula II. In some embodiments, the prodrugs of the compounds of Formula I and Formula II are esters such as methyl, ethyl, propyl, butyl, pentyl, and hexyl esters.

[065] The term "solvate" refers to the compound formed by the interaction of a solvent and a compound. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[066] "Alkenyl" refers to an unsaturated branched, straight-chain, or cyclic hydrocarbon group having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the Z- or E- form (*cis* or *trans*) about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl; and the like. In

certain embodiments, an alkenyl group has from 2 to 20 carbon atoms and in other embodiments, from 2 to 6 carbon atoms, i.e. "lower alkenyl."

[067] "Alkynyl" refers to an unsaturated branched or straight-chain hydrocarbon having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyl; butynyl, 2-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl and the like. In certain embodiments, an alkynyl group has from 2 to 20 carbon atoms and in other embodiments, from 2 to 6 carbon atoms, i.e. "lower alkynyl."

[068] "Alkoxy" refers to a radical –OR where R represents an alkyl group as defined herein. Representative examples include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, cyclohexyloxy, and the like.

[069] "Alkoxycarbonyl" refers to a radical –C(O)–OR where R is as defined above.

[070] "Alkyl" refers to a saturated, branched, straight-chain, or cyclic monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkyl groups include, but are not limited to, methyl, ethyl, propyls such as propan-1-yl, propan-2-yl, and cyclopropan-1-yl, butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, tert-butyl, and the like. In certain embodiments, an alkyl group comprises from 1 to 20 carbon atoms. As used herein the term "lower alkyl" refers to an alkyl group comprising from 1 to 6 carbon atoms.

[071] "Alkylene" refers to a divalent saturated hydrocarbon group derived from a parent alkane by removal of two hydrogen atoms. Examples of alkylene group include, but are not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)(H)-$, and the like.

[072] "Alkenylene" refers to a divalent unsaturated hydrocarbon group having at least one carbon-carbon double bond derived by the removal of two hydrogen atoms from a parent alkene. The group may be in either the Z- or E-form (*cis* or *trans*) about the double bond(s). Examples of alkenylene groups,

include, but are not limited to, -CH=CH-, -CH=C(H)CH_2-, -CH_2C(H)=C(H)CH_2-, and the like.

[073] "Alkynylene" refers to a divalent unsaturated hydrocarbon group having at least one carbon-carbon triple bond derived by the removal of two hydrogen atoms from a parent alkyne. Example of alkynylene groups, include, but are not limited to, -C≡C-, -CH_2C≡C-, -CH_2C≡CCH_2-.

[074] "Aryl" refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aryl encompasses 5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocyclic ring containing 1 or more heteroatoms chosen from N, O, and S. In certain embodiments, an aryl group can comprise from 6 to 10 carbon atoms. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings is fused with a heterocyclic aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[075] "Arylalkyl" or "aralkyl" refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically, but not necessarily, a terminal carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. In certain embodiments, an arylalkyl group can be (C_{6-30}) arylalkyl, e.g., the alkyl group of the arylalkyl group can be (C_{1-10}) and the aryl moiety can be (C_{5-20}).

[076] "Arylalkenyl" refers to an alkenyl group in which a bond to one of the hydrogen atoms of the alkenyl group is replaced with a bond to an aryl group.

[077] "Arylalkynyl" refers to an alkynyl group in which a bond to one of the hydrogen atoms of the alkynyl group is replaced with a bond to an aryl group.

[078] "Carbonyl" refers to the radical –C(O) group.

[079] "Carboxy" refers to the radical –C(O)OH.

[080] "Cyano" refers to the radical –CN.

[081] "Cycloalkyl" refers to a saturated or unsaturated cyclic alkyl group. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. In certain embodiments, the cycloalkyl group can be C_{3-10} cycloalkyl, such as, for example, C_{3-6} cycloalkyl.

[082] "Heterocyclic", "heterocyclo" or "heterocyclyl" refer to a saturated or unsaturated, but non-aromatic, cyclic hydrocarbon group in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom and its associated hydrogen atoms, where appropriate. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, O, and S. Typical heterocyclyl groups include, but are not limited to, groups derived from epoxides, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran and the like. Substituted heterocyclyl also includes ring systems substituted with one or more oxo (=O) or oxide ($-O^-$) substituents, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[083] "Heterocyclylalkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced with a bond to a heterocyclyl group. Examples of heterocyclylalkyl groups, include, but are not limited to, morpholinylmethyl, morpholinylethyl, tetrahydrofuranylmethyl, piperidinylmethyl, and the like.

[084] "Disease" refers to any disease, disorder, condition, symptom, or indication.

[085] "Halo" or "halogen" refers to a fluoro, chloro, bromo, or iodo group.

[086] "Haloalkyl" refers to an alkyl group in which at least one hydrogen is replaced with a halogen. Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with two or more halogen atoms). The term "perhaloalkyl" means, unless otherwise stated, an alkyl group in which each of the hydrogen atoms is replaced with a halogen atom. For example, the term "perhaloalkyl", includes, but is not limited to, trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[087] "Heteroaryl" refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Heteroaryl encompasses 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and polycyclic ring systems containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring. For example, heteroaryl includes a 5- to 7-membered heteroaromatic ring fused to a 5- to 7-membered cycloalkyl ring or a carbocyclic aromatic ring and a 5- to 7-membered heteroaromatic ring fused to a 5- to 7-membered heterocyclic ring. For fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the carbocyclic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Heteroaryl does not encompass or overlap with aryl as defined above. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, arsindole,

carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. In certain embodiments, the heteroaryl group can be between 5 to 20 membered heteroaryl, such as, for example, a 5 to 10 membered heteroaryl. In certain embodiments, heteroaryl groups can be those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole, and pyrazine.

[088] "Heteroarylalkyl" or "heteroaralkyl" refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylalkenyl, and/or heteroarylalkynyl is used. In certain embodiments, the heteroarylalkyl group can be a 6 to 30 membered heteroarylalkyl, e.g., the alkyl moiety of the heteroarylalkyl can include 1 to 10 members and the heteroaryl moiety of the heteroarylalkyl can include from 5 to 20-members.

[089] "Sulfonyl" refers to a radical $-S(O)_2R$ where R is an alkyl, substituted alkyl, substituted cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl group as defined herein. Representative examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, and the like.

[090] "Sulfanyl" refers to a radical –SR where R is an alkyl, substituted alkyl, substituted cycloalkyl, substituted heterocyclyl, substituted aryl, or substituted heteroaryl group as defined herein that may be optionally substituted as defined herein. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio, butylthio, and the like.

[091] "Pharmaceutically acceptable" refers to generally recognized for use in animals, and more particularly in humans.

[092] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, dicyclohexylamine, and the like.

[093] "Pharmaceutically acceptable excipient," "pharmaceutically acceptable carrier," or "pharmaceutically acceptable adjuvant" refer, respectively, to an excipient, carrier or adjuvant with which at least one compound of the present disclosure is administered. "Pharmaceutically acceptable vehicle" refers to any of a diluent, adjuvant, excipient or carrier with which at least one compound of the present disclosure is administered.

[094] Spirocyclic ring systems found in compounds of the invention contain from 3 to 7, from 4 to 7, from 5 to 6, 5, or 6 ring members. Spirocyclic ring systems may be carbocyclic and thus contain only carbon atoms as ring members. Examples of carbocyclic spirocyclic ring systems include cycloalkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl rings. Spirocyclic ring systems found in compounds of the invention may contain 1 or 2 hetero atoms chosen from –O-, -S-, and –NR-, a "heterocyclic spirocyclic ring system". Spirocyclic ring systems may be unsubstituted or may be substituted. For example, spirocyclic

ring systems may include substituents such as, but not limited to, an oxo (=O) group, an optionally substituted alkyl group, an optionally substituted arylalkyl group, an optionally substituted heteroarylalkyl group, an optionally substituted heterocyclylalkyl group, a halogen, a group of formula –C(=O)-alkyl, a group of formula –C(=O)-aryl, a group of formula –C(=O)-heteroaryl, a group of formula –C(=O)-heterocyclyl, and the like.

[095] "Stereoisomer" refers to an isomer that differs in the arrangement of the constituent atoms in space. Stereoisomers that are mirror images of each other and optically active are termed "enantiomers," and stereoisomers that are not mirror images of one another and are optically active are termed "diastereomers."

[096] "Subject" includes mammals and humans. The terms "human" and "subject" are used interchangeably herein.

[097] "Substituted" refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, –X, $-R_{11}$, –OH, =O, $-OR_{11}$, $-SR_{11}$, –SH, =S, $-NR_{11}R_{12}$, $=NR_{11}$, $-CX_3$, $-CF_3$, –CN,$-NO_2$,$-S(O)_2R_{11}$, $-OS(O_2)OH$, $-OS(O)_2R_{11}$, $-OP(O)(OR_{11})(OR_{12})$, $-C(O)R_{11}$, $-C(S)R_{11}$, $-C(O)OR_{11}$, $-C(O)NR_{11}R_{12}$, –C(O)OH, $-C(S)OR_{11}$, $-NR_{13}C(O)NR_{11}R_{12}$, $-NR_{13}C(S)NR_{11}R_{12}$, $-NR_{13}C(NR_{11})NR_{11}R_{12}$,$-C(NR_{11})NR_{11}R_{12}$, $-S(O)_2NR_{11}R_{12}$, $-NR_{13}S(O)_2R_{11}$, $-NR_{13}C(O)R_{11}$, and $-S(O)R_{11}$ where each X is independently a halo; each R_{11} and R_{12} are independently hydrogen, alkyl, substituted alkyl, alkyl interrupted by one or more -O- or -S- groups, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl,$-NR_{13}R_{14}$, $-C(O)R_{13}$ or $-S(O)_2R_{13}$ or optionally R_{11} and R_{12} together with the atom to which R_{11} and R_{12} are attached form one or more heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl rings; and R_{13} and R_{14} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl,

arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, or optionally R_{13} and R_{14} together with the nitrogen atom to which R_{13} and R_{14} are attached form one or more heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl rings. In certain embodiments, a tertiary amine or aromatic nitrogen may be substituted with on or more oxygen atoms to form the corresponding nitrogen oxide.

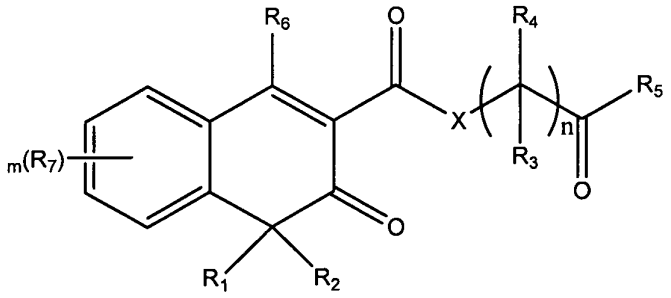
[098] "Therapeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary depending on the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be readily apparent to those skilled in the art or capable of determination by routine experimentation.

[099] "Treating" or "treatment" of any disease or disorder refers to arresting or ameliorating a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the risk of acquiring a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the development of a disease, disorder or at least one of the clinical symptoms of the disease or disorder, or reducing the risk of developing a disease or disorder or at least one of the clinical symptoms of a disease or disorder. "Treating" or "treatment" also refers to inhibiting the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, or inhibiting at least one physical parameter which may not be discernible to the subject. Further, "treating" or "treatment" refers to delaying the onset of the disease or disorder or at least symptoms thereof in a subject which may be exposed to or predisposed to a

disease or disorder even though that subject does not yet experience or display symptoms of the disease or disorder.

[0100] Reference will now be made in detail to embodiments of the present disclosure. While certain embodiments of the present disclosure will be described, it will be understood that it is not intended to limit the embodiments of the present disclosure to those described embodiments. To the contrary, reference to embodiments of the present disclosure is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the embodiments of the present disclosure as defined by the appended claims.

[0101] In one aspect, the invention provides at least one compound of Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or

substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[0102] In some embodiments of the compound of Formula I, R_5 is OH.

[0103] In some embodiments of the compound of Formula I, R_6 is selected from OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl. In some such embodiments, R_6 is OH.

[0104] In some embodiments of the compound of Formula I, m is 1 to 4 and at least one instance of R_7 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group. In some such embodiments, m is 1 to 4 and at least one instance of R_7 is a heterocyclyl group. In other such embodiments, m is 1 to 4 and at least one instance of R_7 is a heteroaryl group. For example, in some embodiments, at least one instance of R_7 is a heteroaryl group such as a substituted or unsubstituted pyridine group. In some embodiments, at least one instance of R_7 is selected from an optionally substituted 2-, 3-, or 4-pyridyl group. In some such embodiments, at least one instance of R_7 is a pyridine group substituted with one or more substituents selected from lower alkyl, halo, hydroxy, alkoxy, or the like. In other such embodiments, m is 1 to 4 and at least one instance of R_7 is a phenyl or substituted phenyl group. For example, in some embodiments, at least one instance of R_7 is selected from a phenyl or a phenyl substituted with at least one substituent selected from lower alkyl, halo, alkoxy, a dialkylamino group such as a dimethylamino group, and the like.

[0105] In some embodiments, at least one instance of R_7 is selected from a lower alkyl group such as a methyl group. In other embodiments, at least one instance of R_7 is selected from an alkyl group, a substituted alkyl group, an alkenyl group, a substituted alkenyl group, an alkynyl group, or a substituted alkynyl group. For example, in some embodiments, at least one instance of R_7 is selected from a group of formula methyl, ethyl, propyl, butyl, pentyl, hexyl,

heptyl, octyl, -CH=CH-CH_2-O-CH_3, -CH_2-CH_2-CH_2-O-CH_3, -CH=CH-phenyl, -CH_2-CH_2-phenyl, -C≡C-phenyl, -C≡C-pyridyl, -C≡C-CH_2-O-CH_3, or the like.

[0106] In some embodiments of the compound of Formula I, m is 1 to 4 and at least one instance of R_7 is independently selected from halo or a moiety substituted with at least one halo. In some embodiments, at least one instance of R_7 is a perhaloalkyl group such as a perfluoroalkyl such as a CF_3. In some embodiments, at least one instance of R_7 is a halo group selected from F, Cl, or Br. In some embodiments, at least two instances of R_7 are halo groups independently selected from F, Cl, and Br.

[0107] In some embodiments, at least one instance of R_7 is an OR_8 group where R_8 is H, a lower alkyl, or a substituted lower alkyl. For example, in some embodiments, at least one instance of R_8 is selected from an -OH, a methoxy group, an ethoxy group, a benzyloxy group, a group of formula –OCH_2-$CH(CH_3)_2$, or the like.

[0108] In some embodiments of the compound of Formula I, m is 0. In other embodiments, m is 1.

[0109] In some embodiments of the compound of Formula I, n is 1. In some such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group. In other such embodiments where n is 1, both of R_3 and R_4 are H. In some embodiments where n is 1, one of R_3 and R_4 is a lower alkyl group or a substituted lower alkyl group such as, but not limited to, a methyl, ethyl, propyl, -CH_2-OH group, or the like. In some such embodiments, one of R_3 and R_4 is H and the other of R_3 and R_4 is a lower alkyl groups.

[0110] In some embodiments of the compound of Formula I, R_1 and R_2 are independently selected from CN, lower alkyl, aryl, or substituted aryl. In some such embodiments, R_1 and R_2 are both lower alkyl. In some such embodiments, R_1 and R_2 are both methyl groups. In other embodiments, R_1 and R_2 join to form a spirocyclic ring system. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered ring. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered cycloalkyl ring such as a cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring. In some such embodiments, the cycloalkyl ring may be substituted. For example, the cycloalkyl ring may include an oxo (=O) group or other substituent. In some such embodiments, R_1 and R_2 join to form a heterocyclic spirocyclic ring system. In some such embodiments, the heterocyclic spirocyclic ring system includes one O, N, or S atom and in some cases includes one O atom. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring that comprises one N atom. In some such embodiments, R_1 and R_2 join to form a piperidine ring that is optionally substituted. For example, in some embodiments, R_1 and R_2 join to form a piperidine in which the N atom of the piperidine is bonded to a benzyl group, a group of formula -C(=O)-phenyl, or a lower alkyl group such as a methyl group, whereas in other embodiments, the piperidine ring is not substituted. In some embodiments, R_1 and R_2 join to form a 5 or 6 membered ring comprising one O atom. In still other such embodiments, R_1 and R_2 join to form a six membered ring comprising one O atom. In some such embodiments, R_1 and R_2 join to form a 6 membered ring. In some embodiments, R_1 and R_2 join to form a tetrahydrofuran ring whereas in other embodiments they join to form a pyran ring.

[0111] In some embodiments of the compound of Formula I, R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$. In other embodiments, R_1 and R_2 join to form the group $-CH_2-O-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-CH_2-$.

[0112] In some embodiments of the compound of Formula I, R_1 is CN. In some embodiments R_1 is CN and R_2 is a C_1-C_4 alkyl group. In some such embodiments, R_1 is CN and R_2 is a methyl group.

[0113] In some embodiments of the compound of Formula I, at least one of R_1 and R_2 is selected from aryl or substituted aryl. For example, in some embodiments, at least one of R_1 and R_2 is phenyl or a phenyl substituted with one or more of F, Cl, Br, lower alkyl, OH, or lower alkoxy. In some such

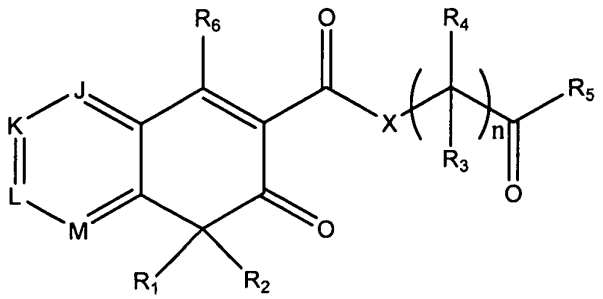
embodiments, the other of R_1 and R_2 is a lower alkyl group such as, but not limited to a methyl or ethyl group.

[0114] In some embodiments of the compound of Formula I, X is NH, n is 1, R_3 and R_4 are independently selected from H, lower alkyl or substituted lower alkyl, and R_6 is OH. In some such embodiments R_5 is OH. In some such embodiments, at least one of R_3 and R_4 is a methyl group. In other such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[0115] In some embodiments of the compound of Formula I, R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring. In some such embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl. In some such embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl and R_3 or is H. In some embodiments, one of R_3 or R_4 is a methyl group. In some such embodiments, n is 1. In still other such embodiments, X is –NH-.

[0116] In some embodiments of the compound of Formula I, X is $-(CR_bR_c)-$. In some such embodiments, X is $–CH_2-$. In other embodiments, X is –O-. In still other embodiments, X is $–NR_a-$. In some such embodiments, X is -NH-.

[0117] In another aspect, the invention provides at least one compound of Formula II:



II

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, a chelate thereof, a non-covalent complex thereof, a prodrug thereof, or a mixture of any of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[0118] In some embodiments of the compound of Formula II, each of J, K, L, and M is CR_7.

[0119] In some embodiments of the compound of Formula II, one of J, K, L, and M is N, and the other three of J, K, L, and M are CR_7. In some such embodiments, J is N and K, L, and M are CR_7. In other such embodiments, K is N and J, L, and M are CR_7. In still other such embodiments, L is N and J, K, and M are CR_7. In still further such embodiments, M is N and J, K, and L are CR_7.

[0120] In some embodiments of any embodiments of the compound of Formula II, R_5 is OH.

[0121] In some embodiments of any embodiments of the compound of Formula II, R_6 is OH.

[0122] In some embodiments of the compound of Formula II, at least one instance of R_7 is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group. In some such embodiments, at least one instance of R_7 is a heterocyclyl group. In some embodiments, at least one instance of R_7 is a heteroaryl group. For example, in some embodiments, at least one instance of R_7 is a heteroaryl group such as a substituted or unsubstituted pyridine group. In some embodiments, at least one instance of R_7 is selected from an optionally substituted 2-, 3-, or 4-pyridyl group. In some such embodiments, at least one instance of R_7 is a pyridine group substituted with one or more substituents selected from lower alkyl, halo, hydroxy, alkoxy, or the like. In some embodiments, at least one instance of R_7 is a phenyl or substituted phenyl group. For example, in some embodiments, at least one instance of R_7 is selected from a phenyl or a phenyl substituted with at least one substituent selected from lower alkyl, halo, alkoxy, a dialkylamino group such as a dimethylamino group, and the like.

[0123] In some embodiments, at least one instance of R_7 is selected from a lower alkyl group such as a methyl group. In other embodiments, at least one instance of R_7 is selected from an alkyl group, a substituted alkyl group, an alkenyl group, a substituted alkenyl group, an alkynyl group, or a substituted alkynyl group. For example, in some embodiments, at least one instance of R_7 is selected from a group of formula methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -CH=CH-CH_2-O-CH_3, -CH_2-CH_2-CH_2-O-CH_3, -CH=CH-phenyl, -CH_2-CH_2-phenyl, -C≡C-phenyl, -C≡C-pyridyl, -C≡C-CH_2-O-CH_3, or the like.

[0124] In some embodiments of the compound of Formula II, at least one instance of R_7 is chosen from a halo or a moiety substituted with at least one halo. In some embodiments, at least one instance of R_7 is a perhaloalkyl group such as a perfluoroalkyl such as a CF_3. In some embodiments, at least one instance of R_7 is a halo group selected from F, Cl, or Br. In some embodiments, at least two instances of R_7 are halo groups independently selected from F, Cl, and Br.

[0125] In some embodiments, at least one instance of R_7 is an OR_8 group where R_8 is H, a lower alkyl, or a substituted lower alkyl. For example, in some embodiments, at least one instance of R_8 is selected from an -OH, a methoxy group, an ethoxy group, a benzyloxy group, a group of formula $-OCH_2-CH(CH_3)_2$, or the like.

[0126] In some embodiments of the compound of Formula II, n is 1. In some such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group. In other such embodiments where n is 1, both of R_3 and R_4 are H. In some embodiments where n is 1, at least one of R_3 and R_4 is a lower alkyl group or a substituted lower alkyl group such as, but not limited to, a methyl, ethyl, propyl, $-CH_2-OH$ group, or the like. In some embodiments where n is 1, at least one of R_3 and R_4 is a lower alkyl group or a substituted lower alkyl group and the other of R_3 and R_4 is H. In some embodiments, both of R_3 and R_4 are lower alkyl groups

[0127] In some embodiments of the compound of Formula II, R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring. In some such embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl. In some embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl and R_3 is H. In some such embodiments, one of R_3 or R_4 is a methyl group. In some such embodiments, n is 1. In still other such embodiments, X is –NH-.

[0128] In some embodiments of the compound of Formula II, R_1 and R_2 are independently selected from CN, lower alkyl, aryl, or substituted aryl. In some such embodiments, R_1 and R_2 are both lower alkyl. In some such embodiments, R_1 and R_2 are both methyl groups. In other embodiments, R_1 and R_2 join to form a spirocyclic ring system. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered ring. In some such embodiments, R_1 and R_2 join to form a 3 to 7 membered cycloalkyl ring such as a cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring. In some such embodiments, the cycloalkyl ring may be substituted. For example, the cycloalkyl ring may include an oxo (=O) group or other substituent. In some such embodiments, R_1 and R_2 join to form a heterocyclic spirocyclic ring system. In some such embodiments, the heterocyclic spirocyclic ring system includes one O, N, or S atom and in some cases includes one O atom. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring. In some embodiments, R_1 and R_2 join to form a 5-7 or 5-6 membered ring that comprises one N atom. In some such embodiments, R_1 and R_2 join to form a piperidine ring that is optionally substituted. For example, in some embodiments, R_1 and R_2 join to form a piperidine in which the N atom of the piperidine is bonded to a benzyl group, a group of formula -C(=O)-phenyl, or a lower alkyl group such as a methyl group, whereas in other embodiments, the piperidine ring is not substituted. In some embodiments, R_1 and R_2 join to form a 5 or 6 membered ring comprising one O atom. In still other such embodiments, R_1 and R_2 join to form a six membered ring comprising one O atom. In some such embodiments, R_1 and R_2 join to form a 6 membered ring. In some embodiments, R_1 and R_2 join to form a tetrahydrofuran ring whereas in other embodiments they join to form a pyran ring.

[0129] In some embodiments of the compound of Formula II, R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$. In other embodiments, R_1 and R_2 join to form the group $-CH_2-O-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-CH_2-$

[0130] In some embodiments of the compound of Formula II, R_1 is CN. In some embodiments R_1 is CN and R_2 is a C_1-C_4 alkyl group. In some such embodiments, R_1 is CN and R_2 is a methyl group.

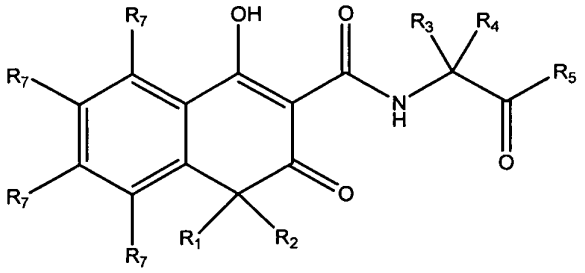
[0131] In some embodiments of the compound of Formula II, at least one of R_1 and R_2 is selected from aryl or substituted aryl. For example, in some embodiments, at least one of R_1 and R_2 is phenyl or a phenyl substituted with one or more of F, Cl, Br, lower alkyl, OH, or lower alkoxy. In some such

embodiments, the other of R_1 and R_2 is a lower alkyl group such as, but not limited to a methyl or ethyl group.

[0132] In some embodiments of the compound of Formula II, X is NH, n is 1, R_3 and R_4 are independently selected from H, lower alkyl or substituted lower alkyl, and R_6 is OH. In some such embodiments R_5 is OH. In some such embodiments, one of R_3 or R_4 is a substituted lower alkyl. In some such embodiments, one of R_3 or R_4 is a perhaloalkyl such as a CF_3 group.

[0133] In some embodiments of the compound of Formula II, X is $-(CR_bR_c)-$. In some such embodiments, X is $-CH_2-$. In other embodiments, X is –O-. In still other embodiments, X is $-NR_a-$. In some such embodiments, X is -NH-.

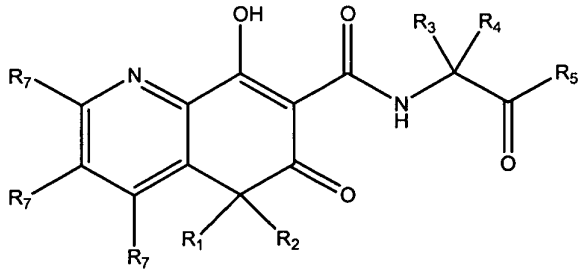
[0134] In some embodiments, the compound of Formula II has the Formula IIA, and the variables R_1, R_2 R_3, R_4, R_5, and R_7 have the definitions provided in any of the aspects and embodiments described above.



IIA

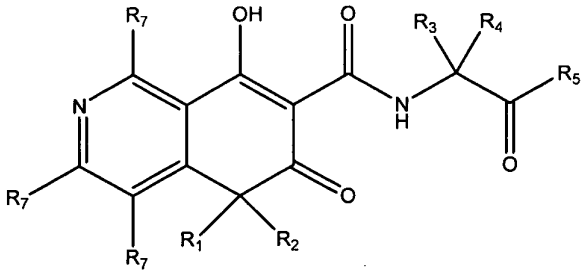
[0135] In some embodiments of the compound of Formula IIA, R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring. In some such embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl. In some embodiments, R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl and R_3 is H. In some such embodiments, R_4 is a methyl group.

[0136] In some embodiments, the compound of Formula II has the Formula IIB, and the variables R_1, R_2 R_3, R_4, R_5, and R_7 have the definitions provided in any of the aspects and embodiments described above



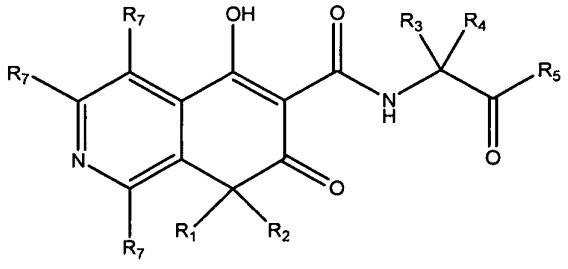
IIB

[0137] In some embodiments, the compound of Formula II has the Formula IIC, and the variables R_1, R_2 R_3, R_4, R_5, and R_7 have the definitions provided in any of the aspects and embodiments described above.



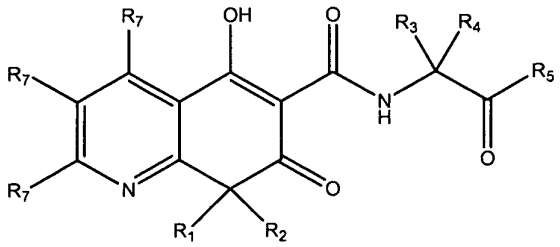
IIC

[0138] In some embodiments, the compound of Formula II has the Formula IID, and the variables R_1, R_2 R_3, R_4, R_5, and R_7 have the definitions provided in any of the aspects and embodiments described above.



IID

[0139] In some embodiments, the compound of Formula II has the Formula IIE, and the variables R_1, R_2 R_3, R_4, R_5, and R_7 have the definitions provided in any of the aspects and embodiments described above.



IIE

[0140] In certain embodiments the compound of the present invention can be

- N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-((4-hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine
- N-((6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine
- N-((7,8-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N((1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-((7-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine
- N-((6-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-((6,7-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine
- N-((6,7-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

- N-((6,7-dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine
- N-((6,7-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-(((1R)-6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-(((1S)-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-(((1R)-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-(((1S)-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine
- N-((7-chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

or a pharmaceutically acceptable salt thereof.

[0141] In some embodiments, the compound is selected from any one of the Example compounds or is a salt or (C_1-C_6) alkyl ester thereof.

[0142] Compounds of the present disclosure can contain one or more chiral centers. Such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers, and enriched mixtures thereof, are included within the scope of the present disclosure. Pure stereoisomers, and enriched mixtures thereof, can be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

[0143] In some embodiments, the at least one compound is a salt. Such salts may be anhydrous or associated with one or more molecules of water as a hydrate.

[0144] In some embodiments, the compound is a prodrug. In some such embodiments, the compound is a (C_1-C_6)alkyl ester such as a methyl, ethyl, propyl, butyl, pentyl, or hexyl ester.

[0145] Also provided herein are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, excipient, or diluent, and a therapeutically effective amount of at least one compound of any of the embodiments described herein. In such embodiments, the at least one compound is present in an amount effective for the treatment of at least one disease selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[0146] Further provided are pharmaceutical compositions that include at least one pharmaceutically acceptable carrier, and a therapeutically effective amount of at least one compound of any of the embodiments described herein in combination with at least one additional compound such as an erythropoiesis stimulating agent or a chemotherapeutic agent.

[0147] Additionally provided is a method of increasing or stabilizing HIF levels or activity in a subject by administering to the subject at least one compound of any of the embodiments described herein.

[0148] Further provided is a method of treating a condition where it is desired to modulate HIF activity comprising administering to a subject at least one compound of any of the embodiments described herein. In some such embodiments, the condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[0149] Also provided is a method of treating a hypoxic or ischemic related disorder in a subject comprising administering to a subject at least one compound of any of the embodiments described herein.

[0150] Also provided is a method of treating anemia in a subject comprising administering to a subject at least one compound of any of the embodiments described herein.

[0151] Further provided is a method of modulating the amount of HIF in a cell comprising contacting the cell with at least one compound of any of the embodiments described herein.

[0152] Additionally provided is a method of increasing the amount of hemoglobin F in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[0153] Also provided is a method of modulating angiogenesis in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[0154] Additionally provided is a method of treating at least one disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound of any of the embodiments described herein. In some such embodiments, the at least one disease is selected from ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[0155] Also provided is a method of inhibiting HIF hydroxylation in a subject comprising administering to the subject at least one compound of any of the embodiments described herein.

[0156] In some embodiments, the HIF PHD inhibitory activity IC_{50} value of the compound is 40 μM or less. In other embodiments, the HIF PHD inhibitory activity IC_{50} value of the compound is 10 μM or less. In still other embodiments, the HIF PHD inhibitory activity IC_{50} value of the compound is 100 nM or less, whereas in others it is 10 nM or less.

[0157] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament.

[0158] In some such embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for increasing or stabilizing HIF levels or activity in a subject.

[0159] In some such embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating a condition where it is desired to modulate HIF activity. In some such embodiments, the condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

[0160] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating a hypoxic or ischemic related disorder in a subject.

[0161] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for modulating the amount if HIF in a cell. In some embodiments, the at least one compound according to any of the embodiments is used to modulate the amount of HIF in a cell.

[0162] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for modulating angiogenesis in a subject.

[0163] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for inhibiting HIF hydroxylation in a subject.

[0164] In some embodiments, the at least one compound of any of the embodiments is used in the preparation of a medicament for treating anemia.

[0165] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant that the carrier, excipient, or diluent is

compatible with the other ingredients of the formulation and is not deleterious to the recipient thereof.

[0166] Composition formulation may improve one or more pharmacokinetic properties (*e.g.*, oral bioavailability, membrane permeability) of a compound of the invention (herein referred to as the active ingredient).

[0167] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0168] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The

tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108, 4,160,452, and 4,265,874 to form osmotic therapeutic tablets for control release.

[0169] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0170] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0171] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl

alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0172] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0173] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0174] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

[0175] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or

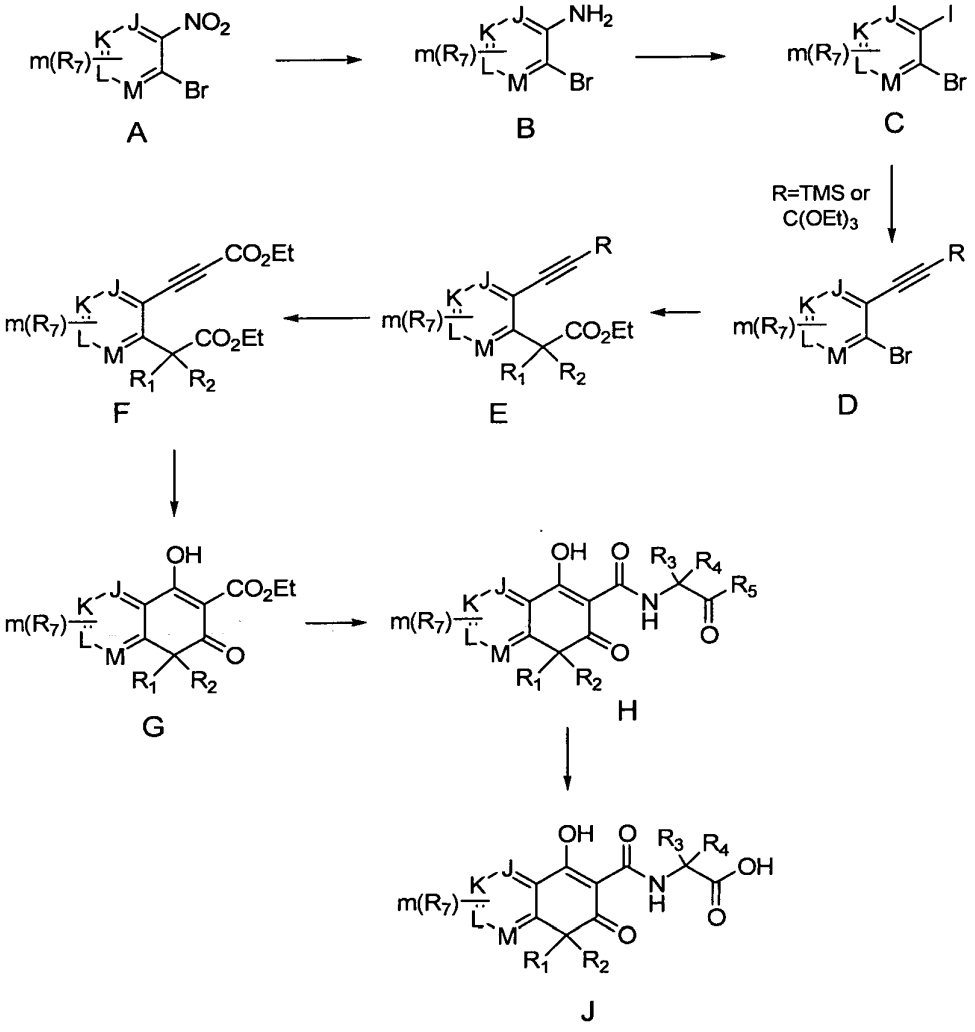
suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0176] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols.

[0177] For topical use, creams, ointments, jellies, solutions, or suspensions, *etc.*, containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[0178] The compounds of the invention can be prepared using the general synthetic route shown below in Scheme 1 and described more fully in the Examples.

Scheme 1

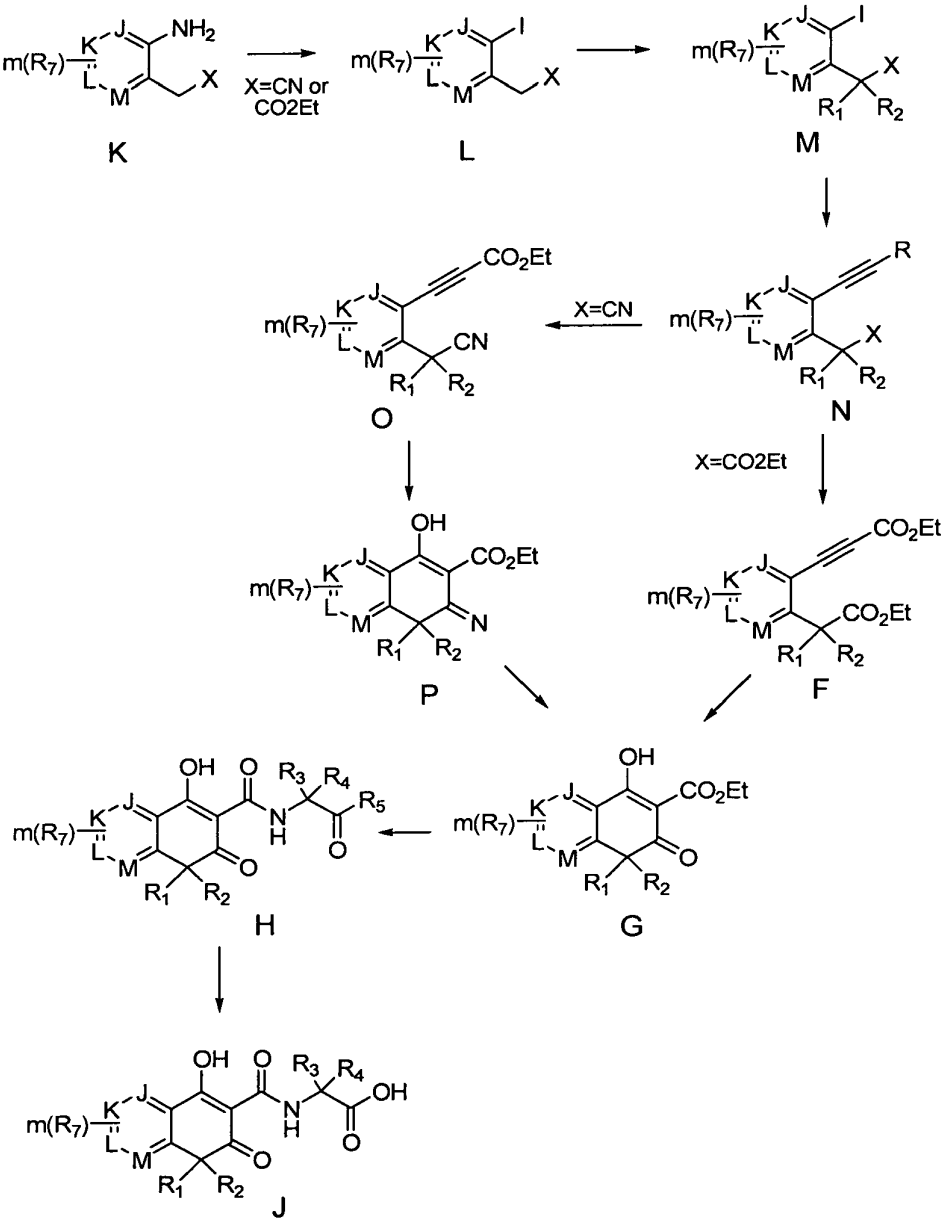


[0179] As shown in Scheme 1, the nitro bromo compound A is reduced to the amino bromo compound B by standard reducing agents like $SnCl_4$ or Fe/HCl. Compound B can be converted to iodo compound C by reaction with nitrous acid to form the appropriate diazonium ion, followed by Sandmeyer reaction by reduction of the diazonium ion by Cu(I) and halide transfer from copper. Iodo compound C can selectively be reacted with an appropriately substituted alkyne under Sonogashira or Stephens-Castro reaction conditions to give compound D. Sonogashira reactions typically involve palladium catalysis,

whereas the Stephens-Castro reactions involve copper arylacetylenes. Conversion of bromide D to compound E can be accomplished by palladium mediated cross-coupling of an appropriate metal enolate or silyl enolether derivative. Compound F can be generated by acidic deprotection of an appropriate orthoester derivative E or by deprotection of an appropriate trialkyl silane E followed by deprotonation and quenching with various electrophiles such as ethylchloroformate or ethyl cyanoformate. Compound F can be cyclized to compound G by reaction of a nucleophilic benzaldoxime derivative and subsequent elimination of aryl cyanide. Alternatively, compound F could be cyclized to compound G with additional oxygen nucleophiles such as allylic alcohol, benzylic alcohol or other protected alcohols. Compound H can generated by heating ester G in the presence of an amine. Specifically, compound H can be formed by heating compound G with a glycine alkyl ester derivative. Compound J can be formed by deprotecting an appropriate ester under basic saponification conditions. Alternatively, compound J can be formed by deprotecting an appropriate ester by acidic hydrolysis conditions.

[0180] The compounds of the invention can also be prepared using the general synthetic route shown below in Scheme 2 and described more fully in the Examples.

Scheme 2

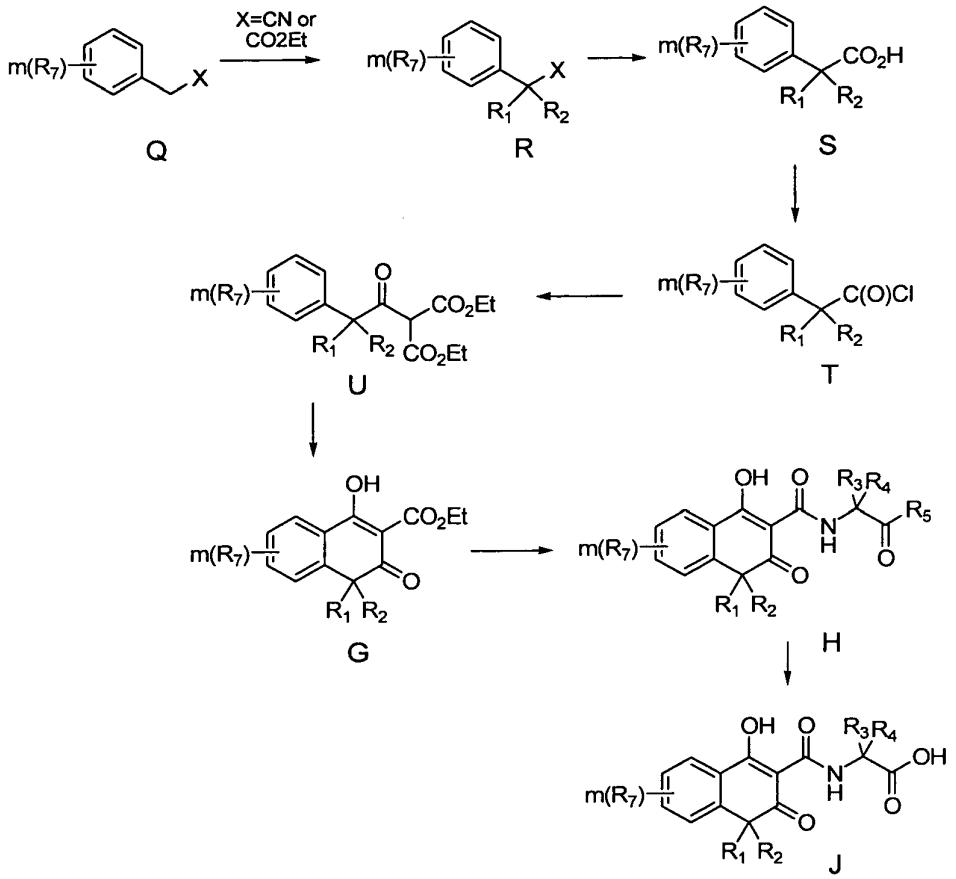


[0181] As shown in Scheme 2, iodo compound L can be prepared from amino compound K by diazotization with nitrous acid followed by Sandmeyer reaction with copper iodide. Compound L can be converted to compound M by deprotonation with reagents such as sodium hydride or potassium tert-butoxide

followed by alkylation with alkyl halides or sulfonates such as methyl iodide or methyl sulfate. Compound N can be prepared from compound M by reaction with an appropriate alkyne under Sonogashira or Castro-Stevens reaction conditions as described in Scheme 1. Compound N can be converted to either compound O or compound F by acidic deprotection of an appropriate orthoester derivative N or by deprotection of an appropriate trialkyl silane N followed by deprotonation and quenching with various electrophiles as described in Scheme 1. Compound O can be converted to compound P or compound F can be converted to compound G utilizing the cyclization conditions described with respect to Scheme 1. Furthermore, compound G can be generated by reaction of compound P with acidic hydrolysis conditions such as refluxing hydrochloric acid. The conversion of compound G to compounds H and compounds J are as described in Scheme 1.

[0182] The compounds of the invention can also be prepared using the general synthetic route shown below in Scheme 3 and described more fully in the Examples.

Scheme 3

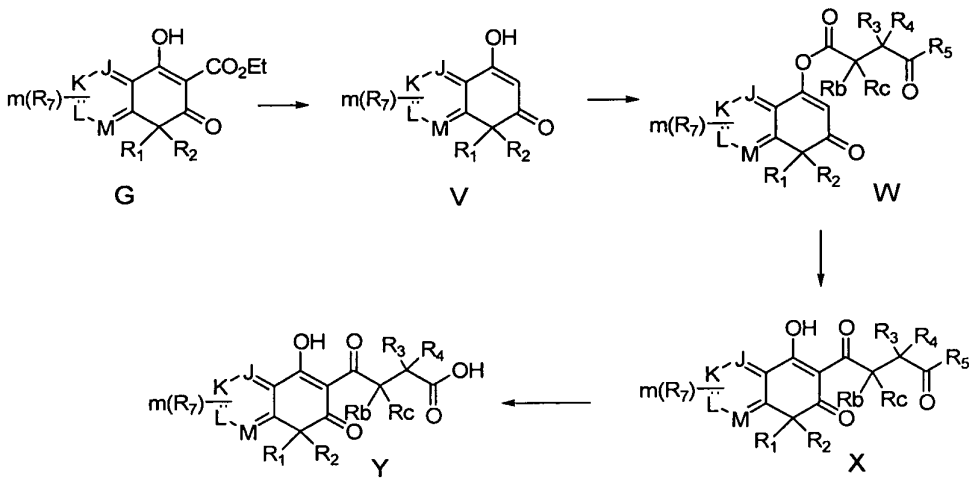


[0183] As shown in Scheme 3, compound Q can be alkylated to give compound R using the methodology described with respect to Scheme 2. Compound S can be prepared by acidic hydrolysis of an appropriate cyano derivative under conditions of refluxing hydrochloric acid. Alternatively, compound S can be prepared by an appropriate ester derivative under typical saponification deprotection conditions. Carboxylic acid S can be converted to the corresponding acid chloride by reaction with thionyl chloride or oxalyl chloride following typical protocols. Acid chloride T can be converted to compound U by reaction of an appropriate malonate anion, such as, but not limited to, the magnesium anion of diethylmalonate. Compound G is formed by a Friedel-Crafts acylation using reagents such as aluminum chloride,

polyphosphoric acid or P_2O_5. Compound G is converted to compound H and compound J by conditions described with respect to Scheme 1.

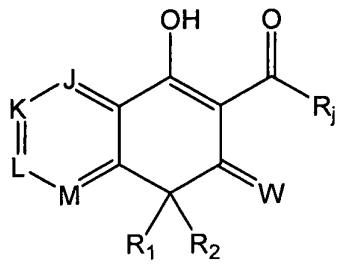
[0184] The compounds of the invention can further be prepared using the general synthetic route shown below in Scheme 4 and described more fully in the Examples.

Scheme 4



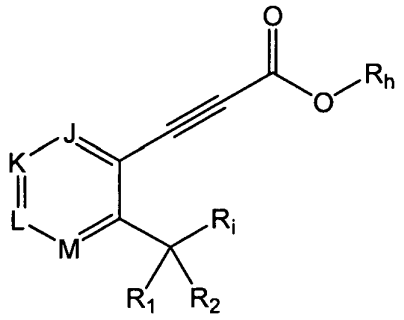
[0185] As shown in Scheme 4, Compound V can be prepared from ester compound G by decarboxylation under typical acidic conditions analogous to refluxing concentrated hydrochloric acid. Acylation of compound V by reaction with an appropriate acid chloride with compound V is accomplished by general base catalysis using triethylamine and analogous bases. Compound W can be rearranged via a Fries rearrangement to give compound X. Typical reagents for this include aluminum trichloride and sodium acetate. Compound Y can be prepared from an appropriate ester X by conditions analogous to those described with respect to Scheme 1.

[0186] In one aspect, the invention provides a method for synthesizing a compound of Formula IV or a tautomer thereof.



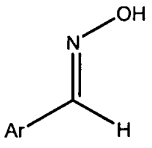
IV.

Typically, such methods include cyclizing a compound of Formula III to form a compound of Formula IV



III.

Generally, the cyclization is carried out in the presence of a nucleophile and a base in a polar aprotic solvent or solvent system. In such methods, a compound of the formula Ar-C(H)=N-OH where Ar is substituted or unsubstituted aryl, or a salt thereof, is typically included or present in the reaction as the nucleophile. In some embodiments, the nucleophile has the following formula:



. Typically, an aryl cyanide is eliminated from the reaction. In some embodiments Ar is phenyl. Examples of other Ar groups that may be utilized include, but are not limited to, nitro substituted phenyls such as 2-nitrophenyl, 3-nitrophenyl, or 4-nitrophenyl; methyl substituted phenyls such as 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, and xylyl; cyanophenyls such as 2-cyanophenyl, 3,cyanophenyl, and 4-cyanophenyl; trifluoromethyl substituted phenyls such as 2-trifluoromethylphenyl, 3-trifluoromethylphenyl,

and 4-trifluoromethylphenyl; various halophenyls such as fluoro, chloro, and bromophenyls, and the like. In some embodiments, a nucleophile such as allyl alcohol or benzyl alcohol may be utilized that may require deprotecting to provide the compound of Formula IV. Typically, a base such as a metal hydride is also included in the reaction mixture during cyclization of the compound of Formula III.

[0187] In compounds of Formula III and Formula IV,

J, K, L, and M are selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

R_h is a C_1-C_6 alkyl group;

R_j is a -O-C_1-C_6 alkyl group;

R_1 and R_2 are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents and may include 0, 1, or 2 heteroatom ring members selected from S, N, and O, or one of R_1 and R_2 may be a CO_2R_z wherein R_z is C_1-C_6 alkyl if R_i is CO_2R_k;

R_i is selected from –CN or CO_2R_k, wherein k is a C_1-C_6 alkyl group;

W is O when R_i is CO_2R_k, and W is NH when R_i is –CN;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or -Y-R_{10};

Y is selected from $–N(R_{11})$-Z- or –Z-$N(R_{11})$-;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

[0188] In certain embodiments of the method for synthesizing compounds of Formula IV, each of J, K, L, and M is a CR_7. In some embodiments, one of J, K, L, and M is N and the other three of J, K, L, and M is a CR_7.

[0189] In certain embodiments of the method for synthesizing compounds of Formula IV, R_h is selected from methyl, ethyl, or propyl. In some such embodiments, R_h and is ethyl. In other embodiments, R_h is a branched C_1-C_6 alkyl such as an isopropyl or t-butyl group.

[0190] In certain embodiments of the method for synthesizing compounds of Formula IV, R_j is selected from –O-methyl, -O-ethyl, or –O-propyl. In some such embodiments, R_j and is –O-ethyl. In still other such embodiments, R_h is methyl, ethyl, or propyl.

[0191] In certain embodiments of the method for synthesizing compounds of Formula IV, R_i is –CN.

[0192] In certain embodiments of the method for synthesizing compounds of Formula IV, R_i is a CO_2R_k. In some such embodiments, R_k is selected from methyl, ethyl, or propyl. In some such embodiments, R_k is ethyl.

[0193] In some embodiments when R_i is –CN, the method may further include reacting the compound of Formula IV with water under aqueous acidic conditions to convert W from –NH to O. In some such embodiments, where W is –NH, W is converted to O by reacting the compound with aqueous hydrochloric acid or aqueous sulfuric acid.

[0194] In some embodiments, R_i is CO_2R_k and W is O.

[0195] In one embodiment of the method of synthesizing compounds of Formula IV, R_1 and R_2 are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents and may include 0, 1, or 2 heteroatom ring members selected from S, N, and O. In some such embodiments, R_1 and R_2 are independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl. In some embodiments, R_1 and R_2 join to form a spirocyclic ring system that may be substituted with one or more substituents and may include 0, 1, or 2 heteroatom ring members selected from S, N, and O. In some embodiments at least one of R_1 and R_2 is selected from methyl, ethyl, propyl or butyl. In some such embodiments, at least one of R_1 and R_2 is a methyl group. In still other embodiments, R_1 and R_2 are independently selected from C_1-C_4 alkyl groups. In some such embodiments, both R_1 and R_2 are methyl groups. In some embodiments, one or both of R_1 and R_2 is a substituted alkyl group. In some such embodiments, one or both of R_1 and R_2 is a CF_3 group.

[0196] In other embodiments of the method of synthesizing compounds of Formula IV, each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, OR_9,

halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, or perhaloalkyl.

[0197] Various protecting groups may be used for the various substituents as will be readily contemplated by those skilled in the art to form a protected group for the reaction. The term "protected" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in Protective Groups in Organic Synthesis, Greene, T. W.; Wuts, P. G. M., John Wiley & Sons, New York, N.Y., (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoroacetate. Examples of protected amine groups include, but are not limited to, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

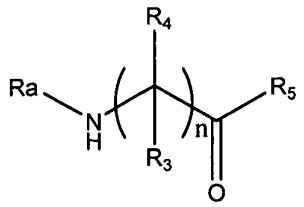
[0198] The cyclization of a compound of Formula III to form a compound of Formula IV is typically accomplished by reacting the compound of Formula III with a nucleophiles as described above and a base in a polar aprotic solvent or in a polar aprotic solvent system. The reaction typically does

not require heating, but may be heated if so desired. The reaction may be carried out at various temperatures, but is typically conducted at temperatures ranging from -20°C to 40°C. Various bases may be used to carry out the reaction. Examples of some suitable bases include, but are not limited to non-nucleophilic bases such as metal hydrides such as, but not limited to NaH, LiH, and KH. In some embodiments, the base is NaH. Examples of other suitable bases include lithium hexamethyldisilazide (LiHMDS) or analogous potassium or sodium analogs. Other suitable bases may include potassium, lithium, or sodium t-butoxide. In an alternative procedure anion of the nucleophile is preformed and then added to the compound of Formula III.

[0199] Various aprotic solvents and solvent systems may be used in conjunction with the reaction to convert compounds of Formula III to compounds of Formula IV. Examples of suitable solvents and solvent systems include ethereal solvents such as diethyl ether, dimethoxyethane, tetrahydrofuran, dioxane, and the like. Other suitable solvents include, but are not limited to, DMF, DMSO, N-methylpyrrolidone, and the like. In some embodiments, an ethereal solvent is used in conjunction with DMF, DMSO, or N-methylpyrrolidone. In some such embodiments, an ethereal solvent is used in conjunction with DMF. In some embodiments, a cyclic ethereal solvent such as THF or dioxane is used in conjunction with DMF.

[0200] In some embodiments where W is O, the method may further include reacting a compound of Formula IV where R_j is an $-O-C_1-C_6$ alkyl group with an amine of Formula V to form an amide compound of Formula VI. In alternative embodiments, R_j is first converted to –OH or a halogen such as Cl or Br. Therefore, in some embodiments where the compound of Formula IV is reacted with amine of Formula V, R_j is selected from a halogen, -OH, or a $-O-C_1-C_6$ alkyl group

[0201] The amine of Formula V has the following structure:



V

wherein n is 1 to 6;

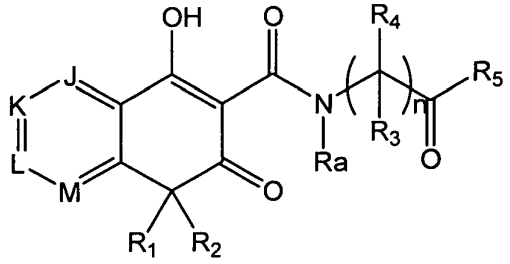
R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl.

[0202] In some embodiments, n is 1. In still other embodiments R_5 is OH or alkoxy. In still other embodiments, R_3 and R_4 are both H. In still other embodiments, at least one of R_3 and R_4 is a lower alkyl such as a methyl, ethyl, or propyl group. In other embodiments, R_a is H.

[0203] The compound of Formula VI has the following formula



VI

where the variables have the same values as described for the compounds of Formula IV and the amines of Formula V.

[0204] Typically, an amine of Formula V is reacted with a compound of Formula IV where W is O, by treating the compound of Formula IV with the amine in a polar aprotic solvent or solvent system such as those described above. Suitable solvents include ethereal solvent such as THF, dioxane, and the

like. If desired, a non-nucleophilic base such as DIPEA, TEA, or the like may be used. If R_5 is an alkoxy group such that the compound includes an ester, the reaction of the amine with the compound of Formula V may be followed by a saponification to produce the carboxylic acid or salt thereof.

[0205] As noted above, in some embodiments, the method may include converting the -C(=O)R_j group of the compound of Formula IV (where R_j is an-O-C_1-C_6 alkyl) to a carboxylic acid (–C(=O)OH) or an acyl halide (–C(=O)($R_{j'}$) where $R_{j'}$ is a halide such as Cl or Br). In some such embodiments, the carboxylic acid or the acyl halide of the compound of Formula IV is then reacted with an amine of Formula V under standard amide forming conditions to produce the compound of Formula VI.

[0206] The invention is further described by reference to the following examples, which are intended to exemplify the claimed invention but not to limit it in any way.

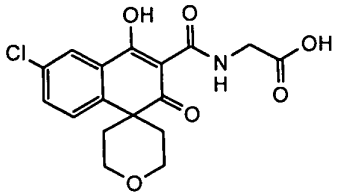
EXAMPLES

[0207] Unless otherwise stated, all compounds were obtained from commercial sources or were prepared using the methods and experimental procedures described herein. The following Abbreviations are used to refer to various reagents and solvents:

AcOH	Acetic Acid
ACN	Acetonitrile
dba	dibenzylidene acetone
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	N,N-Dimethyl Formamide
DMSO	Dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EtOAc	Ethyl Acetate
EtOH	Ethanol
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide

IPAc	Isopropyl acetate
LDA	Lithium Diisopropylamide
MeI	Methyl Iodide
MeOH	Methanol
NMP	N-methyl-2-pyrrolidone
PPh_3	Triphenylphosphine
p-TSA	para-toluenesulfonic acid
tBu	tert-butyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TR-FRET	Time Resolved-Fluorescence Resonance Energy Transfer

[0208] **Example 1.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0209] **Step A**: Preparation of 4-(4-Chlorophenyl)tetrahydro-2H-pyran-4-carboxylic acid.

[0210] To a solution of (4-chlorophenyl)acetonitrile (1.15 g, 7.59 mmol) in DMF (11.5 mL) at 10°C, was added sodium tert-butoxide (0.80 g, 8.34 mmol). The resulting mixture was aged for 10 minutes and then treated with bis(2-chloroethyl)ether (1.19 g, 8.34 mmol). The mixture was aged at 10°C for 1 hour, warmed to ambient temperature and treated with a second portion of sodium tert-butoxide (0.80 g, 8.34 mmol). After 10 minutes, the mixture was quenched with a 1.0M H_3PO_4 solution and extracted with EtOAc (2 x 25 mL). The combined extracts were washed with saturated brine, dried ($MgSO_4$), and

concentrated in vacuo to give a brown solid. The product was dissolved in 1,4-dioxane (5 mL) and treated with a 9.0M H_2SO_4 solution at 100°C for 48 hours. The cooled mixture was then brought to pH = 10 and extracted with diethyl ether (2 x 25 mL). The aqueous phase was acidified to pH = 2 with 5N HCl, and the resulting precipitate was collected by vacuum filtration. The solid was dried under vacuum at 50°C overnight. MS m/e = 241.2 $(M+H)^+$.

[0211] **Step B**: Preparation of Diethyl 2-(4-(4-chlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate.

[0212] To a solution of 4-(4-chlorophenyl)tetrahydro-2H-pyran-4-carboxylic acid (0.500 g, 2.08 mmol) in IPAc (2.5 mL) was added DMF (0.050 mL). Oxalyl chloride (0.277 g, 0.19 mL, 2.18 mmol) was then added at ambient temperature over a period of 20 minutes. The resulting solution was stirred at room temperature for a period of 2 hours. In a separate flask, a solution of diethyl malonate (0.420 g, 0.40 mL, 2.60 mmol) in IPAc (3.5 mL) was treated with $MgCl_2$ (0.247 g, 2.60 mmol). The resulting slurry was aged at room temperature for 30 minutes and subsequently treated with TEA (0.704 g, 0.97 mL, 2.60 mmol). After a further 2 hours at ambient temperature, the malonate slurry was cooled to 5°C and treated with the acyl chloride solution. The resulting mixture was aged at room temperature for 2 hours then treated with a 5N HCl solution (2.5 mL). The organic layer was separated, and the aqueous layer was extracted 3 times with IPAc (2.5 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford the title compound as an orange oil. MS m/e = 383.2 $(M+H)^+$.

[0213] **Step C**: Preparation of Ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0214] Concentrated H_2SO_4 (9.5 mL, 18.0M) was treated with P_2O_5 (4.25 g, 29.9 mmol). The resulting slurry was stirred at room temperature for 2 hours. The mixture was cooled in an ice bath and treated with a solution of diethyl 2-(4-(4-chlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (1.70

g, 4.44 mmol) in IPAc (3.0 mL). The resulting green solution was aged for 15 minutes and subsequently poured into ice water. The resulting mixture was extracted with IPAc (3X 20 mL), and the combined organic extracts were dried ($MgSO_4$). The organic solution was concentrated in vacuo to furnish a brown solid. The crude product was recrystallized from hot heptane to give the title compound as a pale yellow solid (0.81 g). MS m/e = 337.2 $(M+H)^+$.

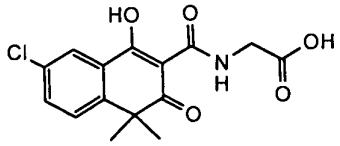
[0215] **Step D**: Preparation of Methyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0216] A mixture of ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.810 g, 2.41 mmol), glycine methyl ester hydrochloride (0.39 g, 3.11 mmol, 1.3 eq.), 1,4-dioxane (7.0 mL) and DIPEA (1.3 mL, 7.46 mmol) was heated at 80°C for 6 hours. The mixture was then cooled to room temperature and extracted with EtOAc (3X 25 mL). The combined organic extracts were washed with 2N HCl and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow solid. The product was recrystallized from EtOAc to give a colorless solid (0.68 g). MS m/e = 380.0 $(M+H)^+$.

[0217] **Step E**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0218] Methyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.684 g, 1.79 mmol, 1.0 eq.) was suspended in water (10.0 mL) and treated with lithium hydroxide monohydrate (0.227 g, 5.40 mmol). After 30 minutes at ambient temperature, the resulting homogeneous mixture was quenched with 1N HCl solution to pH = 2. The white solid that precipitated upon acidification was collected by vacuum filtration and washed with 1:1 H_2O/acetone (2 x 2.0 mL). The product was dried under vacuum at 80°C for 24 hours to give the title compound in quantitative yield. MS m/e = 366.0 $(M+H)^+$. Calculated for $C_{17}H_{16}ClNO_6$ 365.07.

[0219] **Example 2.** N-((6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0220] **Step A**: Preparation of Diethyl 2-(2-(4-chlorophenyl)-2-methylpropanoyl)malonate

[0221] A solution of 2-(4-chlorophenyl)-2-methylpropionic acid (1.99 g, 10.0 mmol, 1.0 eq.) in IPAc (10 mL) was treated with DMF (0.02 mL) and oxalyl chloride (0.92 mL, 10.5 mmol). The resulting solution was stirred at room temperature for 2 hours. In a separate vessel, was charged diethyl malonate (1.91 mL, 12.5 mmol), IPAc (14 mL), and $MgCl_2$ (11.9 g, 12.5 mmol). The resulting malonate slurry was stirred at room temperature for 30 minutes and subsequently treated with TEA (4.7 mL, 33.5 mmol). The resulting suspension was aged at room temperature for 2 hours, cooled to 5°C and treated with the above acyl chloride solution. The resulting mixture was warmed to ambient temperature and aged for 1 hour. The slurry was quenched with a 5N HCl solution (10 mL) and the phases were split. The organic phase was washed with saturated $NaHCO_3$ solution (2 x 10 mL) and water (1 x 10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford an orange oil. MS m/e = 341.2 $(M+H)^+$.

[0222] **Step B**: Preparation of Ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0223] Concentrated H_2SO_4 (5.0 mL, 18.0M) was cooled to -4°C and treated with diethyl 2-(2-(4-chlorophenyl)-2-methylpropanoyl)malonate (1.00 g, 2.93 mmol). The resulting green solution was warmed to room temperature and allowed to stir for 1 hour. The solution was then poured into a 0°C chilled mixture of water (10 mL) and heptane (5 mL). The resulting precipitate was collected by vacuum filtration, washed with cold water (10 mL) and heptane (1

mL). The product was dried at 40°C overnight under vacuum to give 0.69 g of the title compound. MS m/e = 295.2 $(M+H)^+$.

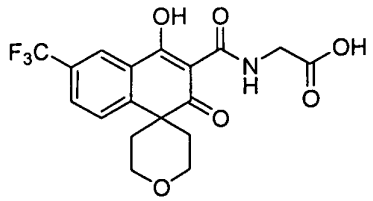
[0224] **Step C**: Preparation of Methyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate

[0225] A mixture of ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.224 g, 0.761 mmol), glycine methyl ester hydrochloride (0.115 g, 0.914 mmol, 99% Aldrich), 1-methyl-2-pyrrolidinone (1.5 mL), and TEA (0.32 mL, 2.28 mmol) was heated at 80°C for 4 hours. The resulting mixture was cooled to room temperature and treated with water (10 mL) causing a white solid to precipitate. The product was collected by vacuum filtration and rinsed with water. MS m/e = 338.0 $(M+H)^+$.

[0226] **Step D**: Preparation of N-((6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0227] Methyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (0.256 g, 0.760 mmol) was suspended in water (3.0 mL) and treated with a 5N NaOH solution (0.38 mL, 1.90 mmol). After 20 minutes at ambient temperature, the resulting homogeneous mixture was quenched with a 1N HCl solution to pH = 2. The white solid that precipitated upon acidification was collected by vacuum filtration and washed with 1:1 H_2O/acetone (2 x 2.0 mL). The product was subsequently dried at 80°C under vacuum for 24 hours. MS m/e = 324.0 $(M+H)^+$. Calculated for $C_{15}H_{14}ClNO_5$ 323.06.

[0228] **Example 3.** N-((4-Hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0229] **Step A**: Preparation of Ethyl 2-(4-(trifluoromethyl)phenyl)acetate

[0230] A solution of (trifluoro-p-tolyl)-acetic acid (19.85 g, 97.2 mmol) in EtOH (200 mL) was treated with H_2SO_4, 36N (16.4 mL, 194 mmol). The reaction was heated at reflux. After 48 hours, the reaction was cooled to 23°C, diluted with EtOAc (750 mL), washed with saturated $NaHCO_3$ solution (2 x 400 mL) and brine (400 mL), dried over $MgSO_4$, and concentrated in vacuo affording 20.98 g of ethyl 2-(4-(trifluoromethyl)phenyl)acetate.

[0231] **Step B**: Preparation of 4-(4-(Trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0232] A suspension of NaH (60% dispersion in mineral oil (2.3 g, 60 mmol)) in NMP (80 mL) was cooled to 0°C under nitrogen. The reaction mixture was treated with a solution of ethyl 2-(4-(trifluoromethyl)phenyl)acetate (4.672 g, 20 mmol) in NMP (20 mL) in a dropwise fashion over 10 minutes (effervescence occurred), followed by bis(2-bromoethyl) ether (2.8 mL, 22 mmol). After 15 minutes, the reaction was warmed to 23°C. After 20 hours, the reaction was diluted with a 10% HCl solution (300 mL; slowly, a lot of effervescence was observed) and extracted with diethyl ether (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (eluant: 25-50% EtOAc/hexane) affording 3.76 g of 4-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carboxylic acid. MS m/e = 275.1 $(M+H)^+$.

[0233] **Step C**: Preparation of Diethyl 2-(4-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0234] A suspension of 4-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carboxylic acid (3.749 g, 13.7 mmol) and thionyl chloride (9.97 mL, 137 mmol) was heated at reflux. After 2 hours, the reaction was cooled to 23°C and concentrated in vacuo, azeotroped with toluene (2 x 20 mL) and further dried on the vacuum line for 90 minutes. A solution of diethyl malonate (2.17 mL, 14.4 mmol) in ACN (50 mL) in an oven-dried round-bottomed flask, was cooled to 0°C and treated with $MgCl_2$ (1.30 g, 13.7 mmol), followed by TEA (3.99 mL, 28.7 mmol). The reaction was warmed to 23°C. After 2 hours and 30 minutes, a solution of the crude acid chloride in ACN (10 mL) was added, and the reaction was heated to 50°C. After 15 hours, the reaction was cooled to 23°C, diluted with EtOAc (400 mL), and washed with a 10% HCl solution (300 mL). The aqueous layer was extracted with EtOAc (300 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo affording 5.50 g of diethyl 2-(4-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate. MS m/e = 417.2 $(M+H)^+$.

[0235] **Step D**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0236] H_2SO_4 (4897 µL, 88139 µmol) was cooled to 0°C and treated with P_2O_5 (1501 mg, 10577 µmol). The reaction was warmed to 23°C and treated with diethyl 2-(4-(4-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (734 mg, 1763 µmol) after 10 minutes. After 75 minutes, the reaction was diluted with EtOAc (10 mL) and poured into an ice-water mixture (~50 mL). The suspension was extracted with EtOAc (3x50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo affording 650 mg of the crude cyclized product. MS m/e = 371.2 $(M+H)^+$.

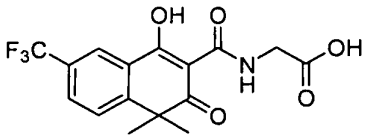
[0237] A solution of the crude product from the previous step (797 mg, 2152 µmol), glycine tert-butyl ester hydrochloride (433 mg, 2583 µmol) and

DIPEA (937 µL, 5380 µmol) in 1,4-dioxane (20 mL) was heated to 120°C in a sealed vessel. After 4 hours, the reaction was cooled to 23°C, diluted with EtOAc (300 mL), washed with a 10% HCl solution (150 mL), water (150 mL), and brine (150 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 10-25% EtOAc/hexane) affording 502 mg of the title compound. MS m/e = 456.2 $(M+H)^+$.

[0238] **Step E**: Preparation of N-((4-Hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0239] A solution of 1,1-dimethylethyl N-((4-hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (500 mg, 1098 µmol) in TFA (4 mL) was stirred at 23°C. After 25 minutes, the reaction was concentrated in vacuo and azeotroped with DCM (2 x 10 mL). The crude solid was washed with diethyl ether affording 356 mg of N-((4-hydroxy-2-oxo-6-(trifluoromethyl)-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine. MS m/e = 400.1 $(M+H)^+$. Calculated for $C_{18}H_{16}F_3NO_6$ 399.09.

[0240] **Example 4.** N-((4-Hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycine



[0241] **Step A**: Preparation of Methyl 2-methyl-2-(4-(trifluoromethyl)phenyl)propanoate

[0242] A suspension of NaH (60% dispersion in mineral oil (1805 mg, 45123 µmol)) in DMF (100 mL) was cooled to 0°C in an oven-dried round bottomed flask. A solution of ethyl 2-(4-(trifluoromethyl)phenyl)acetate (4191 mg, 18049 µmol) and MeI (3372 µL, 54148 µmol) in DMF (10 mL) was cooled to 0°C, and was added to the reaction mixture in a dropwise fashion over 15

minutes. The flask was rinsed with DMF (2 x 5 mL), and the rinse was added to the reaction mixture. After 15 minutes, the reaction was warmed to 23°C. After 48 hours, the reaction was diluted with EtOAc (250 mL) and washed with a 10% HCl solution (200 mL), water (200 mL), and brine (100 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 3% EtOAc/hexane) affording 2580 mg of the title compound. MS m/e = 261.2 $(M+H)^+$.

[0243] **Step B**: Preparation of 2-Methyl-2-(4-(trifluoromethyl)phenyl)propanoic acid

[0244] A solution of methyl 2-methyl-2-(4-(trifluoromethyl)phenyl)propanoate (1528 mg, 6206 μmol) in MeOH (60 mL) and water (15 mL), was treated with KOH (1741 mg, 31028 μmol). The reaction was heated to reflux. After 18 hours, the reaction was cooled to 23°C and concentrated in vacuo. The crude mixture was partitioned between water/diethyl ether (100 mL each). The aqueous layer was separated and washed with diethyl ether (100 mL). The combined ether layers were extracted with a 1N NaOH solution (25 mL). The combined aqueous washes were acidified with concentrated HCl to pH = 2 and were then extracted with EtOAc (3x100 mL). The combined EtOAc layers were dried over $MgSO_4$ and concentrated in vacuo to afford 1323 mg of the title compound. MS m/e = 233.1 $(M+H)^+$.

[0245] **Step C**: Preparation of Diethyl 2-(2-methyl-2-(4-(trifluoromethyl)phenyl)propanoyl)malonate

[0246] A solution of 2-methyl-2-(4-(trifluoromethyl)phenyl)propanoic acid (1325 mg, 5706 μmol) in thionyl chloride (4162 μL, 57063 μmol) was heated at reflux under nitrogen. After 2 hours, the reaction was cooled to 23°C and concentrated in vacuo to afford the crude acid chloride. In an oven-dried round-bottomed flask, magnesium (208 mg, 8559 μmol) and diethyl malonate (1293 μL, 8559 μmol) were added to EtOH (15 mL) and CCl_4 (0.2 mL). The

reaction was stirred at 23°C for 30 minutes followed by the addition of THF (15 mL). The reaction was heated to reflux under nitrogen. After 1 hour, a solution of the crude acid chloride in THF (10 mL) was added in a drop wise fashion. After 30 minutes, the reaction was cooled to 23°C, diluted with diethyl ether (150 mL), and washed with water (150 mL). The aqueous layer was extracted with diethyl ether (150 mL). The combined ether layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated in vacuo, and purified on silica gel (eluant: 5-20% EtOAc/hexane) affording 1115 mg of the title compound. MS m/e = 375.2 $(M+H)^+$.

[0247] **Step D**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycinate

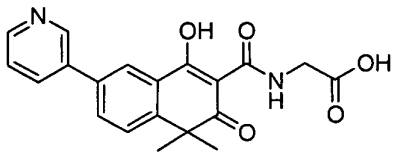
[0248] Diethyl 2-(2-methyl-2-(4-(trifluoromethyl)phenyl)propanoyl)malonate (1000 mg, 2671 µmol) was cooled to 0°C in a round-bottomed flask and was then treated with concentrated H_2SO_4 (10 mL). The ice-bath was removed, and the reaction was stirred at 23°C. After 2 hours, the reaction was poured into an ice-water mixture (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo affording 861 mg crude product of ethyl 4-hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalene-3-carboxylate. MS m/e = 329.1 $(M+H)^+$.

[0249] A solution of crude ethyl 4-hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalene-3-carboxylate (562 mg, 1712 µmol), glycine tert-butyl ester hydrochloride (316 mg, 1883 µmol) and DIPEA (447 µL, 2568 µmol) in 1,4-dioxane (20 mL) was heated to 120°C in a sealed vessel. After 14 hours, the reaction was cooled to 23°C, and the solvent was removed under vacuum. The residue was diluted with EtOAc (100 mL), washed with water (75 mL) and brine (75 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 4-8% EtOAc/hexane) affording 435 mg of the title compound. MS m/e = 358.1 $(M-C_4H_8+H)^+$.

[0250] **Step E**: Preparation of N-((4-Hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycine

[0251] A solution of 1,1-dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-6-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycinate (432 mg, 1045 μmol) in toluene (5 mL), was treated with silica gel (314 mg, 5225 μmol). The reaction was heated at 110°C. After 4 hours, the reaction was cooled to 23°C and filtered. The residue was washed with DCM (150 mL), and the filtrates were discarded. The residue was subsequently washed with a 10% MeOH/DCM solution (1000 mL). The filtrate was concentrated in vacuo, affording 312 mg of the title compound. MS m/e = 358.1 $(M+H)^+$. Calculated for $C_{16}H_{14}F_3NO_5$ 357.08.

[0252] **Example 5.** N-((4-Hydroxy-1,1-dimethyl-2-oxo-6-(3-pyridinyl)-naphthalen-3-yl)carbonyl)glycine



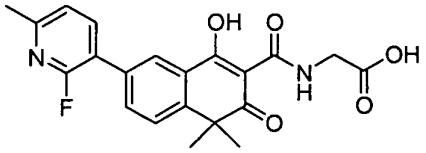
[0253] **Step A**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-6-(3-pyridinyl)-naphthalen-3-yl)carbonyl)glycinate

[0254] A suspension of 1,1-dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (284 mg, 669 μmol, see Example 39), pyridin-3-ylboronic acid (165 mg, 1339 μmol), and Na_2CO_3 (2.0M aqueous solution (669 μL, 1339 μmol)) in 1,4-dioxane (5 mL) was treated with $Pd(PPh_3)4$ (77 mg, 67 μmol) in a microwave vial. The vessel was capped, degassed, backfilled with argon (2 x), and heated at 150°C in a microwave for 1200 sec. The reaction was diluted with EtOAc (50 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 20-28-40% EtOAc/hexane) affording 113 mg of the title compound. MS m/e = 423.2 $(M+H)^+$.

[0255] **Step B**: Preparation of N-((4-Hydroxy-1,1-dimethyl-2-oxo-6-(3-pyridinyl)-naphthalen-3-yl)carbonyl)glycine

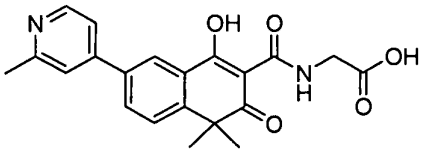
[0256] A suspension of 1,1-dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-6-(pyridin-3-yl)-naphthalen-3-yl)carbonyl)glycinate (109 mg, 258 μmol) and silica gel (230-400 mesh, EMD Chemicals) (78 mg, 1290 μmol) in toluene (5 mL) was heated to 110°C. After 2 hours, the reaction was cooled to 23°C, filtered and washed with DCM (25 mL). The washings were discarded. The residue was subsequently washed with a 10% MeOH/DCM solution (1000 mL). The filtrate was then concentrated in vacuo affording 91 mg of the title compound. MS m/e = 367.2 $(M+H)^+$. Calculated for $C_{20}H_{18}N_2O_5$ 366.12.

[0257] **Example 6.** N-((6-(2-Fluoro-6-methyl-3-pyridinyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



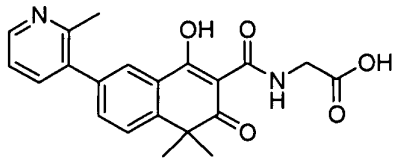
[0258] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 399.0 $(M+H)^+$. Calculated for $C_{21}H_{19}FN_2O_5$ 398.13.

[0259] **Example 7.** N-((4-Hydroxy-1,1-dimethyl-6-(2-methyl-4-pyridinyl)-2-oxo-naphthalen-3-yl)carbonyl)glycine



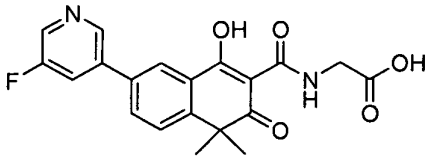
[0260] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 381.0 $(M+H)^+$. Calculated for $C_{21}H_{20}N_2O_5$ 380.14.

[0261] **Example 8.** N-((4-Hydroxy-1,1-dimethyl-6-(2-methyl-3-pyridinyl)-2-oxo-naphthalen-3-yl)carbonyl)glycine



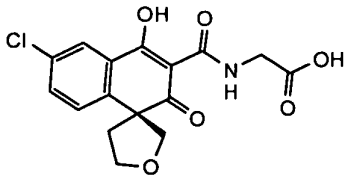
[0262] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 381.2 $(M+H)^+$. Calculated for $C_{21}H_{20}N_2O_5$ 380.14.

[0263] **Example 9.** N-((6-(5-Fluoro-3-pyridinyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

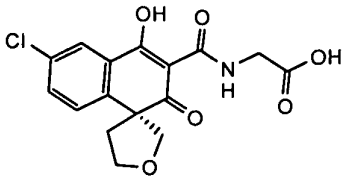


[0264] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 385.0 $(M+H)^+$. Calculated for $C_{20}H_{17}FN_2O_5$ 384.11.

[0265] **Examples 10 and 11.** N-(((3R)-6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycine and N-(((3S)-6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycine

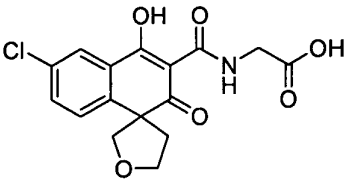


and



[0266] The title compounds were obtained as separate enantiomers by chiral separation of N-((6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-2'H-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycine (Example 12) using chiral HPLC. MS m/e = 352.0 $(M+H)^+$. Calculated for $C_{16}H_{14}ClNO_6$ 351.05.

[0267] **Example 12.** N-((6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-2'H-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycine



[0268] **Step A**: Preparation of 3-(4-Chlorophenyl)-tetrahydrofuran-3-carbonitrile

[0269] To a solution of the NaH (60% by weight, 4g, 98 mmol) and 1-methylpyrrolidin-2-one (82.5 mL) at -20 °C, was added dropwise a mixture of 2-(4-chlorophenyl)acetonitrile (5g, 33 mmol) and 2-chloroethyl chloromethyl ether (4 mL, 33 mmol) in diethyl ether (16.5 mL, 33 mmol). The mixture was allowed to warm to room temperature over 24 hours. The reaction was then slowly quenched with ice water and extracted with ether (3x). The organic layers were combined, washed with H_2O (3x) and brine, dried over Na_2SO_4, concentrated in vacuo, and purified by silica flash chromatography (13% EtOAc/hexane) to give the desired compound as a yellow oil. MS m/e = 208.0 $(M+H)^+$.

[0270] **Step B**: Preparation of 3-(4-Chlorophenyl)-tetrahydrofuran-3-carboxylic acid

[0271] To a solution of 3-(4-chlorophenyl)-tetrahydrofuran-3-carbonitrile (9.18g, 44.21 mmol) in dioxane (26 mL, 44 mmol) was added 9M (aq) H_2SO_4 (44.21 mL, 44 mmol). The resulting mixture was heated at 110 °C for 12 hours. The mixture was then cooled and extracted with EtOAc. The organic layer was then washed with 2N NaOH. The aqueous wash was acidified with concentrated HCl and extracted with EtOAc. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to give the desired carboxylic acid as a light yellow solid. MS m/e = 227.2 $(M+H)^+$.

[0272] **Step C**: Preparation of Diethyl 2-(3-(4-chlorophenyl)-tetrahydrofuran-3-carbonyl)malonate

[0273] 3-(4-Chlorophenyl)-tetrahydrofuran-3-carboxylic acid (375.2mg, 1655 μmol) was mixed with thionyl chloride (1.21 mL, 16554 μmol) and heated at 70 °C for 3 hours. The solution was cooled, concentrated in vacuo, and pumped on under high vacuum for 3 hours. To a flame-dried round bottom flask containing diethyl malonate (0.25 mL, 1655 μmol) in ACN (3 mL), was added $MgCl_2$ (158 mg, 1655 μmol). The resulting solution was cooled to 0°C. The reaction was then stirred for 15 minutes at 0 °C. To the resulting mixture was slowly added TEA (0.48 mL, 3476 μmol), and the reaction was stirred at room temperature for 3 hours. The acid chloride intermediate in ACN (1.9 mL), was added to the malonate solution, and the resulting mixture was stirred at 50 °C for 13 hours. The reaction was then cooled and concentrated in vacuo to give a light yellow solid which was mixed with 1N HCl and EtOAc. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica flash chromatography (10-30% EtOAc/hexane) gave the title compound as a light yellow oil. MS m/e = 369.2 $(M+H)^+$.

[0274] **Step D**: Preparation of Ethyl (6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carboxylate

[0275] Concentrated H_2SO_4 (66483 mg, 677858 µmol) was cooled to 0 °C and treated with P_2O_5 (11546 mg, 81343 µmol). The reaction was stirred for 60 minutes and treated with diethyl 2-(3-(4-chlorophenyl)-tetrahydrofuran-3-carbonyl)malonate (5 g, 13557 µmol). After 60 minutes, the reaction was diluted with EtOAc and poured onto ice. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were washed with brine and dried over $MgSO_4$. Purification by silica flash chromatography (2-5% MeOH/DCM) gave the title compound as a white solid. MS m/e = 323.2 $(M+H)^+$.

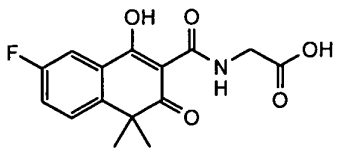
[0276] **Step E**: Preparation of 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycinate

[0277] To a solution of ethyl (6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carboxylate (284.4 mg, 881 µmol) in 1,4-dioxane (8812 µL, 881 µmol) was added DIPEA (460 µL, 2644 µmol), and the resulting solution was warmed to 80 °C for 2 hours. The reaction was then cooled, diluted with EtOAc, washed with water (2x) and brine, dried over Na_2SO_4, and purified by silica flash chromatography (10-30% EtOAc/hexanes) to give the title compound as a light yellow solid. MS m/e = 430.0 $(M+Na)^+$.

[0278] **Step F**: Preparation of N-((6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycine

[0279] 1,1-Dimethylethyl N-(6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-2'H-spiro[furan-3,1'-naphthalen]-3'-yl)carbonyl)glycinate (430.5 mg, 1056 µmol) was dissolved in TFA (10555 µL, 1056 µmol) and stirred for 30 minutes. The reaction was then concentrated in vacuo to give the title compound as a white solid. MS m/e = 352.0 $(M+H)^+$. Calculated for $C_{16}H_{14}ClNO_6$ 351.05.

[0280] **Example 13.** N-((6-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycine



[0281] **Step A**: Preparation of Ethyl 2-(4-fluorophenyl)acetate

[0282] A mixture of 2-(4-fluorophenyl)acetic acid (23.5 g, 152 mmol) in thionyl chloride 56 mL, 762 mmol) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 200 mL DCM, and stirred at 0°C. The mixture was treated with EtOH (9.8 mL, 168 mmol) and TEA (26 mL) dropwise. The mixture was then stirred for 2 hours. The mixture was quenched with 20 mL H_2O and extracted with DCM (3 x 50 mL). The combined organics were washed with H_2O (3 x 50 mL) and brine 20 mL, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 24.7 g of a pale yellow oil.

[0283] **Step B**: Preparation of Ethyl 2-(4-fluorophenyl)-2-methylpropanoate

[0284] A mixture of NaH (5 g, 115 mmol) in 100 mL NMP and stirred at 0°C, was treated dropwise with a mixture of ethyl 2-(4-fluorophenyl)acetate (7 g, 38 mmol) and MeI (5 mL, 85 mmol) in 20 mL ether. The mixture was allowed to warm to room temperature and was stirred for 15 hours. The resulting mixture was quenched with 100 mL H_2O carefully and the pH was adjusted to 5. The mixture was extracted with ether (3 x 100 mL). The combined organics were washed with H_2O (3 x 50 mL) and brine 20 mL. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10% EtOAc/hexane to give 6.0 g of the product as a pale yellow oil. MS m/e = 211 $(M+H)^+$.

[0285] **Step C**: Preparation of 2-(4-Fluorophenyl)-2-methylpropanoic acid

[0286] A mixture of ethyl 2-(4-fluorophenyl)-2-methylpropanoate (6 g, 29 mmol), KOH (3 g, 57 mmol) and 100 mL EtOH/H_2O (4:1) was refluxed for 4

hours. The mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 3.1 g of the product as a white solid. MS m/e = 211$(M-1)^-$.

[0287] **Step D**: Preparation of Diethyl 2-(2-(4-fluorophenyl)-2-methylpropanoyl)malonate

[0288] A mixture of diethyl malonate (3 g, 16 mmol) in 50 mL ACN was stirred at 0°C, was treated with $MgCl_2$ (2 g, 18 mmol) in one portion, and was treated dropwise with TEA (3 g, 33 mmol). The mixture was stirred at room temperature for 2.5 hours. A mixture of 2-(4-fluorophenyl)-2-methylpropanoic acid (3 g, 16 mmol) in thionyl chloride (20 mL) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 10 mL ACN, and was added dropwise to the above mixture. The mixture was stirred at 50°C for 15 hours. The resulting mixture was then cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine 20 mL, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20% EtOAc/hexane to give 5 g of the product as pale yellow oil. MS m/e = 325 $(M+H)^+$.

[0289] **Step E**: Preparation of Ethyl 6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0290] To 5 mL concentrated H_2SO_4 stirred at 0°C, was slowly added diethyl 2-(2-(4-fluorophenyl)-2-methylpropanoyl)malonate (1.6 g, 4.9 mmol). The reaction was stirred at 0°C to room temperature for 1 hour, M+1= 279. The resulting mixture was poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 20%

EtOAc/hexane to give 1.2 g of the product as pale yellow solid. MS m/e = 279 $(M+H)^+$.

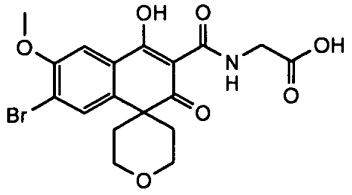
[0291] **Step F**: Preparation of 1,1-Dimethylethyl N-((6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0292] A mixture of ethyl 6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (1.1 g, 4.0 mmol), tert-butyl 2-aminoacetate hydrochloride (0.99 g, 5.9 mmol) in 10 mL dioxane, was treated with N-ethyl-N-isopropylpropan-2-amine (1.5 g, 12 mmol). The mixture was warmed to 95°C and stirred for 15 hours. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 1.13 g of the title compound as a white solid. MS m/e = 364 $(M+Na)^+$.

[0293] **Step G**: N-((6-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0294] A mixture of 1,1-dimethylethyl N-((6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.6 g, 2 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes. The mixture was concentrated and triturated in ether 20 mL. The solid was filtered, washed with 10 mL ether, and dried under high vacuum to give 0.46 g of the product as an off-white solid. MS m/e = 308 $(M+H)^+$. Calculated for $C_{15}H_{14}FNO_5$ 307.09.

[0295] **Example 14.** N-((7-Bromo-4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0296] **Step A**: Preparation of 4-(3-Bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0297] A mixture of sodium tert-butoxide (6.7 g, 70 mmol) in 100 mL NMP stirred at 0°C was treated dropwise with a mixture of 2-(3-bromo-4-methoxyphenyl)acetonitrile (6.3g, 28 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (6.5 g, 28 mmol) in 30 mL ether. The mixture was allowed to warm to room temperature and was stirred for 3 hours, M+Na = 318/320. The mixture was quenched with 100 mL H_2O carefully and the pH was adjusted to 5. The mixture was extracted with ether (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (20 mL). The organic layer was then dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-20 % EtOAc/hexane to give 5.18 g of crude product as a yellow solid. MS m/e = 318/320 $(M+Na)^+$.

[0298] **Step B**: Preparation of 4-(3-Bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0299] A mixture of 4-(3-bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile (5.7 g, 19 mmol) in 20 mL dioxane was treated with 6M aqueous H_2SO_4 (64 mL, 385 mmol). The resulting mixture was then stirred at 180°C for 30 minutes, M-1 = 313/315. The reaction mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 5.5 g of the product as an off white solid. MS m/e = 315/317 $(M+H)^+$.

[0300] **Step C**: Preparation of Diethyl 2-(4-(3-bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0301] A mixture of diethyl malonate (2.8 g, 17 mmol) in 50 mL ACN was stirred at 0°C. This mixture was treated with $MgCl_2$ (1.7 g, 17 mmol) in one portion and dropwise with TEA (3.9 g, 38 mmol). The resulting mixture was then stirred at room temperature for 2.5 hours. A mixture of 4-(3-bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid (5.5 g, 17 mmol) in

thionyl chloride (21 g, 175 mmol) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 10 mL ACN and added dropwise to the above mixture. The mixture was stirred at 50°C for 15 hours, M-1 = 455/457. The mixture was cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20% EtOAc/hexane to give 1.25 g of the intermediate as a pale yellow oil. MS m/e = 455/457 $(M+H)^+$.

[0302] **Step D**: Preparation of Ethyl 7-bromo-4-hydroxy-6-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0303] In a 100 mL round bottom flask, 5 mL concentrated H_2SO_4 stirred at 0°C was carefully treated with 2.5 g P_2O_5. The resulting mixture was stirred for 10 minutes. A mixture of diethyl 2-(4-(3-bromo-4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (1.25 g, 2.7 mmol) in 2 mL EtOAc was added to the above H_2SO_4 mixture, and the mixture was stirred at room temperature for 2 hours, M+1= 411/413. The reaction mixture was then poured into 200 g crushed ice. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-50 % EtOAc/hexane to give 0.28 g of the product as a pale yellow solid. MS m/e = 411/413 $(M+H)^+$.

[0304] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

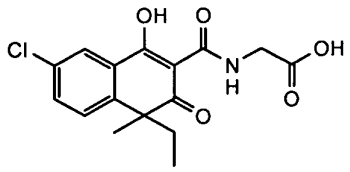
[0305] A mixture of ethyl 7-bromo-4-hydroxy-6-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.28 g, 0.68 mmol) and tert-butyl 2-aminoacetate hydrochloride (0.17 g, 1.0 mmol) in 5 mL dioxane was treated with DIPEA (0.26 g, 2.0 mmol). The mixture was warmed to 95°C and stirred for 3 hours, M+1= 496/498. The mixture was then cooled to

room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 0.28 g of the title compound as a white yellow solid. MS m/e = 496/498 $(M+H)^+$.

[0306] **Step F**: Preparation of N-((7-Bromo-4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0307] A mixture of 1,1-dimethylethyl N-((7-bromo-4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.27 g, 0.54 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes, M+1= 440/442. The mixture was concentrated and triturated in ether (20 mL). The solid was filtered, washed with 10 mL ether and dried under high vacuum to give 0.22 g of the product as a white solid. MS m/e = 440/442 $(M+H)^+$. Calculated for $C_{18}H_{18}BrNO_7$ 439.03/441.02.

[0308] **Example 15.** N-((6-Chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0309] **Step A**: Preparation of 2-(4-Chlorophenyl)butanenitrile

[0310] A mixture of NaH (4.0 g, 99 mmol) in 50 mL NMP stirred at 0°C, was treated dropwise with a mixture of bromoethane (11 g, 99 mmol) and 2-(4-chlorophenyl)acetonitrile (15 g, 99 mmol) in 20 mL ether. The mixture was stirred at room temperature for 2 hours, cooled to 0°C, and quenched carefully with H_2O. The resulting mixture was neutralized with 10% HCl to a pH of 5. The mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 5 % EtOAc/hexane to give 9.1 g of the product as a pale yellow oil.

[0311] **Step B**: Preparation of 2-(4-Chlorophenyl)-2-methylbutanenitrile

[0312] A mixture of 2-(4-chlorophenyl)butanenitrile (6.2 g, 35 mmol) in 50 mL DMF stirred at 0°C, was treated with NaH (0.99 g, 41 mmol). The mixture was stirred at 0°C for 30 minutes, and was treated with MeI (7.3 g, 52 mmol). The mixture was stirred at 0°C to room temperature for 2 hours, and was carefully quenched with H_2O, and neutralized with 10% HCl to pH = 5. The mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10% EtOAc/hexane to give 6.5 g of the product as a pale yellow oil.

[0313] **Step C**: Preparation of 2-(4-Chlorophenyl)-2-methylbutanoic acid

[0314] A mixture of 2-(4-chlorophenyl)-2-methylbutanenitrile (6.5 g, 34 mmol) in 50 mL EtOH/H_2O (5:1) was treated with KOH (3.8 g, 67 mmol). The mixture was stirred at 120°C for 4 hours and then at 180°C for 30 minutes. The mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 1.16 g of the product as a pale yellow oil. MS m/e = 213 $(M+H)^+$.

[0315] **Step D**: Preparation of 2-(4-Chlorophenyl)-2-methylbutanoic acid

[0316] A mixture of diethyl malonate (0.874 g, 5.45 mmol) in 30 mL ACN stirred at 0°C was treated with $MgCl_2$ (0.224 mL, 5.45 mmol) in one portion and then was treated dropwise with TEA (1.59 mL, 11.5 mmol). The mixture was then stirred at room temperature for 2.5 hours. A mixture of 2-(4-chlorophenyl)-2-methylbutanoic acid (1.16 g, 5.45 mmol) in thionyl chloride (3.98 mL, 54.5 mmol) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 10 mL ACN and added dropwise to the above

mixture. The resulting mixture was stirred at 50°C for 15 hours, M+Na =377. The mixture was cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine 20 mL, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20% EtOAc/hexane to give 1.71 g of the title intermediate compound as a pale yellow oil. MS m/e = 355 $(M+H)^+$.

[0317] **Step E**: Preparation of Ethyl 6-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate

[0318] A mixture of diethyl 2-(2-(4-chlorophenyl)butan-2-yl)malonate (1.71 g, 5.23 mmol) in concentrated H_2SO_4 (5.58 mL, 105 mmol) was stirred at room temperature for 2 hours, M+1 = 309, M-1 = 307. The mixture was poured into 200 g ice. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-50% EtOAc/hexane to provide 1.18 g of the title product as a pale yellow oil. MS m/e = 309 $(M+H)^+$.

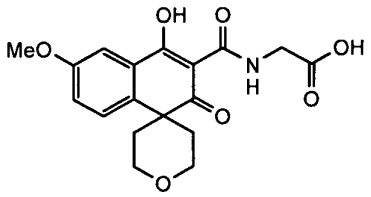
[0319] **Step F**: Preparation of 1,1-Dimethylethyl N-((6-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0320] A mixture of ethyl 6-chloro-4-ethyl-1-hydroxy-4-methyl-3-oxo-naphthalene-2-carboxylate (0.5g, 2 mmol), and tert-butyl 2-aminoacetate hydrochloride (0.4 g, 2 mmol) in 5 mL dioxane, was treated with N-ethyl-N-isopropylpropan-2-amine (0.6 g, 5 mmol). The resulting mixture was warmed to 95°C and stirred for 4 hours, M+Na= 416, M-1 = 392. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20 % EtOAc/hexane to give 0.44g of the title compound as a white yellow solid. MS m/e = 416 $(M+Na)^+$.

[0321] **Step G**: Preparation of N-((6-Chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0322] A mixture of 1,1-dimethylethyl N-((6-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.4 g, 1 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes, M+1= 338, M-1= 336. The mixture was concentrated in vacuo and the residue was sonicated in 10 mL heptane. The solid was filtered, washed with 10 mL heptane, and dried under high vacuum to give 0.27g of the title compound as an off-white solid. MS (m/z) = 338 $(M+H)^+$. Calculated for $C_{16}H_{16}ClNO_5$ 337.07.

[0323] **Example 16.** N-((4-Hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0324] **Step A**: Preparation of 4-(4-Methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0325] A mixture of NaH (3.1 g, 76 mmol) in 100 mL NMP stirred at 0°C, was treated dropwise with the mixture of 2-(4-methoxyphenyl)acetonitrile (4.5 g, 31 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (7.1 g, 31 mmol) in 30 mL ether. The mixture was allowed to warm to room temperature and stirred for 5 hours, M+Na= 240. The mixture was carefully quenched with 100 mL H_2O, and the pH was adjusted to 5. The mixture was extracted with ether (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-20% EtOAc/hexane to give 5.2 g of the product as a pale yellow oil. MS (m/z) = 240 $(M+H)^+$.

[0326] **Step B**: Preparation of 4-(4-Methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0327] A mixture of 4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile (5.2 g, 24 mmol) in 10 mL dioxane was treated with 6M aqueous H_2SO_4 (40 mL, 239 mmol), and the mixture was stirred at 180°C for 1 hour, M+Na = 259, M-1 = 235. The resulting mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 4.88 g of the product as an off white solid. MS (m/z) = 237 $(M+H)^+$.

[0328] **Step C**: Preparation of Diethyl 2-(4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0329] A mixture of magnesium (0.28 g, 12 mmol) and diethyl malonate (1.9 g, 12 mmol) was treated with 2 mL anhydrous EtOH and 0.1 mL CCl_4. The mixture was stirred at room temperature for 20 minutes, was diluted with 50 mL anhydrous ether, and was then refluxed for 1 hour under nitrogen. All the magnesium was consumed.

[0330] A mixture of 4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid (2.5 g, 11 mmol) in thionyl chloride (13 g, 106 mmol) was refluxed for 2 hours, and the resulting mixture was then concentrated in vacuo. The residue was diluted with 20 mL ether, and was added dropwise to the above refluxed mixture. The resulting mixture was refluxed for 20 minutes, M+Na =401. The mixture was then cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20% EtOAc/hexane to give 2.2 g of the intermediate as a pale yellow oil. MS (m/z) = 377 $(M-1)^-$.

[0331] **Step D**: Preparation of Ethyl 4-hydroxy-6-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0332] Diethyl 2-(4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (2.2g) in 1 mL IPAc was added to 20 mL of concentrated H_2SO_4, and the resulting mixture was stirred at room temperature for 2 hours, M+1 = 333, M-1 = 331. The mixture was then poured into 200 g of ice. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-50% EtOAc/hexane to give 0.66 g of the title product as a yellow oil. MS (m/z) = 333 $(M+H)^+$.

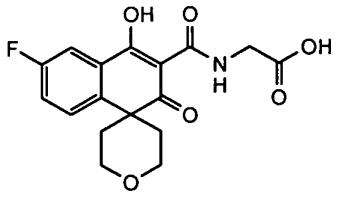
[0333] **Step E**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0334] A mixture of ethyl 4-hydroxy-6-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.6 g, 2 mmol), tert-butyl 2-aminoacetate hydrochloride (0.5 g, 3 mmol) in 5 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.7 g, 5 mmol). The mixture was warmed to 95°C and stirred for 4 hours, M+1= 418. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 0.74 g of the title compound as a white yellow solid. MS (m/z) = 418 $(M+H)^+$.

[0335] **Step F**: Preparation of N-((4-Hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0336] A mixture of 1,1-dimethylethyl N-((4-hydroxy-6-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.66 g, 1.6 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes, M+1=362, M-1= 360. The mixture was concentrated and triturated in DCM/heptane (5:10). The solid was filtered, washed with 10 mL DCM/heptane (5:10), and dried under high vacuum to give 0.52 g of the product as a white solid. MS (m/z) = 362 $(M+H)^+$. Calculated for $C_{18}H_{19}NO_7$ 361.12.

[0337] **Example 17.** N-((6-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0338] **Step A**: Preparation of Ethyl 4-(4-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylate

[0339] A mixture of NaH (1.7 g, 71 mmol) in 100 mL NMP stirred at 0°C, was treated dropwise with a mixture of ethyl 2-(4-fluorophenyl)acetate (5.2 g, 29 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (6.6 g, 29 mmol) in 20 mL ether. The mixture was allowed to warm to room temperature and stirred for 5 hours, M+1= 253. The mixture was then carefully quenched with 100 mL H_2O, and the pH was adjusted to 5. The mixture was extracted with ether (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 7.1 g of the crude product as a pale yellow oil. MS (m/z) = 253 $(M+H)^+$.

[0340] **Step B**: Preparation of 4-(4-Fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0341] A mixture of ethyl 4-(4-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylate (7.1 g, 28 mmol) and KOH (3.2 g, 56 mmol) in 100 mL EtOH/H_2O (4:1) was refluxed for 4 hours, M-1= 223. The mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 4.9 g of the product as a white solid. MS (m/z) = 223 $(M-1)^-$.

[0342] **Step C**: Preparation of Diethyl 2-(4-(4-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0343] A mixture of diethyl malonate (2.1 g, 13 mmol) in 50 mL ACN stirred at 0°C, was treated with $MgCl_2$ (1.4 g, 15 mmol) in one portion and dropwise with TEA (2.7 g, 27 mmol). The mixture was stirred at room temperature for 2.5 hours.

[0344] A mixture of 4-(4-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (3.0 g, 13 mmol) in thionyl chloride 50 mL was refluxed for 2 hours, then concentrated in vacuo. The residue was diluted with 10 mL ACN, and was then added dropwise to the above mixture. The resulting mixture was stirred at 50°C for 15 hours, M+Na=389. The mixture was cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20% EtOAc/hexane to give the intermediate 2.1 g as pale yellow oil. MS (m/z) = 367 $(M+H)^+$.

[0345] **Step D**: Preparation of Ethyl 6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0346] The diethyl 2-(4-(4-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl) malonate (2.1 g, 6 mmol) was added to 5 mL H_2SO_4 stirred at 0°C. The mixture was stirred at room temperature for 1 hour, M-1= 319. The mixture was then poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 20% EtOAc/hexane to give 0.5 g product. MS (m/z) = 321 $(M+H)^+$.

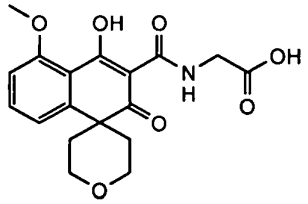
[0347] **Step E**: Preparation of 1,1-Dimethylethyl N-(6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0348] A mixture of ethyl 6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxlate (0.5 g, 2 mmol), tert-butyl 2-aminoacetate hydrochloride (0.4 g, 2 mmol) in 5 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.6 g, 5 mmol). The mixture was warmed to 95°C and stirred for 13 hours, M-1= 404. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane and further purified by HPLC to give 0.12 g of the title compound as a pale yellow solid. MS (m/z) = 406 $(M+H)^+$.

[0349] **Step F**: Preparation of N-(6-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0350] A mixture of 1,1-dimethylethyl N-(6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.12 g, 0.30 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes, M+1= 350, M-1= 348. The mixture was concentrated and then triturated in ether 5 mL. The solid was filtered, washed with 1 mL ether and dried under high vacuum to give 0.1 g of the product as a white solid. MS (m/z) = 350 $(M+H)^+$. Calculated for $C_{17}H_{16}FNO_6$ 349.1.

[0351] **Example 18.** N-((5-Methoxy-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0352] **Step A**: Preparation of 4-(3-Methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0353] A mixture of NaH (3.2 g, 79 mmol) in 50 mL NMP stirred at 0°C, was treated dropwise with a mixture of 2-(3-methoxyphenyl)acetonitrile (3.9 g, 26 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (6.1 g, 26 mmol) in 20 mL. The mixture was allowed to warm to room temperature and stirred for 15 hours, M+1= 218. The mixture was then carefully quenched with 100 mL H_2O and the pH was adjusted to 5. The mixture was extracted with ether (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-20% EtOAc/hexane to give 5.28 g of the crude product 5.28 g as a pale yellow oil. MS (m/z) = 218 $(M+H)^+$.

[0354] **Step B**: Preparation of 4-(3-Methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0355] A mixture of 4-(3-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile (5.2 g, 24 mmol) in 10 mL dioxane was treated with 6N H_2SO_4 (40 mL, 239 mmol), and the mixture was refluxed at 120°C for 15 hours, M-1= 235 and starting material. The mixture was then stirred at 180°C in a sealed tube for another 0.5 hours, M-1= 235 (all starting material was consumed). The mixture was cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 5.14 g of the product as a pale yellow solid. MS (m/z) = 237 $(M+H)^+$.

[0356] **Step C**: Preparation of Diethyl 2-(4-(3-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0357] A mixture of magnesium (149 mg, 6146 µmol), and diethyl malonate (984 mg, 6146 µmol) was treated with anhydrous EtOH 2 mL and 0.1

mL CCl_4. The mixture was stirred at room temperature for 20 minutes and was then diluted with 50 mL anhydrous ether and refluxed for 1 hour under nitrogen. All magnesium was consumed.

[0358] 4-(3-Methoxyphenyl)-tetrahydro-2H-pyran-4-carboxylic acid (1.32 g, 5587 μmol) in thionyl chloride (4.078 mL, 55 mmol) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 20 mL ether and added dropwise to the above refluxed mixture, and the resulting mixture was refluxed for 20 minutes, M+1 = 379, M-1= 377. The mixture was cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 2.1 g of the intermediate, diethyl 2-(4-(3-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate, as a pale yellow oil. MS (m/z) = 379 $(M+H)^+$.

[0359] **Step D**: Preparation of Ethyl 5-methoxy-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0360] Diethyl 2-(4-(3-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (2.1 g) was added to 5 mL H_2SO_4 stirred at 0°C. The mixture was stirred at room temperature for 1 hour, M+1 = 379. The mixture was then poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography eluting with 20% EtOAc/hexane to give 0.05 g of the title compound. MS (m/z) = 379 $(M+H)^+$.

[0361] **Step E**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-5-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

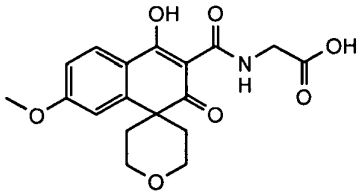
[0362] A mixture of ethyl 5-methoxy-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (44 mg, 132 μmol), tert-butyl 2-aminoacetate hydrochloride (33 mg, 199 μmol) in 2 mL dioxane was

treated with N-ethyl-N-isopropylpropan-2-amine (51 mg, 397 μmol). The mixture was warmed to 86°C and stirred for 14 hours, M+1= 418. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 35 mg of the title compound as a yellow oil. MS (m/z) = 418 $(M+H)^+$.

[0363] **Step F**: Preparation of N-((4-Hydroxy-5-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0364] A mixture of 1,1-dimethylethyl N-((4-hydroxy-5-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (32 mg, 77 μmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1= 362, M-1= 360. The mixture was concentrated in vacuo, and purified by column chromatography eluting with 0.1:10:100 TFA/MeOH/DCM to give 9 mg of the product as a pale yellow solid. MS (m/z) = 362 $(M+H)^+$. Calculated for $C_{18}H_{19}NO_7$ 361.12.

[0365] **Example 19.** N-((4-Hydroxy-7-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0366] **Step A**: Preparation of Ethyl 4-hydroxy-7-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0367] Diethyl 2-(4-(3-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (2.1 g, see Example 18) was added to 5 mL H_2SO_4 stirred at 0°C. The mixture was stirred at room temperature for 1 hour, M+1 = 379. The mixture was then poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The

crude product was purified by column chromatography eluting with 20% EtOAc/hexane to give 0.55 g of the title compound. MS (m/z) = 379 $(M+H)^+$.

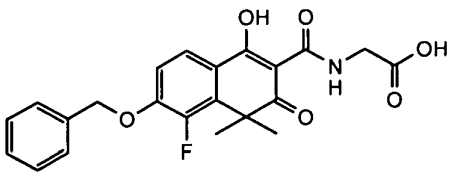
[0368] **Step B**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-7-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0369] A mixture of ethyl 4-hydroxy-7-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.52 g, 1.6 mmol), tert-butyl 2-aminoacetate hydrochloride (0.39 g, 2.3 mmol) in 5 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.61 g, 4.7 mmol). The mixture was warmed to 86°C and stirred for 4 hours, M+1= 418. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 0.35 g of the title compound as a pale yellow solid. MS (m/z) = 418 $(M+H)^+$.

[0370] **Step C**: Preparation of N-((4-Hydroxy-7-(methyloxy)-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0371] A mixture of 1,1-dimethylethyl N-((4-hydroxy-7-methoxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.36 g, 0.9 mmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1= 362, M-1= 360. The mixture was concentrated and then triturated in DCM/hexane (5:10). The solid was filtered, washed with 10 mL DCM/hexane (5:10), and dried under high vacuum to give 0.3 g of the product as an off-white solid. MS (m/z) = 362 $(M+H)^+$. Calculated for $C_{18}H_{19}NO_7$ 361.12.

[0372] **Example 20.** N-((8-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-7-((phenylmethyl)oxy)-naphthalen-3-yl)carbonyl)glycine



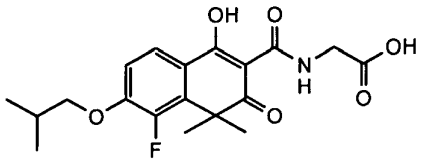
[0373] **Step A**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-7-((phenylmethyl)oxyl)-naphthalen-3-yl)carbonyl)glycinate

[0374] A mixture of 1,1-dimethylethyl N-((8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (0.29 g, 0.76 mmol, prepared in Example 23 A-D) and K_2CO_3 (0.21 g, 1.5 mmol) in 5 mL ACN stirred at room temperature, was treated with 1-(bromomethyl)benzene (0.26 g, 1.5 mmol), and the resulting mixture was stirred for 12 hours, M+Na = 492. The mixture was concentrated in vacuo and purified by column chromatography eluting with 10-30% EtOAc/hexane to give 0.27 g of the title compound as a white solid. MS (m/z) = 492 $(M+H)^+$.

[0375] **Step B**: Preparation of N-((8-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-7-((phenylmethyl)oxy)-naphthalen-3-yl)carbonyl)glycine

[0376] A mixture of 1,1-dimethylethyl N-((8-fluoro-2-hydroxy-1,1-dimethyl-4-oxo-7-((phenylmethyl)oxyl)-naphthalene-3-yl)carbonyl)glycinate (0.21 g, 447 μmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1= 414. The mixture was concentrated and then triturated in DCM/hexane (5:10). The solid was filtered, washed with 10 mL DCM/hexane (5:10), and dried under high vacuum to give 0.16 g of a pale yellow solid. LCMS showed about 10% of debenzylated product. The product was further purified by column chromatography eluting with 1:10:100 TFA/MeOH/DCM to give 108 mg of the pure compound. MS (m/z) = 414 $(M+H)^+$. Calculated for $C_{22}H_{20}FNO_6$ 413.13.

[0377] **Example 21.** N-((8-Fluoro-4-hydroxy-1,1-dimethyl-7-((2-methylpropyl)oxy)-2-oxo-naphthalen-3-yl)carbonyl)glycine



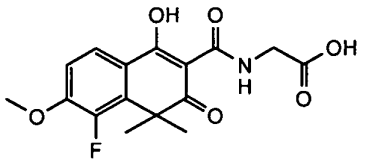
[0378] **Step A**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-7-((2-methylpropyl)oxy)-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0379] A mixture of 1,1-dimethylethyl N-((8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.29 g, 0.76 mmol, see Example 23) and K_2CO_3 (0.21 g, 1.5 mmol) in 5 mL ACN stirred at room temperature, was treated with 1-bromo-2-methylpropane (0.52 g, 3.8 mmol). The mixture was stirred at room temperature for 12 hours. The mixture was then warmed to 80°C and stirred for 24 hours. The mixture was concentrated in vacuo and purified by column chromatography eluting with 10-30% EtOAc/hexane to give 0.25 g of the title compound as a white solid. MS (m/z) = 458 $(M+Na)^+$.

[0380] **Step B**: Preparation of N-((8-Fluoro-4-hydroxy-1,1-dimethyl-7-((2-methylpropyl)oxy)-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0381] A mixture of 1,1-dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-7-((2-methylpropyl)oxy)-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.22g, 0.51 mmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1= 380. The mixture was concentrated and triturated in DCM/hexane (5:10). The solid was filtered, washed with 10 mL DCM/hexane (5:10), and dried under high vacuum to give 0.18 g of the product as a pale yellow solid. MS (m/z) = 380 $(M+H)^+$. Calculated for $C_{19}H_{22}FNO_6$ 379.14.

[0382] **Example 22.** N-((8-Fluoro-4-hydroxy-1,1-dimethyl-7-(methyloxy)-2-oxo-naphthalen-3-yl)carbonyl)glycine



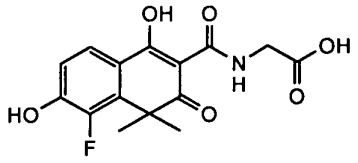
[0383] **Step A**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-7-methoxyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0384] A mixture of 1,1-dimethylethyl N-((8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.1 g, 0.3 mmol, see Example 23), and K_2CO_3 (0.04 g, 0.3 mmol) in 4 mL ACN stirred at room temperature, was treated with MeI (0.06 g, 0.4 mmol), and the resulting mixture was stirred for 12 hours, M+Na = 416. The mixture was concentrated in vacuo and purified by column chromatography eluting with 10-30% EtOAc/hexane to give 98 mg of the title compound as a white solid. MS (m/z) = 416 $(M+H)^+$.

[0385] **Step B**: Preparation of N-((8-Fluoro-4-hydroxy-1,1-dimethyl-7-methoxyl-2-oxo-naphthalene-3-yl)carbonyl)glycine

[0386] A mixture of 1,1-dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-7-methoxyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (92 mg, 234 μmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1= 338. The mixture was concentrated and then triturated in DCM/hexane (5:10). The solid was filtered, washed with 10 mL DCM/hexane (5:10), and dried under high vacuum to give 72 mg of the product as a pale yellow solid. MS (m/z) = 338 $(M+H)^+$. Calculated for $C_{16}H_{16}FNO_6$ 337.10.

[0387] **Example 23.** N-((8-Fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0388] **Step A**: Preparation of 2-(2,3-Difluorophenyl)-2-methylpropanenitrile

[0389] A mixture of NaH (5.7 g, 144 mmol) in 100 mL NMP stirred at 0°C, was treated dropwise with a mixture of MeI (9.0 mL, 144 mmol) and 2-(2,3-difluorophenyl)acetonitrile (10 g, 65 mmol) in 50 mL ether. The mixture was stirred at room temperature for 15 hours. The mixture was then carefully quenched with 20 mL H_2O and extracted with ether (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-20 % EtOAc/hexane to give 11.4 g of the title compound as a pale yellow oil.

[0390] **Step B**: Preparation of 2-(2-Fluoro-3-hydroxyphenyl)-2-methylpropanoic acid

[0391] A mixture of 2-(2,3-difluorophenyl)-2-methylpropanenitrile (11.4 g, 63 mmol) in 100 mL ethylene glycol was treated with KOH (11 g, 189 mmol) and stirred at 200°C for 3 hours, M-1 = 197. The mixture was then cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the title compound in 10 g. MS (m/z) = 197 $(M-1)^-$.

[0392] **Step C**: Preparation of Diethyl 2-(2-(2-fluoro-3-hydroxyphenyl)-2-methylpropanoyl)malonate

[0393] A mixture of magnesium (1.2 g, 50 mmol) and diethyl malonate (8.1 g, 50 mmol) was treated with anhydrous EtOH 10 mL and 0.1 mL CCl_4. The mixture was stirred at room temperature for 20 minutes and was then diluted with 50 mL anhydrous THF and refluxed for 1 hour under nitrogen.

[0394] A mixture of 2-(2-fluoro-3-hydroxyphenyl)-2-methylpropanoic acid (10 g, 50 mmol) in thionyl chloride (37 mL, 505 mmol) was refluxed for 2

hours and then concentrated in vacuo. The residue was diluted with 20 mL THF and added dropwise to the above refluxed mixture, and the resulting mixture was refluxed for 20 minutes M+1= 341, M-1= 339. The mixture was then cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-30 % EtOAc /hexane to give 3.7 g of the title compound. MS (m/z) = 341 $(M+H)^+$.

[0395] **Step D**: Preparation of Ethyl 8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0396] To 20 mL concentrated H_2SO_4 stirred at room temperature, was added diethyl 2-(2-(2-fluoro-3-hydroxyphenyl)-2-methylpropanoyl)malonate (3.6 g, 11 mmol). The mixture was stirred at room temperature for 2 hours, M+1= 295. The mixture was then poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10–30% EtOAc/hexane to give 2.9 g of the title compound as a pale yellow solid. MS (m/z) = 295 $(M+H)^+$.

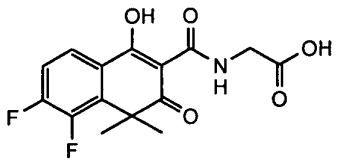
[0397] **Step E**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0398] A mixture of ethyl 8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.4 g, 1 mmol) and tert-butyl 2-aminoacetate hydrochloride (0.3 g, 2 mmol) in 2 mL dioxane, was treated with N-ethyl-N-isopropylpropan-2-amine (0.5 g, 4 mmol). The resulting mixture was warmed to 85°C and stirred for 4 hours, M+Na = 402, M+1= 380. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc/hexane to give 0.4 g of the title compound as a pale white solid. MS (m/z) = 378 $(M-1)^-$.

[0399] **Step F**: Preparation of N-((8-Fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0400] A mixture of 1,1-dimethylethyl N-((8-fluoro-4,7-dihydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.21g, 0.55 mmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1 =324 , M-1= 322. The mixture was concentrated and triturated in ether/hexane (1:10). The solid was filtered, washed with 10 mL ether/hexane (1:10), and dried under high vacuum to give 0.17 g of the product as a yellow solid. MS (m/z) = 324 $(M+H)^+$. Calculated for $C_{15}H_{14}FNO_6$ 323.08.

[0401] **Example 24.** N-((7,8-Difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0402] **Step A**: Preparation of 2-(2,3-Difluorophenyl)-2-methylpropanoic acid

[0403] A mixture of 2-(2,3-difluorophenyl)-2-methylpropanenitrile (9.5 g, 52 mmol) in 50 mL dioxane was treated with 10 mL H_2O and concentrated H_2SO_4 (3 mL, 105 mmol). The resulting mixture was stirred at 110°C for 16 hours, M+1 = 201. The reaction was then cooled to room temperature. The mixture was extracted with EtOAc and the organic layer discarded. The water layer was acidified with concentrated HCl, extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 4.74 g of the title compound as a pale yellow solid. MS (m/z) = 201 $(M+H)^+$.

[0404] **Step B**: Preparation of Diethyl 2-(2-(2,3-difluorophenyl)-2-methylpropanoyl)malonate

[0405] A mixture of magnesium (0.57 g, 23 mmol), and diethyl malonate (3.8 g, 23 mmol) was treated with anhydrous EtOH 10 mL and 0.1 mL CCl_4.

The mixture was stirred at room temperature for 20 minutes and was then diluted with 50 mL anhydrous THF and refluxed for 1 hour under nitrogen.

[0406] A mixture of 2-(2,3-difluorophenyl)-2-methylpropanoic acid (4.7 g, 23 mmol) in thionyl chloride (28 g, 235 mmol) was refluxed for 2 hours and then concentrated in vacuo. The residue was diluted with 20 mL THF, and added dropwise to the above refluxed mixture, and the resulting mixture was refluxed for 20 minutes, M+1= 343 M-1= 341. The mixture was then cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-30 % EtOAc /hexane to give 1.53 g of the title compound as a colorless oil. MS (m/z) = 343 $(M+H)^+$.

[0407] **Step C**: Preparation of Ethyl 7,8-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0408] To 10 mL concentrated H_2SO_4 stirred at room temperature, was added diethyl 2-(2-(2,3-difluorophenyl)-2-methylpropanoyl)malonate (1.53 g, 4.5 mmol). The mixture was stirred at room temperature for 2 hours, M+1= 297. The mixture was then poured into 100 g crushed ice and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 1.2 g of the title compound as a pale yellow solid. MS (m/z) = 297 $(M+H)^+$.

[0409] **Step D**: Preparation of 1,1-Dimethylethyl N-((7,8-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

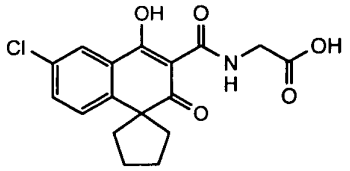
[0410] A mixture of ethyl 7,8-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.46 g, 1.6 mmol) and tert-butyl 2-aminoacetate hydrochloride (0.39 g, 2.3 mmol) in 2 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.60 g, 4.7 mmol). The mixture was warmed to 85°C and stirred for 15 hours, M+Na= 404, M-1= 380. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified

by column chromatography eluting with 10-30 % EtOAc/hexane to give the title compound (0.53 g) as a pale yellow solid. MS (m/z) = 404 $(M+Na)^+$.

[0411] **Step E**: Preparation of N-((7,8-Difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0412] A mixture of 1,1-dimethylethyl N-((7,8-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.4 g, 1 mmol) in 3 mL TFA was stirred at room temperature for 30 minutes, M+1 =325, M-1= 324. The mixture was concentrated and then triturated in DCM/hexane (5:10). The solid was filtered, washed with 10 mL DCM/hexane (5:10), and dried under high vacuum to give 0.24 g of the product as a pale yellow solid. MS (m/z) = 326 $(M+H)^+$. Calculated for $C_{15}H_{13}F_2NO_5$ 325.07.

[0413] **Example 25.** N-((6'-Chloro-4'-hydroxy-2'-oxo-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycine



[0414] **Step A**: Preparation of Ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclopentane-1,1'-naphthalen]-3'-carboxylate

[0415] A mixture of diethyl malonate (5.3 g, 33 mmol) and magnesium (0.80 g, 33 mmol) was treated with anhydrous EtOH 10 mL and 0.1 mL CCl_4. The mixture was stirred at room temperature for 20 minutes and was then diluted with 50 mL anhydrous ether and refluxed for 1 hour under nitrogen. 1-(4-Chlorophenyl)cyclopentanecarbonyl chloride (7.3 g, 30 mmol) in 20 mL ether was then added dropwise to the above refluxed mixture, and the resulting mixture was refluxed for 20 minutes, M+1= 341. The mixture was cooled to room temperature, diluted with 100 mL ether, washed with H_2O (2 x 50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 11 g of the crude product as a pale yellow solid. The crude product was

treated with concentrated H_2SO_4 (48 mL, 900 mmol) and stirred for 4 hours, M+1=321. The mixture was poured into 500 g ice and extracted with ether (3 x100 mL). The organic layers were combined and washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 10-20% ether/hexane to give the title compound (6.5 g) as a pale yellow solid. MS (m/z) = 321 $(M+H)^+$.

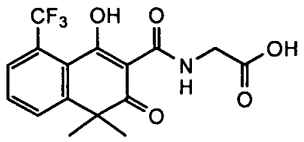
[0416] **Step B**: Preparation of 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate

[0417] A mixture of ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclopentane-1,1'-naphthalen]-3'-carboxylate (0.66g, 2 mmol) and glycine tert-butyl ester hydrochloride (0.5 g, 3 mmol) in 10 mL dioxane was treated with DIPEA (1 mL, 6 mmol). The mixture was warmed to 85°C and stirred for 4 hours, M+1 = 406. The mixture was then cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-30 % EtOAc hexane to give the title compound (0.8 g) as a pale yellow solid. MS (m/z) = 406 $(M+Na)^+$.

[0418] **Step C**: Preparation of N-((6'-Chloro-4'-hydroxy-2'-oxo-2'H-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycine

[0419] A mixture of 1,1-dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-2'H-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate (0.2 g, 0.5 mmol) in 2 mL TFA was stirred at room temperature for 30 minutes, M+1 = 350. The mixture was concentrated and triturated in ether/hexane (10:1). The solid was filtered, washed with 10 mL ether/hexane (10:1), and dried under high vacuum to give 135 mg of the salt as an off-white solid. MS (m/z) = 350 $(M+H)^+$. Calculated for $C_{17}H_{16}ClNO_5$ 349.07.

[0420] **Example 26.** N-((4-Hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycine



[0421] **Step A**: Preparation of 2-Iodo-3-(trifluoromethyl)benzoic acid

[0422] 30% H_2SO_4 (30 mL) was added to a solution of 3-(trifluoromethyl)anthranilic acid (10.0 g, 48.8 mmol) in DMSO (10 mL) at room temperature. The mixture was cooled to 0°C, and a solution of sodium nitrite (5.05 g, 73.2 mmol) in water (10 mL) was added dropwise over 5 minutes. The mixture was stirred for 1 hour at 0°C, and a solution of KI in water (10 mL) was added dropwise over 5 minutes. The ice bath was removed, and the mixture was stirred for 1 hour. EtOAc was added, and the solution was washed with 2N sodium nitrite twice, brine once, and dried over $MgSO_4$. The solvent was then removed under vacuum to give the product as an off-white solid (12.6 g). [M-H]- = 315.2.

[0423] **Step B**: Preparation of 2-Iodo-3-(trifluoromethyl)benzoyl chloride

[0424] 2-Iodo-3-(trifluoromethyl)benzoic acid (10.0 g, 31.6 mmol) was stirred in thionyl chloride (100 mL, 31.6 mmol) at reflux for 2 hours. The mixture was then cooled to room temperature. The thionyl chloride was removed under vacuum, and the residue was azeotroped with dry toluene to give the product as a yellow-orange semi-solid (10.51 g).

[0425] **Step C**: Preparation of Ethyl 2-(2-iodo-3-(trifluoromethyl)phenyl)acetate

[0426] (Trimethylsilyl)diazomethane (2.0M in diethyl ether, 55 mL, 110 mmol) was added to 2-iodo-3-(trifluoromethyl)benzoyl chloride (9.24g, 27.6 mmol) in 25 mL Et_2O in a heavy-walled reaction vessel. The reaction was stirred for 5 hours at room temperature. The mixture was then cooled to 0°C, and AcOH was added until gas evolution ceased. The mixture was partitioned between EtOAc and saturated $NaHCO_3$, the layers were separated, and the

organic layer was washed twice with saturated $NaHCO_3$, once with brine, and then dried over $MgSO_4$. The solvent was removed under vacuum to give the product as a yellow oil (9.10 g).

[0427] Silver(I) oxide (0.97 g, 4.2 mmol) was added to a solution of the material obtained from the above reaction (7.10 g, 21 mmol) in anhydrous, 200 proof EtOH (180 mL), and the mixture was heated to 75°C for 30 minutes. The mixture was cooled to room temperature, filtered through celite, and concentrated under vacuum. The resulting yellow oil was purified by column chromatography (0-60% DCM/hexane gradient) to give the product as a light yellow solid (5.4 g).

[0428] **Step D**: Preparation of Ethyl 2-(3,3,3-triethoxyprop-1-ynyl)-3-(trifluoromethyl)phenyl)acetate

[0429] Copper(I) iodide (160 mg, 0.840 mmol), dichlorobis(triphenylphosphine)palladium(II) (197 mg, 0.280 mmol), and ethyl 2-(2-iodo-3-(trifluoromethyl)phenyl)acetate (1.00 g, 2.80 mmol) were mixed in a heavy-walled microwave tube, and ACN (6 mL) and TEA (3 mL) were added. The tube was sealed and placed under an argon atmosphere before 3,3,3-triethoxyprop-1-yne (723 mg, 4.20 mmol) was added via syringe. The mixture was stirred overnight at 65°C. An additional 0.5 equiv alkyne was added, and the resulting mixture was stirred at 75°C for 4 hours. The mixture was cooled to room temperature, concentrated under vacuum, and purified by column chromatography to give the product as a light yellow oil (500 mg).

[0430] **Step E**: Preparation of Ethyl 3-(2-(1-ethoxy-2-methyl-1-oxopropan-2-yl)-6-(trifluoromethyl)phenyl)propiolate

[0431] A solution of ethyl 2-(2-(3,3,3-triethoxyprop-1-ynyl)-3-(trifluoromethyl)phenyl)acetate (500 mg, 1.24 mmol) in DMF (3 mL) was added to a suspension of NaH (89 mg, 3.72 mmol) in DMF (2 mL) at 0°C. After 10 minutes, MeI (0.31 mL, 4.96 mmol) was added, and the mixture was stirred at room temperature overnight. One more equivalent of NaH and MeI were then

added, and the mixture was stirred for 3 hours, at which time distilled HMPA (2 mL) was added. After 2 hours at room temperature, the mixture was cooled to 0°C and partitioned between Et_2O and saturated NH_4Cl. The layers were separated, and the organic layer was washed twice with water, once with brine, and then dried over $MgSO_4$. The solvent was removed under vacuum to give a colorless oil (530 mg). The oil was dissolved in 4mL EtOH and 1 mL H_2O. p-TSA monohydrate (5 mg) was added, and the mixture was stirred at room temperature for 1 hour. Saturated $NaHCO_3$ and EtOAc were added, and the layers were separated. The organic layer was dried ($MgSO_4$) and then concentrated under vacuum. The residue was purified by column chromatography to give the product as a colorless oil (276 mg).

[0432] **Step F**: Preparation of Ethyl 4-hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalene-3-carboxylate

[0433] Benzaldehyde oxime (112 mg, 0.92 mmol) in 6 mL dry DMF under argon, was added via syringe to a suspension of NaH (22 mg, 0.92 mmol) in dry dioxane (6 mL) under argon at room temperature. The mixture was stirred for 30 minutes, and ethyl 3-(2-(1-ethoxy-2-methyl-1-oxopropan-2-yl)-6-(trifluoromethyl)phenyl)propiolate (275 mg, 0.77 mmol) was added as a solution in dry DMF (6 mL) via syringe. The reaction was stirred at room temperature for 11 hours. The dioxane was removed under vacuum, and the remaining DMF was partitioned between EtOAc and water. The layers were separated, and the organic layer was washed with twice with water and once with brine. The combined aqueous extracts were back extracted twice with EtOAc, and these organic layers were added to the organic layer already obtained. The combined extracts were dried over $MgSO_4$, concentrated under vacuum, and the resulting residue was purified by column chromatography to give the product as a light yellow oil (50 mg). MS (m/z) = 329 $(M+H)^+$

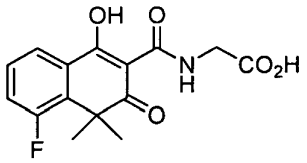
[0434] **Step G**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycinate

[0435] DIPEA (40 μL, 0.23 mmol), tert-butylglycine hydrochloride (38 mg), and ethyl 4-hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalene-3-carboxylate (50 mg, 0.15 mmol) were heated in dioxane (2 mL) for 5 hours, cooled to room temperature, and then concentrated under vacuum. The residue was purified by column chromatography to give the product as a yellow oil (30 mg). MS (m/z) = 358.4$[M\text{-}tBu]^+$

[0436] **Step H**: Preparation of N-((4-Hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycine

[0437] 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-5-(trifluoromethyl)-naphthalen-3-yl)carbonyl)glycinate (30 mg, 73 μmol) was stirred in TFA (5 mL) for 15 minutes. The TFA was then removed under vacuum. The residue was purified by preparatory scale TLC (5% MeOH/DCM eluent) to give the desired product as a light yellow oil (1.6 mg). MS (m/z) = 358.4 $(M+H)^+$. Calculated for $C_{16}H_{14}F_3NO_5$ 357.08.

[0438] **Example 27.** N-((8-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0439] **Step A:** Preparation of Methyl 2-(2-fluorophenyl)acetate

[0440] To a stirred solution of 2-fluorophenylacetic acid (9.6 g, 62 mmol) in MeOH (100 mL) was added concentrated HCl (0.7 mL, 19 mmol). The mixture was heated at 68°C for 4 hours, and then the reaction was concentrated in vacuo to remove MeOH. The residue was dissolved in ether and then washed with saturated $NaHCO_3$ solution (1 x 50 mL). The organic extracts were separated, dried with Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil (10g). MS (m/z) = 169.0 $(M+H)^+$.

[0441] **Step B**: Preparation of Methyl 2-(2-fluorophenyl)-2-methylpropanoate

[0442] A stirred solution of methyl 2-(2-fluorophenyl)acetate (10.0 g, 59 mmol), MeI (11 mL, 178 mmol), and 18-crown-6 (4 g, 15 mmol) in THF (150 mL) was carefully treated with potassium tert-butoxide (20 mL, 178 mmol). After stirring the reaction mixture at room temperature for 24 hours, NaH (2 g, 62 mmol) was added, and the resulting white mixture was stirred for an additional 12 hours. Water (100 mL) was added cautiously, and then the solution was extracted with EtOAc (2 x 150 mL). Organic extracts were separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a yellow oil. Purification via flash chromatography (5% EtOAc/hexanes) provided a pale yellow oil (5.2 g). MS (m/z) = 197 $(M+H)^+$.

[0443] **Step C**: Preparation of 2-(2-Fluorophenyl)-2-methylpropanoic acid

[0444] A flask containing a solution of methyl 2-(2-fluorophenyl)-2-methylpropanoate (5.2 g, 27 mmol), KOH (2.9 mL, 106 mmol), water (20.0 mL), and EtOH (100 mL) was sealed and heated at 130°C for 2 hours. Removal of solvent in vacuo provided a yellow oil that was diluted with water. The aqueous mixture was extracted with DCM (1 x 100 mL), and the organic layer was separated. The aqueous layer was acidified to a pH of 1 with 5N HCl and then extracted with EtOAc (2 x 100 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 4 g of the product as a solid. MS (m/z) = 181 $(M-1)^-$.

[0445] **Step D**: Preparation of Diethyl 2-(2-(2-fluorophenyl)-2-methylpropanoyl)malonate

[0446] To a solution of 2-(2-fluorophenyl)-2-methylpropanoic acid (3.98 g, 22 mmol), IPAc (31 mL) and DMF (0.017 mL), was slowly added oxalyl chloride (2.0 mL, 23 mmol) over 10 minutes. The resulting solution was stirred for 16 hours and then concentrated in vacuo to afford an oil. In a separate flask,

IPAc (30.0 mL) and diethyl malonate (4.2 mL, 27 mmol) were combined. To this mixture was added anhydrous $MgCl_2$ (2.6 g, 27 mmol). The resulting white slurry was stirred at room temperature for 30 minutes, and then TEA (10 mL, 73 mmol) was added. After stirring for an additional 2.5 hours, the reaction was chilled in an ice water bath for 10 minutes, and then the crude acid chloride (previously prepared above) was added to the white mixture via syringe over 10 minutes. The ice bath was removed, and the reaction was stirred for 1.5 hours at room temperature. The mixture was acidified with 5N HCl and added IPAc (50 mL) was added. The aqueous layer was separated and set aside. The organic layer was sequentially washed with saturated $NaHCO_3$ solution and then water. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product. MS (m/z) = 325 $(M+H)^+$.

[0447] **Step E**: Preparation of Ethyl 8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0448] A flask containing H_2SO_4 (12 mL, 219 mmol) and P_2O_5 (12 g, 88 mmol) was cooled in an ice-water bath for 20 minutes. To this viscous mixture was slowly added diethyl 2-(2-(2-fluorophenyl)-2-methylpropanoyl)malonate (7.1 g, 22 mmol). The ice bath was removed, and the mixture was stirred at room temperature for 1 hour before being poured over crushed ice and diluted with IPAc (100 mL). Water (50 mL) was added, and the resulting mixture was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil that was further purified using flash chromatography (10% EtOAc/hexane, 2.5 g). MS (m/z) = 279 $(M+H)^+$.

[0449] **Step F**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

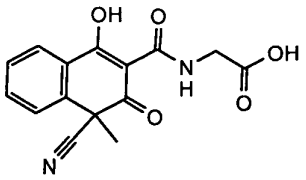
[0450] To a solution of ethyl 5-fluoro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalene-2-carboxylate (2.0 g, 7.2 mmol) in 1,4-dioxane (15 mL), was added N-ethyl-N-isopropylpropan-2-amine (2.3 mL, 13 mmol) and

tert-butyl 2-aminoacetate hydrochloride (1.6 g, 9.3 mmol). After heating at 80°C for 12 hours, the solvent was removed in vacuo, and the residue was purified using flash chromatography (15 % EtOAc/hexane) to afford the product as a white solid (1.6 g). MS (m/z) = 362 $(M+H)^+$.

[0451] **Step G**: Preparation of N-((8-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0452] To a flask containing 1,1-dimethylethyl N-((8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (1.5 g, 4.1 mmol) was added TFA (20 mL). The reaction was stirred under nitrogen for 1 hours and then concentrated in vacuo to afford an oil. Addition of water caused a white precipitate to form. The solid was collected by filtration, washed with water, washed with ether, and then dried in vacuo (0.68 g). MS (m/z) = 308 $(M+H)^+$. Calculated for $C_{15}H_{14}FNO_5$ 307.08.

[0453] **Example 28.** N-((1-Cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0454] **Step A**: Preparation of 2-(2-Iodophenyl)propanenitrile

[0455] 2-(2-Iodophenyl)acetonitrile (3.0 g, 12 mmol) and sodium tert-butoxide (3.6 g, 37 mmol) were stirred in 20 mL of DMF, and MeI (0.77 mL, 12 mmol) was added dropwise. The reaction was then stirred for 3 hours. The solvent was removed under vacuum. The crude residue was purified by silica flash chromatography 0-15% EtOAc/hexanes.

[0456] **Step B**: Preparation of 2-(2-(2-(Trimethylsilyl)ethylnyl)phenyl)-proanenitrile

[0457] Dichlorobis(triphenylphosphine)palladium (II) (0.67 g, 0.95 mmol), copper(I) iodide (0.065 mL, 1.9 mmol), 1-(trimethylsilyl)acetylene (4.0 mL, 29 mmol), and 2-(2-iodophenyl)propanenitrile (2.45 g, 9.5 mmol) were stirred in a 250 mL round bottom flask with 100 mL of TEA at 70°C. The solution was then filtered through a plug of Celite, washed with EtOAc, and the filtrate was concentrated in vacuo. The crude material was purified using silica flash chromatography with a gradient of 0-20% EtOAc/hexanes. MS (m/z) = 228 (M+H) + .

[0458] **Step C**: Preparation of 2-(2-Ethynylphenyl)propanenitrile

[0459] 2-(2-(2-(Trimethylsilyl)ethynyl)phenyl)propanenitrile (2.16 g, 9 mmol) was stirred with 5N NaOH (10 mL, 50 mmol) and THF (20 mL) at room temperature for 1 hour. The reaction mixture was acidified with 5N HCl (13 mL) until the pH was about 2. The aqueous mixture was then extracted with EtOAc (3 x 50 mL). The combined organic layers were extracted with water (3 x 50 mL) and once with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a brown oil. MS (m/z) = 156 (M+H) + .

[0460] **Step D**: Preparation of Ethyl 3-(2-(2-cyano-1-ethoxy-1-oxopropan-2-yl)phenyl)propiolate

[0461] Butyllithium (5.8 mL, 14 mmol) was added to a stirred solution of diisopropylamine (2.1 mL, 15 mmol) in THF at -78°C. The reaction mixture was then allowed to warm to ambient temperature for 5 minutes before being cooled back down to -78°C. 2-(2-Ethynylphenyl)propanenitrile (0.750 g, 4.8 mmol) was added dropwise as a solution in 5 mL of THF, and the reaction was stirred for 30 minutes. Ethyl carbonochloridate (1.5 mL, 15 mmol) in 5 mL of THF was added to the reaction. The resulting solution was allowed to warm to room temperature and was stirred for an additional 30 minutes. 2 mL of MeOH and 20 mL of water were added to the mixture. The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with NH_4Cl (3x20 mL) and brine (1 x 20 mL), dried with $MgSO_4$, and concentrated in

vacuo. The resulting oil was purified using silica flash chromatography with a gradient of 0-15% EtOAc/hexanes. MS (m/z) = 300 (M+H) +.

[0462] **Step E**: Preparation of Ethyl 1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate

[0463] A solution of benzaldehyde oxime (0.37 mL, 3.7 mmol) in dry DMF (4 mL) was added to a stirred suspension of NaH (0.16 mL, 3.7 mmol) in dry dioxane (50 mL) in a nitrogen atmosphere at room temperature. After 30 minutes, a solution of ethyl 3-(2-(2-cyano-1-ethoxy-1-oxopropan-2-yl)phenyl)propiolate (1.12 g, 3.7 mmol) was added in dry DMF (5 mL), and the solution was stirred overnight. The solvent was removed under vacuum, and water was added to the residue. The product was extracted with EtOAc. The organic layer was washed with water, dried with $MgSO_4$, concentrated in vacuo, and purified by silica flash chromatography eluting with 0-30% EtOAc/hexane. MS (m/z) = 272 (M+H) + .

[0464] **Step F**: Preparation of 1,1-Dimethylethyl N-((1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

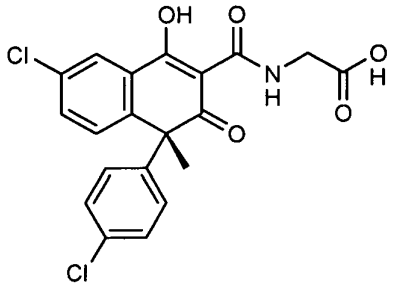
[0465] Ethyl 1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate (0.225 g, 0.829 mmol), glycine tert-butyl ester hydrochloride (0.167 g, 0.995 mmol), and glycine tert-butyl ester hydrochloride (0.167 g, 0.995 mmol) were refluxed in dioxane (50 mL) for 14 hours. The solvent was then removed in vacuo. The resulting residue was concentrated in vacuo and purified using silica flash chromatography (10-40% EtOAc/hexanes). MS (m/z) = 301 (M+H) + (hydrolyzed product) 379.1 (product + Na).

[0466] **Step G**: Preparation of N-((1-Cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

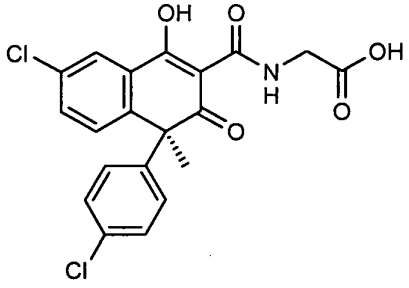
[0467] 1,1-Dimethylethyl N-((1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.100 g, 0.28 mmol) was placed in a 25 mL round bottom flask and TFA (10 mL) was added. The resulting mixture was

then stirred for 45 minutes. TFA was then removed under vacuum, and DCM was used to azeotrope off TFA (3X) resulting in a yellow solid. MS (m/z) = 301 (M+H) +. Calculated for $C_{15}H_{12}N_2O_5$ 300.07.

[0468] **Examples 29 and 30.** N-(((1S)-6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine and N-(((1R)-6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

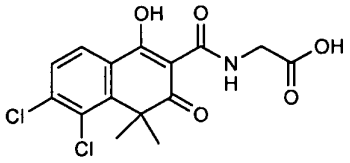


and



[0469] N-((6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine (0.309 g, see Example 34) was dissolved in dimethoxy ethylenegycol (10 mL)and separated into the two enantiomers on a chiralpack ADH (21x250 mm, 5 μm) column in ten 1mL injections (flow: 60 mL/min, eluent: 50% MeOH in supercritical fluid and carbon dioxide). The second peak (t = 5.3 minutes) was concentrated and dried in vacuo to give Example 29 (0.141 g). The first peak (t= 3.38 minutes) was concentrated and dried in vacuo to give Example 30 (0.146 g). MS m/e = 420 $(M+H)^+$. Calculated for $C_{20}H_{15}Cl_2NO_5$ 419.03.

[0470] **Example 31.** N-((7,8-Dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0471] **Step A**: Preparation of Methyl 2-(2,3-dichlorophenyl)-2-methylpropanoate

[0472] A solution of NaH (2.87 g, 71.8 mmol) in DMF (100 mL) was cooled to 0°C. A solution of methyl 2-(2,3-dichlorophenyl)acetate (5.24 g, 23.9 mmol) in DMF(50 mL) was added dropwise, and the resulting mixture was stirred for 5 minutes. A solution of MeI (4.36 mL, 69.8 mmol) in DMF (50 mL) was then added to the reaction. After 10 minutes, the mixture was allowed to warm to 25°C and the reaction was stirred for 16 hours. The mixture was diluted with 10% HCl(aq) (150 mL), and the resulting mixture was extracted with EtOAc (2x200 mL) and washed with 10% HCl(aq) (100 mL), deionized water (2x150 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated and dried in vacuo to give 7.06g crude product. The crude product was purified by flash column chromatography (silica, 0-50% DCM in hexane) to give the title compound (5.53 g). MS m/e = 247 $(M+H)^+$.

[0473] **Step B**: Preparation of 2-(2,3-Dichlorophenyl)-2-methylpropanoic acid

[0474] A mixture of methyl 2-(2,3-dichlorophenyl)-2-methylpropanoate (5.50 g, 22.3 mmol) and KOH (6.24 g, 111 mmol) in EtOH/water (5:1, 150 mL) in a 500 mL round bottom flask, was heated at 95°C for 18 hours. The solution was diluted with diethyl ether (200 mL), and washed with 1N NaOH(aq) (3x75mL). The aqueous solution was made acidic (pH = 2) with concentrated HCl. The mixture was then extracted with EtOAc (3x100 mL), and the combined organic layers were washed with deionized water (100 mL) and with

brine (75 mL). The organic layer was then dried over $MgSO_4$, concentrated, and dried in vacuo. The crude product was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give the title compound (4.1338 g). MS m/e = 233 $(M+H)^+$.

[0475] **Step C**: Preparation of Ethyl 7,8-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0476] A solution of 2-(2,3-dichlorophenyl)-2-methylpropanoic acid (2.00 g, 8.58 mmol) in thionyl chloride (80.0 mL, 1097 mmol) was stirred at 95°C for 2.5 hours. The mixture was then concentrated, azeotroped in toluene (2x100 mL), and dried in vacuo for 2 hours to give the crude acid chloride.

[0477] A solution of diethyl malonate (1.30 mL, 8.58 mmol) in ACN (50 mL) in a 500 mL round bottom flask, was cooled to 0°C. $MgCl_2$ (0.353 mL, 8.58 mmol) followed by TEA (2.51 mL, 18.0 mmol) were added, and the mixture was stirred at 25°C for 2 hours. A solution of the above acid chloride in ACN (50 mL) was added, and the mixture was heated at 50°C for 14 hours. The solution was diluted with 10% HCl(aq) (100 mL) and then extracted with EtOAc (3x100 mL). The organic solution was washed with 10% HCl(aq) (100 mL), with 1N NaOH(aq) (2x100 mL), and then with brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give 3.34 g of crude product. The crude product was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give the intermediate, diethyl 2-(2-(2,3-dichlorophenyl)-2-methylpropanoyl)malonate (1.603 g) MS m/e = 375 $(M+H)^+$.

[0478] P_2O_5 (5.00 g, 35 mmol) was treated with H_2SO_4 (4.5 mL, 81 mmol) at 0°C in a 100 mL round bottom flask. Diethyl 2-(2-(2,3-dichlorophenyl)-2-methylpropanoyl)malonate (0.500 g, 1.0 mmol) was added, and the mixture was stirred at 25°C for 1.5 hours. The reaction was quenched with ice, extracted with EtOAc (2x50 mL), and the combined organic layers were washed with brine (50 mL). The organic layers were then dried over $MgSO_4$, concentrated, and dried in vacuo to give the title compound (0.235 g). MS m/e = 329 $(M+H)^+$.

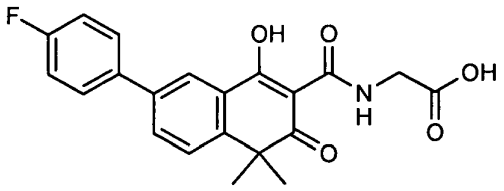
[0479] **Step D**: Preparation of 1,1-Dimethylethyl N-((7,8-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0480] A solution of ethyl 7,8-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.200 g, 0.456 mmol), glycine tert-butyl ester hydrochloride (0.0993 g, 0.592 mmol), and DIPEA (0.159 mL, 0.911 mmol) in 1,4-dioxane (5 mL) was heated to 120°C in a 15 mL sealed vessel for 3 hours. The reaction was then diluted with deionized water (50 mL) and extracted with DCM (2x50 mL). The combined organic layers were washed with deionized water (50 mL) and then with brine (50 mL). The organic layer was then dried over $MgSO_4$, concentrated, and dried in vacuo to give 0.338 g of the crude product. The crude product was purified by flash column chromatography (silica, 0-50% DCM in hexane) to give the title compound (0.185 g). MS m/e = 412 $(M-H)^-$.

[0481] **Step E**: Preparation of N-((7,8-Dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

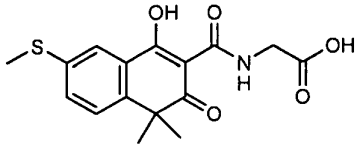
[0482] A solution of 1,1-dimethylethyl N-((7,8-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.130 g, 0.314 mmol) in TFA (5.00 mL, 68.3 mmol) was stirred at 25°C for 10 minutes. The resulting mixture was concentrated, azeotroped using DCM (2x100 mL), and dried in vacuo to give the title compound (0.0925 g). MS m/e = 358 $(M+H)^+$. Calculated for $C_{15}H_{13}Cl_2NO_5$ 357.02.

[0483] **Example 32.** N-((6-(4-Fluorophenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0484] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 384 $(M+H)^+$. Calculated for $C_{21}H_{18}FNO_5$ 383.12.

[0485] **Example 33.** N-((4-Hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0486] **Step A**: Preparation of Ethyl 2-(4-(methylthio)phenyl)acetate

[0487] A mixture of 4-(methylthio)phenylacetic acid (5.10 g, 28.0 mmol) and H_2SO_4 (0.155 mL, 2.80 mmol) in EtOH (150 mL) in a 500 mL round bottom flask, were stirred at 100°C for 26 hours. The reaction was concentrated in vacuo, diluted with EtOAc (200 mL), washed with deionized water (2 x 150 mL), and then with brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo. The crude product was purified by flash column chromatography (silica, 0-20% EtOAc in hexane) to give the title compound (5.95 g). MS m/e = 211 $(M+H)^+$.

[0488] **Step B**: Preparation of 2-Methyl-2-(4-(methylthio)phenyl)propanoic acid

[0489] A mixture of NaH (2.83 g, 70.7 mmol) in DMF (150 mL) in an oven dried 500 mL round bottom flask, was cooled to 0°C. A solution of ethyl 2-(4-(methylthio)phenyl)acetate (5.95 g, 28.3 mmol) and MeI (5.29 mL, 84.9 mmol) in DMF (50 mL) was cooled to 0°C and added dropwise to the mixture over 15 minutes. The mixture was allowed to warm room temperature and

stirred for 20 hours. The solution was diluted with EtOAc (300 mL), and the organic layer was washed with 10% HCl(aq) (200 mL), with deionized water (200 mL), and then with brine (100 mL). The organic layer was then dried over $MgSO_4$, concentrated, and dried in vacuo to give 11.35 g of the crude product. The crude product was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give a 7:3 mixture of ethyl 2-methyl-2-(4-(methylthio)phenyl)propanoate and methyl 2-methyl-2-(4-(methylthio)phenyl)propanoate (6.23 g).

[0490] A solution of the above esters (6.23 g, 26.1 mmol) and KOH (7.33 g, 131 mmol) in EtOH (160 mL) and deionized water (40 mL) in a 250 mL round bottom flask, was refluxed at 95°C for 1.5 hours. The reaction mixture was concentrated in vacuo, diluted with deionized water (100 mL), and then extracted with diethyl ether (3x100 mL). The combined ether solutions were extracted with 1N NaOH(aq) (2x100 mL). All the aqueous solutions were combined, and brought to a pH = 2 with 10% HCl(aq). The resulting mixture was extracted with EtOAc (3 x 100 mL), dried over $MgSO_4$, concentrated, and dried in vacuo to give title compound (4.998 g). MS m/e = 211 $(M+H)^+$.

[0491] **Step C**: Preparation of Ethyl 4-hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-carboxylate

[0492] A mixture of 2-methyl-2-(4-(methylthio)phenyl)propanoic acid (4.00 g, 19.0 mmol) in thionyl chloride (40.0 mL, 548 mmol) in a 500 mL round bottom flask, was refluxed at 75°C for 2 hours. The mixture was concentrated, azeotroped in toluene (2 x 100 mL), and dried in vacuo to give the crude acid chloride.

[0493] A solution of diethyl malonate (2.87 mL, 19.0 mmol) in ACN (100 mL) in a 500 mL round bottom flask was cooled to 0°C. $MgCl_2$ (1.81 g, 19.0 mmol) and TEA (5.57 mL, 39.9 mmol) were added slowly, and the mixture was stirred at room temperature for 3 hours. A solution of the above acid chloride in ACN (40 mL) was added, and the mixture was stirred at 50°C for 16 hours. The solution was concentrated in vacuo and partitioned between EtOAc

(75 mL), and 10% HCl(aq) (75 mL). The aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and dried in vacuo to give 7.05 g of the crude product which was purified by flash column chromatography (silica, 0-75% DCM in hexane) to give the intermediate, diethyl 2-(2-methyl-2-(4-(methylthio)phenyl)propanoyloxy)malonate (4.604 g). MS m/e = 370 $(M+H)^+$.

[0494] A solution of diethyl 2-(2-methyl-2-(4-(methylthio)phenyl)propanoyloxy)-malonate (2.55 g, 6.92 mmol) in H_2SO_4, 36N (0.585 mL, 6.92 mmol) was stirred at 25°C for 30 minutes. The reaction was quenched by adding ice (400 mL) and EtOAc (100 mL) and stirring for 15 minutes. The layers were separated, and the aqueous solution was extracted with EtOAc (2x100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated, and dried in vacuo to give 1.41 g crude product which was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give the title compound (1.098 g). MS m/e = 307 $(M+H)^+$.

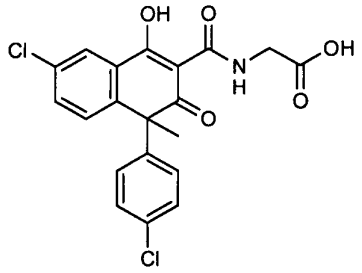
[0495] **Step D**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0496] A solution of ethyl 4-hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-carboxylate (0.800 g, 2.61 mmol), glycine tert-butyl ester hydrochloride (0.525 g, 3.13 mmol) and DIPEA (0.910 mL, 5.22 mmol in 1,4-dioxane(25 mL) in a 75 mL sealed vessel, was stirred at 120°C for 3 hours. Deionized water (75 mL) was added, and the resulting mixture was extracted with EtOAc (2x50 mL). The combined organic layers were then washed with brine (50 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give 1.44 g crude product which was purified by flash column chromatography (silica, 0-50% DCM in hexane) to give the title compound (0.886 g). MS m/e = 336 $(M+H-tBu)^+$.

[0497] **Step E**: Preparation of N-((4-Hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0498] A solution of 1,1-dimethylethyl N-((4-hydroxy-1,1-dimethyl-6-(methylthio)-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.180 g, 0.460 mmol) in TFA (0.0342 mL, 0.460 mmol) was stirred at 25°C for 10 minutes. The solution was concentrated, azeotroped in DCM (2 x 300 mL), and dried in vacuo to give the title compound (0.150 g). MS m/e = 336 $(M+H)^+$. Calculated for $C_{16}H_{17}NO_5S$ 335.08.

[0499] **Example 34.** N-((6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0500] **Step A**: Preparation of Ethyl 2,2-bis(4-chlorophenyl)acetate

[0501] To a solution of bis(4-chlorophenyl)acetic acid (5.00 g, 17.8 mmol) in EtOH (100 mL) in a 500 mL round bottom flask, was added H_2SO_4, 36N (0.0988 mL, 1.78 mmol). The mixture was stirred at 100°C for 18 hours. The mixture was then concentrated in vacuo, diluted with EtOAc (200 mL), and washed with deionized water (3x100 mL) and then with brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give the crude product ethyl 2,2-bis(4-chlorophenyl)acetate (5.473 g). MS m/e = 309 $(M+H)^+$.

[0502] **Step B**: Preparation of 2,2-Bis(4-chlorophenyl)propanoic acid

[0503] A solution of NaH (60% dispersion in mineral oil) (2.1 g, 53 mmol) in DMF (100 mL) in a 500 mL round bottom flask was cooled 0°C. A solution of ethyl 2,2-bis(4-chlorophenyl)acetate (5.47 g, 18 mmol) and MeI (3.3

mL, 53 mmol) in DMF (50 mL) was added dropwise over 15 minutes. The mixture was stirred at 0°C for 15 minutes and then allowed to warm to room temperature and stirred for 20 hours. A mixture of products was observed by LC/MS. The solution was diluted with EtOAc (200 mL), and then washed with 10% HCl(aq) (200 mL), with deionized water (200 mL), and then with brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give 10.11 g crude product which was purified by flash column chromatography (silica, 0-100%, hexane/EtOAc) to give 2,2-bis(4-chlorophenyl)propanoic acid (3.05 g).

[0504] **Step C**: Preparation of Diethyl 2-(2,2-bis(4-chlorophenyl)propanoyl)-malonate

[0505] A solution of 2,2-bis(4-chlorophenyl)propanoic acid (3.05 g, 10.3 mmol) in thionyl chloride (20.0 mL, 274 mmol) in a 500 mL round bottom flask was refluxed at 75°C for 1.5 hours. The solution was concentrated, azeotroped in toluene (2x200 mL), and dried in vacuo to give the crude acid chloride.

[0506] A solution of diethyl malonate (1.56 mL, 10.3 mmol) in ACN (60 mL) in a 500 mL round bottom flask was cooled to 0°C. $MgCl_2$ (0.984 g, 10.3 mmol) and TEA (3.02 mL, 21.7 mmol) were slowly added, and the mixture was then stirred at 25°C for 2 hours. A solution of the acid chloride in ACN (40 mL) was added to the reaction, and the mixture was stirred at 50°C for 16 hours. The solution was concentrated in vacuo and then partitioned between EtOAc (75 mL) and 10% HCl(aq) (75 mL). The aqueous layer was extracted with EtOAc (2x75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give 5.68 g of crude product which was purified by flash column chromatography (silica, 0-50% DCM in hexane) to give diethyl 2-(2,2-bis(4-chlorophenyl)propanoyl)malonate (3.61 g) MS m/e = 437 $(M+H)^+$.

[0507] **Step D**: Preparation of Ethyl 6-chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate

[0508] A solution of diethyl 2-(2,2-bis(4-chlorophenyl)propanoyl)malonate (2.00 g, 4.57 mmol) in H_2SO_4, 36N (10.0 mL, 180 mmol) in a 500 mL round bottom flask was stirred at 25°C for 30 minutes. The reaction was quenched by adding 400 mL of ice and 100 mL of EtOAc and then stirring for 15 minutes. The layers were separated, and the aqueous solution was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo to give 2.24 g of crude product which was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give the title compound (1.448 g). MS m/e = 391 $(M+H)^+$.

[0509] **Step E**: Preparation of 1,1-Dimethylethyl N-((6-chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

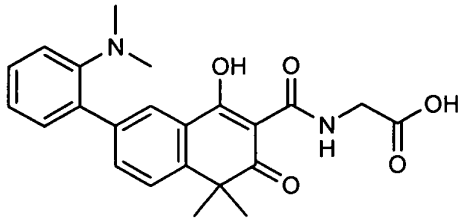
[0510] A solution of ethyl 6-chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate (0.998 g, 2.55 mmol), glycine tert-butyl ester hydrochloride (0.513 g, 3.06 mmol), and DIPEA (0.889 mL, 5.10 mmol) in 1,4-dioxane (15 mL) in a 75 mL sealed vessel was stirred at 120°C for 3 hours. The solution was diluted with deionized water (75 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were then washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give 1.42 g crude product. The crude product was purified by flash column chromatography (silica, 0-25% DCM in hexane) to give the title compound (0.888 g). MS m/e = 420 $(M+H\text{-}tBu)^+$.

[0511] **Step F**: Preparation of N-((6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0512] A solution of 1,1-dimethylethyl N-((6-chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.675 g, 1.42 mmol) in TFA (10.0 mL, 127 mmol) was stirred at 25°C for 10 minutes. The solution was concentrated, azeotroped in DCM (2 x 300 mL), and dried in a

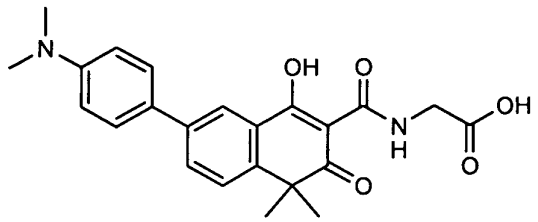
vacuum oven at 60°C to give the title compound (0.580 g). MS m/e = 420 $(M+H)^+$. Calculated for $C_{20}H_{15}Cl_2NO_5$ 419.03.

[0513] **Example 35.** N-((6-(2-(Dimethylamino)phenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



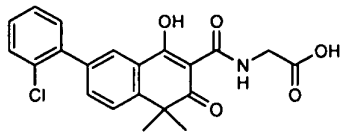
[0514] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 409 $(M+H)^+$. Calculated for $C_{23}H_{24}N_2O_5$ 408.17.

[0515] **Example 36.** N-((6-(4-(Dimethylamino)phenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



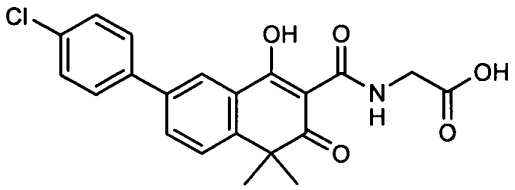
[0516] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 409 $(M+H)^+$. Calculated for $C_{23}H_{24}N_2O_5$ 408.17.

[0517] **Example 37.** N-((6-Chloro-1-(4-chlorophenyl)-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



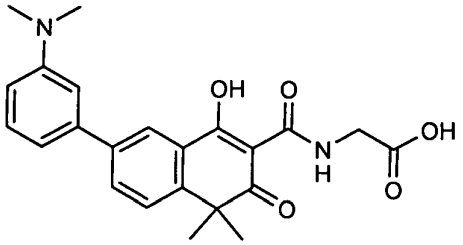
[0518] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 400 $(M+H)^+$. Calculated for $C_{21}H_{18}ClNO_5$ 399.09.

[0519] **Example 38.** N-((6-(4-Chlorophenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



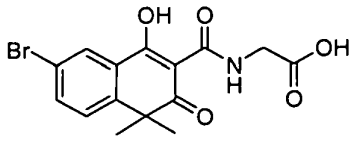
[0520] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 400 $(M+H)^+$. Calculated for $C_{21}H_{18}ClNO_5$ 399.09.

[0521] **Example 39.** N-((6-(3-(Dimethylamino)phenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0522] The title compound was prepared using a procedure similar to that outlined in Example 5. MS m/e = 409 $(M+H)^+$. Calculated for $C_{23}H_{24}N_2O_5$ 408.17.

[0523] **Example 40.** N-((6-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0524] **Step A**: Preparation of 2-(4-Bromophenyl)-2-methylpropanoic acid

[0525] A solution of methyl 2-(4-bromophenyl)-2,2-dimethylacetate (3880 µL, 15090 µmol) in EtOH (80 mL) and water (20 mL) was treated with KOH (4233 mg, 75450 µmol). The reaction was heated to 90°C. After 15 hours, the reaction was cooled to 23°C and concentrated in vacuo. The crude mixture was partitioned between water/diethyl ether (150 mL each). The aqueous layer was separated and extracted with diethyl ether (100 mL). The combined ether layers were then extracted with a 1N NaOH solution (25 mL). The combined aqueous washes were acidified with concentrated HCl to pH = 2.0 and extracted with EtOAc (3 x 100 mL). The combined EtOAc layers were dried over $MgSO_4$, and concentrated in vacuo to afford 3144 mg of 2-(4-bromophenyl)-2-methylpropanoic acid.

[0526] **Steps B-D**: Preparation of 1,1-Dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0527] A solution of 2-(4-bromophenyl)-2-methylpropanoic acid (3144 mg, 12933 µmol) in thionyl chloride (9434 µL, 129331 µmol) was heated at reflux under nitrogen. After 2 hours, the reaction was cooled to 23°C and concentrated in vacuo to afford the crude acid chloride.

[0528] In an oven-dried round-bottomed flask, magnesium turnings (472 mg, 19400 µmol) and diethyl malonate (2931 µL, 19400 µmol) were added to EtOH (20 mL) and CCl_4 (0.2 mL). The reaction was stirred at 23°C for 30 minutes followed by the addition of THF (30 mL). The reaction was then heated at reflux under nitrogen. After 1 hour, a solution of the crude acid chloride in THF (15 mL) was added in a dropwise fashion. After 30 minutes, the reaction was cooled to 23°C, diluted with diethyl ether (150 mL) and washed with water (150 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (150 mL). The combined ether layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo affording

diethyl 2-(2-(4-bromophenyl)-2-methylpropanoyl)malonate as the crude product.

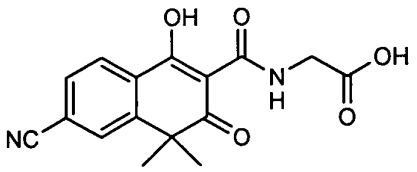
[0529] A solution of the crude diethyl 2-(2-(4-bromophenyl)-2-methylpropanoyl)malonate (4982 mg, 12932 μmol) in concentrated H_2SO_4 (30 mL) was stirred at 23°C. After 2 hours, the reaction was poured into an ice-water mixture (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo affording ethyl 6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-carboxylate as the product.

[0530] A solution of crude ethyl 6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-carboxylate (4100 mg, 12088 μmol) and glycine tert-butyl ester hydrochloride (2229 mg, 13297 μmol) in 1,4-dioxane (100 mL) was treated with DIPEA (4211 μL, 24176 μmol). The reaction was heated at 120°C in a sealed vessel. After 17 hours, the reaction was cooled to 23°C, diluted with EtOAc (200 mL) and washed with 10% HCl solution (2 x 150 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 5-10% EtOAc/hexane) affording 2523 mg of 1,1-dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate. MS m/e = 422.0$(M-H)^-$.

[0531] **Step E**: Preparation of N-((6-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0532] A solution of 1,1-dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (145 mg, 342 μmol) in TFA (2 mL) was stirred at 23°C. After 30 minutes, the reaction was concentrated in vacuo, and diluted with water (25 mL). A white solid precipitated which was collected by filtration, washed with diethyl ether (5 mL), and dried under vacuum, affording 63 mg of N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine. MS m/e = 366.0 $(M-H)^-$. Calculated for $C_{15}H_{14}BrNO_5$ 367.01.

[0533] **Example 41.** N-((7-Cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



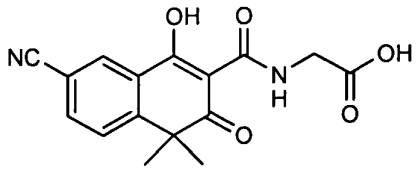
[0534] **Step A**: Preparation of 1,1-Dimethylethyl N-((7-cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0535] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (310 mg, 731 μmol, see Example 53), dppf (162 mg, 292 μmol), tris(dibenzylideneacetone)dipalladium (66.9 mg, 73.1 μmol), copper cyanide (262 mg, 2923 μmol), and tetraethylammonium cyanide (126 mg, 804 μmol) were mixed in dioxane (6 mL) in a microwave tube under a nitrogen atmosphere. The reaction mixture was then stirred at 75°C for 16 hours. The reaction mixture was returned to room temperature, fused to silica gel, and purified by silica flash chromatography (0-100% DCM/hexane) to give the desired ester as a white solid (163 mg). MS (m/e) = 315.1 $(M+H\text{-}tBu)^+$.

[0536] **Step B**: Preparation of N-((7-Cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0537] 1,1-Dimethylethyl N-((7-cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (163 mg, 440 μmol) was stirred in TFA (1 mL, 13462 μmol) at room temperature for 20 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as an off-white solid (126 mg). MS (m/e) = 315.1 $(M+H)^+$. Calculated for $C_{16}H_{14}N_2O_5$ 314.09.

[0538] **Example 42.** N-((6-Cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



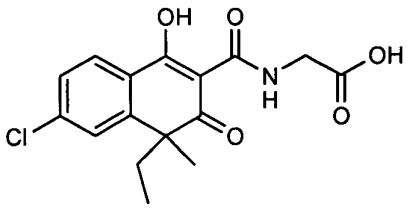
[0539] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0540] 1,1-Dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (297 mg, 700 μmol, prepared in Example 40 A-D), dppf (155 mg, 280 μmol), tris(dibenzylideneacetone)dipalladium (64.1 mg, 70.0 μmol), copper cyanide (251 mg, 2800 μmol), and tetraethylammonium cyanide (120 mg, 770 μmol) were mixed in dioxane (6 mL) in a microwave tube under a nitrogen atmosphere. The reaction mixture was then stirred at 75°C for 5.5 hours. The reaction mixture was returned to room temperature, fused to silica gel, and purified by silica flash chromatography (0-100% DCM/hexane) to give the desired ester as an off-white solid (127 mg). MS (m/e) = 315.1 $(M+H-tBu)^+$.

[0541] **Step B**: Preparation of N-((6-Cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0542] 1,1-Dimethylethyl N-((6-cyano-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (124 mg, 335 μmol) was stirred in TFA (1 mL, 13462 μmol) at room temperature for 15 minutes. Water was added. The resulting precipitate was filtered. The green solid was dissolved in saturated $NaHCO_3$ and washed with DCM. The aqueous layer was separated and acidified with 10% HCl. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (41 mg). MS (m/e) = 315.1 $(M+H)^+$. Calculated for $C_{16}H_{14}N_2O_5$ 314.09.

[0543] **Example 43.** N-((7-Chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0544] **Step A**: Preparation of 2-(3-Chlorophenyl)butanenitrile

[0545] A solution of 2-(3-chlorophenyl)acetonitrile (10.00 g, 66 mmol) and ethyl bromide (4.9 mL, 66 mmol) in DMSO (25 mL) was added dropwise to a stirred solution of NaH (60% dispersion in mineral oil (2.6 g, 66 mmol)) in DMSO (75 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0°C and then brought to room temperature and stirred for 23 hours. The reaction mixture was carefully quenched with water, and was then diluted with EtOAc. The organic layer was separated, washed with water (2 x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude product as an orange oil. The crude oil was purified by silica flash chromatography (0-5% EtOAc/hexane) to give the desired compound as a colorless oil (4.69 g).

[0546] **Step B**: Preparation of 2-(3-Chlorophenyl)-2-methylbutanenitrile

[0547] A solution of 2-(3-chlorophenyl)butanenitrile (4.69 g, 26 mmol) and MeI (2.0 mL, 31 mmol) in DMSO (15 mL) was added dropwise to a stirred solution of NaH (60% dispersion in mineral oil (1.3 g, 31 mmol)) in DMSO (35 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0°C and then brought to room temperature and stirred for 15 hours. The reaction mixture was quenched with water carefully and then diluted with EtOAc. The organic layer was separated, washed with water (2 x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired compound as a light yellow oil (5.54 g).

[0548] **Step C**: Preparation of 2-(3-Chlorophenyl)-2-methylbutanoic acid

[0549] 2-(3-Chlorophenyl)-2-methylbutanenitrile (5.49 g, 28 mmol) was dissolved in AcOH (15 mL, 260 mmol), and the mixture was heated to 100°C. 60% H_2SO_4 (10 mL, 118 mmol) was added dropwise, and the reaction mixture was stirred at 110°C for 45 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were extracted with 2M NaOH (2x). The combined aqueous layers were washed with EtOAc and acidified to pH = 1 with 10% HCl. The aqueous mixture was then extracted with DCM (2x), and the combined organic layers were concentrated in vacuo to give the desired product as a yellow oil (4.63 g). MS (m/e) = 213.1 $(M+H)^+$.

[0550] **Step D**: Preparation of Diethyl 2-(2-(3-chlorophenyl)-2-methylbutanoyl)malonate

[0551] Thionyl chloride (30 mL) was added to 2-(3-chlorophenyl)-2-methylbutanoic acid (4.63 g, 21.8 mmol). The reaction mixture was stirred at 75°C for 1.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0552] Diethyl malonate (3.62 mL, 23.9 mmol) in ACN (50 mL) was cooled to 0°C. $MgCl_2$ (2.28 g, 23.9 mmol) was added, followed by addition of TEA (6.66 mL, 47.9 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes before being brought to room temperature and stirred for 2.5 hours. The above prepared acid chloride was dissolved in ACN (20 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 15 hours. The reaction mixture was then cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as an orange oil (7.67 g). MS (m/e) = 355.2 $(M+H)^+$.

[0553] **Step E**: Preparation of Ethyl 7-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate

[0554] H_2SO_4 (40 mL, 473 mmol) was cooled to 0°C and treated with P_2O_5 (15 g, 106 mmol). The mixture was brought to room temperature and added to diethyl 2-(2-(3-chlorophenyl)-2-methylbutanoyl)malonate (7.67 g, 22 mmol). The reaction mixture was then stirred for 1.5 hours. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a yellow solid (3.16 g). MS (m/e) = 309.1 $(M+H)^+$.

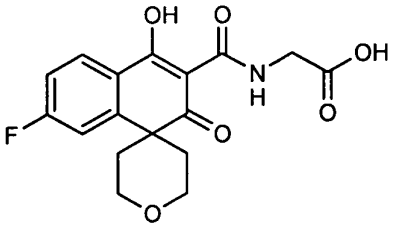
[0555] **Step F**: Preparation of 1,1-Dimethylethyl N-((7-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0556] DIPEA (0.253 mL, 1.45 mmol, 1.2 eq) was added to a mixture of ethyl 7-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate (373 mg, 1.21 mmol) and glycine tert-butyl ester hydrochloride (0.243 g, 1.45 mmol) in dioxane (8 mL). The reaction mixture was stirred at 80°C for 3.5 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow oil. The crude oil was purified by silica flash chromatography (0-75% DCM/hexane) to give the desired compound as a white solid (407 mg). MS (m/e) = 338.1 $(M+H-tBu)^+$.

[0557] **Step G**: Preparation of N-((7-Chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0558] 1,1-Dimethylethyl N-((7-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (393 mg, 998 μmol) was stirred in TFA (3 mL, 40.4 mmol) at room temperature for 20 minutes. The TFA was removed in vacuo, and water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (274 mg). MS (m/e) = 338 $(M+H)^+$. Calculated for $C_{16}H_{16}ClNO_5$ 337.07.

[0559] **Example 44.** N-((7-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0560] **Step A**: Preparation of 4-(3-Fluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0561] Potassium tert-butoxide (5.48 g, 48.8 mmol) was added to a stirred solution of 2-(3-fluorophenyl)acetonitrile (2.58 mL, 22.2 mmol) in DMF (30 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 10 minutes at 0°C before 1-chloro-2-(2-chloroethoxy)ethane (2.86 mL, 24.4 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. The reaction mixture was then cooled to 0°C and quenched with 10% HCl. The aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the product as an orange oil (7.53 g).

[0562] **Step B**: Preparation of 4-(3-Fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0563] 60% H_2SO_4 (30 mL) was added to a stirred mixture of 4-(3-fluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile (7.53 g, 37 mmol) in dioxane (30 mL), and the reaction mixture was refluxed at 110°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were extracted with 2M NaOH (2x). The combined aqueous layers were washed with EtOAc and

acidified to pH 1 with 10% HCl. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (2.37 g).

[0564] **Step C**: Preparation of Diethyl 2-(4-(3-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0565] Thionyl chloride (15 mL) was added to 4-(3-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (2.37 g, 10.6 mmol). The reaction mixture was stirred at 75°C for 3 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0566] Diethyl malonate (1.76 mL, 11.6 mmol) in ACN (25 mL) was cooled to 0°C. $MgCl_2$ (1.11 g, 11.6 mmol) was added, followed by addition of TEA (3.23 mL, 23.3 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes before being brought to room temperature and stirred for 3 hours. The above prepared acid chloride was dissolved in ACN (10 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 16 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as an orange oil (4.23 g). MS (m/e) = 367.2 $(M+H)^+$.

[0567] **Step D**: Preparation of Ethyl 7-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0568] H_2SO_4 (25 mL, 296 mmol) was cooled to 0°C and treated with P_2O_5 (10 g, 70 mmol). The mixture was brought to room temperature and was then added to diethyl 2-(4-(3-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (4.23 g, 12 mmol). The resulting reaction mixture was then stirred for 1 hour. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash

chromatography (50-100% DCM/hexane) to give the desired compound as a white solid (850 mg). MS (m/e) = 321.1 $(M+H)^+$.

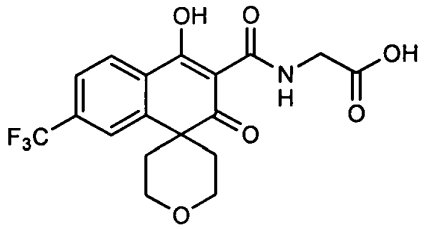
[0569] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0570] DIPEA (0.693 mL, 3.98 mmol, 1.5 eq) was added to a mixture of ethyl 7-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (850 mg, 2.65 mmol, 1.0 eq) and glycine tert-butyl ester hydrochloride (0.534 g, 3.18 mmol, 1.2 eq) in dioxane (20 mL). The reaction mixture was stirred at 75°C for 17 hours. The reaction mixture was then cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude solid was suspended in ether and filtered to give the title compound as an off-white solid (703 mg). MS (m/e) = 406.2 $(M+H)^+$.

[0571] **Step F**: Preparation of N-((7-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0572] 1,1-Dimethylethyl N-((7-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (703 mg, 1.73 mmol) was stirred in TFA (2 mL, 26.9 mmol) at room temperature for 25 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as an off-white solid (237 mg). MS (m/e) = 350.1 $(M+H)^+$. Calculated for $C_{18}H_{16}F_3NO_6$ 349.10.

[0573] **Example 45.** N-((7-Trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0574] **Step A**: Preparation of 4-(3-(Trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0575] Potassium tert-butoxide (4.00 g, 35.6 mmol, 2.20 eq) was added to a stirred solution of 2-(3-(trifluoromethyl)phenyl)acetonitrile (2.53 mL, 16.2 mmol, 1.0 eq) in DMF (30 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 10 minutes at 0°C before 1-chloro-2-(2-chloroethoxy)ethane (2.09 mL, 17.8 mmol, 1.1 eq) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. The reaction mixture was then cooled to 0°C and quenched with 10% HCl. The aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the product as an orange oil (6.73 g).

[0576] **Step B**: Preparation of 4-(3-(Trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0577] 60% H_2SO_4 (30 mL) was added to a stirred mixture of 4-(3-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonitrile (6.73 g, 26 mmol) in dioxane (30 mL), and the reaction mixture was refluxed at 110°C for 21 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were extracted with 2M NaOH (2x). The combined aqueous layers were washed with EtOAc and acidified to pH = 1 with 10% HCl. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (2.39 g).

[0578] **Step C**: Preparation of Diethyl 2-(4-(3-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0579] Thionyl chloride (15 mL) was added to 4-(3-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carboxylic acid (2.39 g, 8.72

mmol). The reaction mixture was stirred at 75°C for 1.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0580] Diethyl malonate (1.45 mL, 9.59 mmol) in ACN (25 mL) was cooled to 0°C. $MgCl_2$ (0.913 g, 9.59 mmol) was added, followed by addition of TEA (2.67 mL, 19.2 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes and then brought to room temperature and stirred for 4 hours. The above prepared acid chloride was dissolved in ACN (10 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 17 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as an orange oil (4.27 g). MS (m/e) = 417.2 $(M+H)^+$.

[0581] **Step D**: Preparation of Ethyl 7-trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0582] H_2SO_4 (25 mL, 296 mmol) was cooled to 0°C and treated with P_2O_5 (10 g, 70 mmol). The mixture was brought to room temperature and added to diethyl 2-(4-(3-(trifluoromethyl)phenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (4.27 g, 10 mmol). The reaction mixture was then stirred for 1.5 hours. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as a brown oil. The crude oil was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a white solid (1.32 g). MS (m/e) = 371.2 $(M+H)^+$.

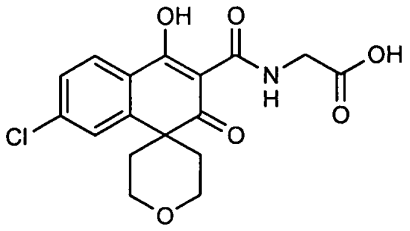
[0583] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0584] DIPEA (0.931 mL, 5.35 mmol) was added to a mixture of ethyl 7-trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (1.32 g, 3.56 mmol) and glycine tert-butyl ester hydrochloride (0.717 g, 4.28 mmol) in dioxane (30 mL). The reaction mixture was stirred at 75°C for 17 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude solid was suspended in ether and filtered to give the desired compound as a light yellow solid (1.29 g). MS (m/e) = 456.2 $(M+H)^+$.

[0585] **Step F**: Preparation of N-((7-Trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0586] 1,1-Dimethylethyl N-((7-trifluoromethyl-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (1.29 g, 2.82 mmol) was stirred in TFA (3 mL, 40.4 mmol) at room temperature for 25 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (550 mg). MS (m/e) = 400.1 $(M+H)^+$. Calculated for $C_{18}H_{16}F_3NO_6$ 399.09.

[0587] **Example 46.** N-((7-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0588] **Step A**: Preparation of 4-(3-Chlorophenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0589] Potassium tert-butoxide (8.90 g, 79.3 mmol, 2.20 eq) was added to a stirred solution of 2-(3-chlorophenyl)acetonitrile (4.26 mL, 36.1 mmol) in DMF (50 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 10 minutes at 0°C before 1-chloro-2-(2-chloroethoxy)ethane (4.65 mL, 39.7

mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was then cooled to 0°C and quenched with 10% HCl. The aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the product as an orange oil (12.51 g).

[0590] **Step B**: Preparation of 4-(3-Chlorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0591] 60% H_2SO_4 (50 mL) was added to a stirred mixture of 4-(3-chlorophenyl)-tetrahydro-2H-pyran-4-carbonitrile (12.51 g, 56 mmol) in dioxane (50 mL), and the reaction mixture was refluxed at 110°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were extracted with 2M NaOH (2x). The combined aqueous layers were washed with EtOAc and acidified to pH = 1 with 10% HCl. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (6.13 g).

[0592] **Step C**: Preparation of Diethyl 2-(4-(3-chlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0593] Thionyl chloride (25 mL) was added to 4-(3-chlorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (6.13 g, 25.5 mmol). The reaction mixture was stirred at 70°C for 2.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0594] Diethyl malonate (4.23 mL, 28.0 mmol) in ACN (50 mL) was cooled to 0°C. $MgCl_2$ (2.67 g, 28.0 mmol) was added, followed by addition of TEA (7.79 mL, 56.0 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes and was then brought to room temperature and stirred for 3.5 hours. The above prepared acid chloride was dissolved in ACN (20 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C

for 17 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as an orange oil (10.66 g). MS (m/e) = 383.2 $(M+H)^+$.

[0595] **Step D**: Preparation of Ethyl 7-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0596] Diethyl 2-(4-(3-chlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (10.66 g, 27.8 mmol) was added to H_2SO_4 (50 mL, 591 mmol), and the mixture was stirred at room temperature for 1 hour. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a yellow solid (4.93 g). MS (m/e) = 337.1 $(M+H)^+$.

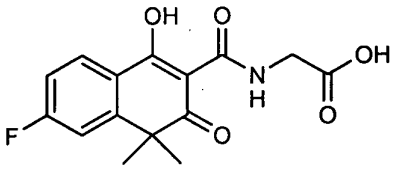
[0597] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0598] DIPEA (1.47 mL, 8.42 mmol, 1.5 eq) was added to a mixture of ethyl 7-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (1.89 g, 5.61 mmol, 1.0 eq) and glycine tert-butyl ester hydrochloride (1.13 g, 6.73 mmol, 1.2 eq) in dioxane (50 mL). The reaction mixture was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude solid was suspended in ether and filtered to give the desired ester as a white solid (2.23 g). MS (m/e) = 422.2 $(M+H)^+$.

[0599] **Step F**: Preparation of N-((7-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0600] The mixture of 1,1-dimethylethyl N-((7-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (2.23 g, 5 mmol) in TFA (8 mL, 108 mmol) was stirred at room temperature for 20 minutes. The majority of the TFA was removed in vacuo and then water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (1.13 g). MS (m/e) = 366.1 $(M+H)^+$. Calculated for $C_{17}H_{16}ClNO_6$ 365.07.

[0601] **Example 47.** N-((7-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0602] **Step A**: Preparation of 2-(3-Fluorophenyl)-2-methylpropanenitrile

[0603] A solution of 2-(3-fluorophenyl)acetonitrile (4.30 mL, 37.0 mmol) and MeI (6.91 mL, 111 mmol) in DMSO (20 mL) was added dropwise to a stirred solution of NaH (60% dispersion in mineral oil (4.43 g, 111 mmol)) in DMSO (40 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0°C and was then brought to room temperature and stirred for 17 hours. The reaction mixture was quenched with water carefully and then diluted with EtOAc. The organic layer was separated, washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired compound as an orange oil (8.58 g).

[0604] **Step B**: Preparation of 2-(3-Fluorophenyl)-2-methylpropanoic acid

[0605] 60% H_2SO_4 (50 mL) was added to a stirred mixture of 2-(3-fluorophenyl)-2-methylpropanenitrile (8.58 g, 53 mmol) in dioxane (50 mL), and the reaction mixture was refluxed at 110°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired acid as a dark brown oil (9.14 g).

[0606] **Step C**: Preparation of Diethyl 2-(2-(3-fluorophenyl)-2-methylpropanoyl)malonate

[0607] Thionyl chloride (25 mL) was added to 2-(3-fluorophenyl)-2-methylpropanoic acid (6.74 g, 37.0 mmol). The reaction mixture was stirred at 70°C for 1.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0608] Diethyl malonate (5.59 mL, 37.0 mmol) in ACN (50 mL) was cooled to 0°C. $MgCl_2$ (3.52 g, 37.0 mmol) was added, followed by addition of TEA (10.8 mL, 77.7 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes and was then brought to room temperature and stirred for 3.5 hours. The above prepared acid chloride was dissolved in ACN (20 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 18 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as a brown oil (13.03 g). MS (m/e) = 325.2 $(M+H)^+$.

[0609] **Step D**: Preparation of Ethyl 7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0610] Diethyl 2-(2-(3-fluorophenyl)-2-methylpropanoyl)malonate (13.03 g, 40 mmol) was added to concentrated H_2SO_4 (65 mL, 769 mmol), and

the mixture was stirred at room temperature for 45 minutes. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a white solid (4.26 g). MS (m/e) = 279.1 $(M+H)^+$.

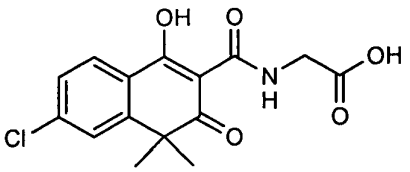
[0611] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0612] DIPEA (939 µL, 5390 µmol) was added to a mixture of ethyl 7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (1.00 g, 3594 µmol) and glycine tert-butyl ester hydrochloride (723 mg, 4312 µmol) in dioxane (25 mL). The reaction mixture was stirred at 75°C for 16 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude solid was suspended in ether and filtered to give the desired ester as a white solid (590 mg). MS (m/e) = 308.1 $(M+H\text{-}tBu)^+$.

[0613] **Step F**: Preparation of N-((7-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0614] 1,1-Dimethylethyl N-((7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (590 mg, 1624 µmol) was stirred in TFA (3 mL, 40386 µmol) at room temperature for 15 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (481 mg). MS (m/e) = 308.1 $(M+H)^+$. Calculated for $C_{15}H_{14}FNO_5$ 307.09.

[0615] **Example 48.** N-((7-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0616] **Step A**: Preparation of 2-(3-Chlorophenyl)-2-methylpropanenitrile

[0617] MeI (14 g, 99 mmol) and 2-(3-chlorophenyl)acetonitrile (5.0 g, 33.0 mmol) were added as a solution in DMSO (75 mL) to a suspension of NaH (2.4 g, 99 mmol) in DMSO (50 mL) that was cooled to 0°C. The mixture was stirred at room temperature overnight, partitioned between EtOAc and water, and the layers were separated. The organic layer was washed with water (2x), dried ($MgSO_4$), and concentrated in vacuo to give the product as a yellow oil (5.7 g).

[0618] **Step B**: Preparation of 2-(3-Chlorophenyl)-2-methylpropanoic acid

[0619] 2-(3-Chlorophenyl)-2-methylpropanenitrile (5.5 g, 30.6 mmol) was dissolved in 1,4-dioxane (50 mL) and 60% aqueous H_2SO_4 (50 mL). The mixture was heated at 120°C for 16 hours, cooled to room temperature, partitioned between EtOAc and water, and the layers were separated. The organic layer was washed with water several times, dried ($MgSO_4$), and concentrated in vacuo to give the product as a brown oil (5.74 g).

[0620] **Step C**: Preparation of 2-(3-Chlorophenyl)-2-methylpropanoyl chloride

[0621] 2-(3-Chlorophenyl)-2-methylpropanoic acid (5.7 g, 28.7 mmol) was stirred in thionyl chloride (100 mL) for 2 hours at reflux. The thionyl chloride was removed under vacuum to give the product (5.69 g).

[0622] **Step D**: Preparation of Diethyl 2-(2-(3-chlorophenyl)-2-methylpropanoyl)malonate

[0623] Diethyl malonate (3.72 mL, 24.6 mmol) in ACN (50 mL) was cooled to 0°C. $MgCl_2$ (2.34 g, 24.6 mmol) was added, followed by addition of TEA (7.18 mL, 51.7 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes before being brought to room temperature and stirred for 2.5 hours. 2-(3-Chlorophenyl)-2-methylpropanoyl chloride (5.69 g, 24.6 mmol) was dissolved in ACN (20 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 16 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as a brown oil (8.76 g). MS (m/e) = 341.2 $(M+H)^+$.

[0624] **Step E**: Preparation of Ethyl 7-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0625] Diethyl 2-(2-(3-chlorophenyl)-2-methylpropanoyl)malonate (8.76 g, 26 mmol) was added to H_2SO_4 (60 mL, 710 mmol), and the mixture was stirred at room temperature for 45 minutes. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash chromatography (0-50% DCM/hexane) to give the desired compound as a white solid (3.90 g). MS (m/e) = 295.1 $(M+H)^+$.

[0626] **Step F**: Preparation of 1,1-Dimethylethyl N-((7-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

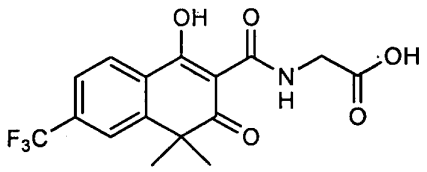
[0627] DIPEA (0.718 mL, 4.12 mmol) was added to a mixture of ethyl 7-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (810 mg, 2.75 mmol) and glycine tert-butyl ester hydrochloride (553 mg, 3.30 mmol) in dioxane (25 mL). The reaction mixture was stirred at 85°C for 2 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to

give a yellow solid. The crude solid was suspended in ether and filtered to give the desired ester as a white solid (1.21 g). MS (m/e) = 324.1 $(M+H-tBu)^+$.

[0628] **Step G**: Preparation of N-((7-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0629] 1,1-Dimethylethyl N-((7-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (1.21 g, 3 mmol) was stirred in TFA (5 mL, 67 mmol) at room temperature for 20 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (650 mg). MS (m/e) = 324.1 $(M+H)^+$. Calculated for $C_{15}H_{14}ClNO_5$ 323.06.

[0630] **Example 49.** N-((7-Trifluoromethyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0631] **Step A**: Preparation of 2-Methyl-2-(3-(trifluoromethyl)phenyl)-propanenitrile

[0632] A solution of 2-(3-(trifluoromethyl)phenyl)acetonitrile (4.21 mL, 27.0 mmol) and MeI (5.05 mL, 81.0 mmol) in DMSO (20 mL) was added dropwise to a stirred solution of NaH (60% dispersion in mineral oil (3.23 g, 81.0 mmol)) in DMSO (40 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0°C and then brought to room temperature and stirred for 17 hours. The reaction mixture was quenched with water carefully and then diluted with EtOAc. The organic layer was separated, washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired compound as a dark orange oil (7.79 g).

[0633] **Step B**: Preparation of 2-Methyl-2-(3-(trifluoromethyl)phenyl)propanoic acid

[0634] 60% H_2SO_4 (50 mL) was added to a stirred mixture of 2-methyl-2-(3-(trifluoromethyl)phenyl)propanenitrile (7.79 g, 37 mmol) in dioxane (50 mL), and the reaction mixture was refluxed at 110°C for 15 hours. The reaction mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired acid as a brown oil (7.85 g).

[0635] **Step C**: Preparation of Diethyl 2-(2-methyl-2-(3-(trifluoromethyl)-phenyl)propanoyl)malonate

[0636] Thionyl chloride (20 mL) was added to 2-methyl-2-(3-(trifluoromethyl)phenyl)propanoic acid (2.45 g, 10.6 mmol). The reaction mixture was stirred at 70°C for 1.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0637] Diethyl malonate (1.59 mL, 10.6 mmol) in ACN (25 mL) was cooled to 0°C. $MgCl_2$ (1.00 g, 10.6 mmol) was added, followed by addition of TEA (3.08 mL, 22.2 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes and then brought to room temperature and stirred for 3.5 hours. The above prepared acid chloride was dissolved in ACN (10 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 18 hours. The reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as a brown oil (3.73 g). MS (m/e) = 375.2 $(M+H)^+$.

[0638] **Step D**: Preparation of Ethyl 4-hydroxy-1,1-dimethyl-2-oxo-7-(trifluoromethyl)-naphthalene-3-carboxylate

[0639] Diethyl 2-(2-methyl-2-(3-(trifluoromethyl)phenyl)propanoyl)malonate (2.80 g, 7.5 mmol) was added to H_2SO_4 (40 mL, 237 mmol), and the mixture was stirred at room temperature for 1 hour. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as a yellow oil. The crude oil was purified by silica flash chromatography (0-50% DCM/hexane) to give the desired compound as a yellow semi-solid (1.07 g). MS (m/e) = 329.1 $(M+H)^+$.

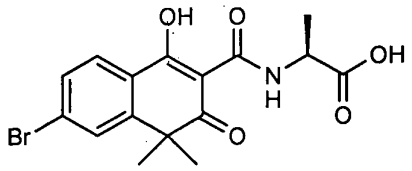
[0640] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-trifluoromethyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0641] DIPEA (1870 µL, 10738 µmol, 2.5 eq) was added to a mixture of ethyl 4-hydroxy-1,1-dimethyl-2-oxo-7-(trifluoromethyl)-naphthalene-3-carboxylate (1.41 g, 4295 µmol) and glycine tert-butyl ester hydrochloride (864 mg, 5154 µmol) in dioxane (50 mL). The reaction mixture was stirred at 75°C for 15 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude solid was purified by silica flash chromatography (0-40% DCM/hexane) to give the desired ester as a white solid (380 mg). MS (m/e) = 358.1 $(M+H-tBu)^+$.

[0642] **Step F**: Preparation of N-((7-Trifluoromethyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0643] 1,1-Dimethylethyl N-((7-trifluoromethyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (380 mg, 919 µmol) was stirred in TFA (2 mL, 26924 µmol) at room temperature for 30 minutes. The reaction mixture was partitioned between water and EtOAc. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid. The solid was then washed with water, ether, and EtOAc to give the desired product as an off-white solid (100 mg). MS (m/e) = 358.1 $(M+H)^+$. Calculated for $C_{16}H_{14}F_3NO_5$ 357.08.

[0644] **Example 50.** N-((7-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alanine



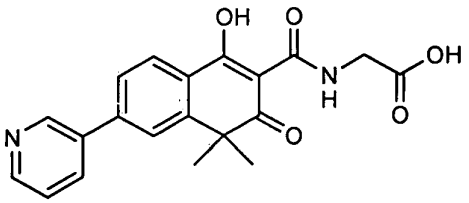
[0645] **Step A**: Preparation of 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alaninate

[0646] DIPEA (120 µL, 690 µmol, 1.5 eq) was added to a mixture of ethyl 7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-carboxylate (156 mg, 460 µmol, prepared in Example 53 A-D) and (S)-tert-butyl 2-aminopropanoate hydrochloride (100 mg, 552 µmol) in dioxane (5 mL). The reaction mixture was stirred at 75°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. The crude oil was purified by silica flash chromatography (0-50% DCM/hexane) to give the desired ester as a transparent oil (137 mg). MS (m/e) = 382.1 $(M+H-tBu)^+$.

[0647] **Step B**: Preparation of N-((7-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alanine

[0648] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alaninate (184 mg, 436 µmol) was stirred in TFA (2 mL, 26924 µmol) at room temperature for 30 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (93 mg). MS (m/e) = 382.1 $(M+H)^+$. Calculated for $C_{21}H_{19}NO_5$ 381.02.

[0649] **Example 51.** N-((7-(3-Pyridyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycine



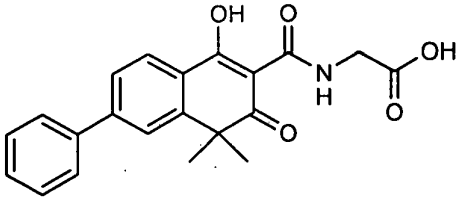
[0650] **Step A**: Preparation of 1,1-Dimethylethyl N-((7-(3-pyridyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0651] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (265 mg, 625 μmol, see Example 53), 3-pyridylboronic acid (115 mg, 937 μmol), and tetrakis(triphenylphosphine)palladium (72 mg, 62 μmol) were mixed in dioxane (4 mL) in a microwave tube under a nitrogen atmosphere. 2M Na_2CO_3 (937 μL, 1874 μmol) was added via syringe, and the reaction mixture was stirred at 75°C for 15 hours. The reaction mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude product as a yellow solid. The crude product was purified by silica flash chromatography (0-10% EtOAc/DCM) to give the desired compound as an off-white solid (190 mg). MS (m/e) = 423.2 $(M+H)^+$.

[0652] **Step B**: Preparation of N-((7-(3-Pyridyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0653] 1,1-Dimethylethyl N-((7-(3-pyridyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (184 mg, 436 μmol) was stirred in TFA (2 mL, 26924 μmol) at room temperature for 30 minutes. The reaction mixture was partitioned between water and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired product as a yellow solid (95 mg). MS (m/e) = 367.2 $(M+H)^+$. Calculated for $C_{21}H_{19}NO_5$ 366.12.

[0654] **Example 52.** N-((7-Phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



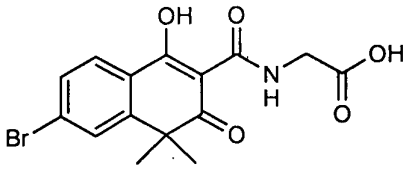
[0655] **Step A**: Preparation of 1,1-Dimethylethyl N-((7-phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0656] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (250 mg, 0.59 mmol, prepared in Example 53 A-E), phenylboronic acid (108 mg, 0.9 mmol), tetrakis(triphenylphosphine)palladium (68 mg, 0.06 mmol), and 2M Na_2CO_3 (885 µL, 2 mmol) were mixed in dioxane (4 mL). The reaction vessel was placed under an argon atmosphere and stirred at 75°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude product. The crude product was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a yellow solid (172 mg). MS (m/e) = 366.2 $(M+H-tBu)^+$.

[0657] **Step B**: Preparation of N-((7-Phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0658] 1,1-Dimethylethyl N-((7-phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (169 mg, 401 µmol) was stirred in TFA (1 mL, 13462 µmol) at room temperature for 20 minutes. The reaction mixture was partitioned between water and EtOAc. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give the desired product as a yellow solid (140 mg). MS (m/z) = 366.2 $(M+H)^+$. Calculated for $C_{21}H_{19}NO_5$ 365.13.

[0659] **Example 53.** N-((7-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0660] **Step A**: Preparation of 2-(3-Bromophenyl)-2-methylpropanenitrile

[0661] A solution of 3-bromophenylacetonitrile (12 g, 61 mmol) and MeI (11 mL, 184 mmol) in DMSO (30 mL) was added dropwise to a stirred solution of NaH (60% dispersion in mineral oil (7.3 g, 184 mmol)) in DMSO (70 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0°C and then brought to room temperature and stirred for 23 hours. The reaction mixture was quenched with water carefully and then diluted with EtOAc. The aqueous layer was separated and extracted again with EtOAc. The combined organic layers were separated, washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired compound as an orange oil (16.75 g).

[0662] **Step B**: Preparation of 2-(3-Bromophenyl)-2-methylpropanoic acid

[0663] 2-(3-Bromophenyl)-2-methylpropanenitrile (14.0 g, 62.47 mmol) was heated in dioxane (150 mL) and 60% H_2SO_4 (150 mL) for 16 hours, cooled to room temperature, and partitioned between DCM and water. The layers were separated, and the aqueous layer was extracted with DCM (2x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the product as an oil that solidified upon standing (14.75 g).

[0664] **Step C**: Preparation of Diethyl 2-(2-(3-bromophenyl)-2-methylpropanoyl)malonate

[0665] Thionyl chloride (50 mL) was added to 2-(3-bromophenyl)-2-methylpropanoic acid (10.63 g, 43.7 mmol). The reaction mixture was stirred at 75°C for 2.5 hours. The mixture was then concentrated in vacuo to give the acid chloride.

[0666] Diethyl malonate (7.27 mL, 48.1 mmol) in ACN (100 mL) was cooled to 0°C. $MgCl_2$ (4.58 g, 48.1 mmol) was added, followed by addition of TEA (13.4 mL, 96.2 mmol) slowly via syringe. The mixture was stirred at 0°C for 15 minutes and was then brought to room temperature and stirred for 2.5 hours. The above prepared acid chloride was dissolved in ACN (20 mL) and added to the malonate solution. The reaction mixture was then stirred at 50°C for 15 hours. The resulting reaction mixture was cooled to room temperature, concentrated in vacuo, and partitioned between 1M HCl and EtOAc. The aqueous layer was separated and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the desired compound as a brown oil (17.44 g). MS (m/z) = 385.1 $(M+H)^+$.

[0667] **Step D**: Preparation of Ethyl 7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0668] H_2SO_4 (60 mL, 710 mmol) was cooled to 0°C and treated with P_2O_5 (20 g, 141 mmol). The mixture was brought to room temperature and added to diethyl 2-(2-(3-bromophenyl)-2-methylpropanoyl)malonate (17.44 g, 45 mmol). The reaction mixture was then stirred for 2 hours. Ice (H_2O) was added, and the aqueous mixture was extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude compound as an orange oil. The crude oil was purified by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a white solid (6.27 g). MS (m/e) = 339.1 $(M+H)^+$.

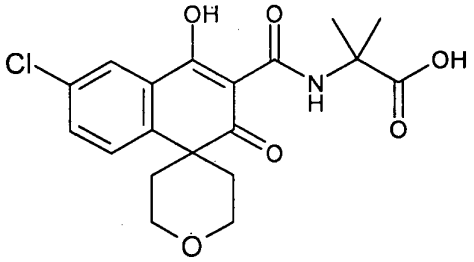
[0669] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0670] DIPEA (3.86 mL, 22.2 mmol, 1.2 eq) was added to a mixture of ethyl 7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (6.27 g, 18.5 mmol) and glycine tert-butyl ester hydrochloride (3.72 g, 22.2 mmol) in dioxane (30 mL). The reaction mixture was stirred at 85°C for 3 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a light yellow solid. The crude solid was suspended in ether, filtered, and washed with water to give the desired ester as a white solid (6.53 g). MS (m/e) = 368.1 $(M+H-tBu)^+$.

[0671] **Step F**: Preparation of N-((7-Bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0672] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (328 mg, 773 μmol) was stirred in TFA (2 mL, 26.9 mmol) at room temperature for 25 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as an off-white solid (263 mg). MS (m/e) = 368.1 $(M+H)^+$. Calculated for $C_{15}H_{14}BrNO_5$ 367.01.

[0673] **Example 54.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-2-methylalanine



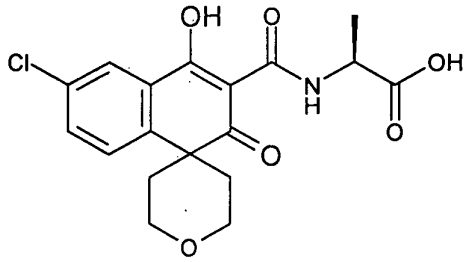
[0674] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-2-methylalaninate

[0675] Ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (320 mg, 950 μmol, prepared according to Example 1 A-C) was dissolved in 1,4-dioxane (950 μL) and N-ethyl-N-isopropylpropan-2-amine (507 μL, 2851 μmol) before tert-butyl 2-amino-2-methylpropanoate hydrochloride (279 mg, 1425 μmol) was added. The resulting mixture was heated at 80°C for 24 hours and then diluted with 150 mL of EtOAc. The resulting mixture was added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed with saturated aqueous $NaHCO_3$ (2 x 75 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (260 mg) after chromatography as an amorphous solid. MS (m/z) = 394(M+H-tert-butyl)$^+$.

[0676] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-2-methylalanine

[0677] 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-2-methylalaninate (245 mg, 545 μmol) was dissolved in TFA at ambient temperature for 1 hour before it was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (179 mg) as a white solid. MS (m/z) = 394 (M+H)$^+$. Calculated for $C_{19}H_{20}ClNO_6$ 393.10.

[0678] **Example 55.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-alanine



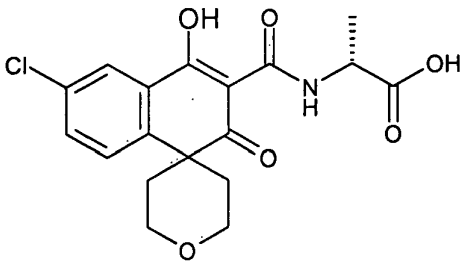
[0679] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-alaninate

[0680] Ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (610 mg, 1811 µmol, prepared in Example 1 A-C) was dissolved in 1,4-dioxane (1811 µL) and N-ethyl-N-isopropylpropan-2-amine (947 µL, 5434 µmol). L-Alanine t-butyl ester hydrochloride (494 mg, 2717 µmol) was added, and the reaction mixture was heated to 80°C for 24 hours. The reaction mixture was then cooled to ambient temperature, diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (525 mg) as an oil after flash chromatography. MS (m/z) = 436 $(M+H)^+$.

[0681] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-alanine

[0682] 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-alaninate (525 mg, 1204 µmol) was dissolved in TFA for 30 minutes before it was concentrated, precipitated with hexanes, washed with hexanes, and dried in a vacuum oven to give the title compound (384 mg) as a white solid. MS (m/z) = 380 $(M+H)^+$. Calculated for $C_{18}H_{18}ClNO_6$ 379.08.

[0683] **Example 56.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-D-alanine



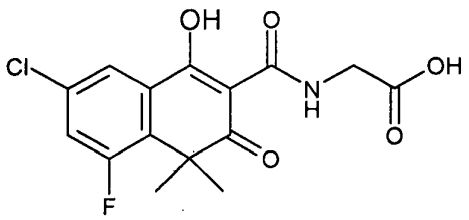
[0684] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-2H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-D-alaninate

[0685] Ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (705 mg, 2093 μmol, prepared in Example 1 A-C) was dissolved in 1,4-dioxane (2093 μL) and N-ethyl-N-isopropylpropan-2-amine (1094 μL, 6280 μmol). D-Alanine tert-butyl ester hydrochloride (570 mg, 3140 μmol) was added, and the reaction mixture was heated to 80°C for 24 hours. The resulting mixture was then diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 75 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (501 mg) after flash chromatography. MS (m/z) = 436 $(M+H)^+$.

[0686] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-D-alanine

[0687] 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-D-alaninate (501 mg, 1149 μmol) was dissolved in TFA at ambient temperature for 30 minutes before it was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (390 mg) as a white solid. MS (m/z) = 380 $(M+H)^+$. Calculated for $C_{18}H_{18}ClNO_6$ 379.08.

[0688] **Example 57.** N-((6-Chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0689] **Step A**: Preparation of Methyl 2-(4-chloro-2-fluorophenyl)acetate

[0690] 2-(4-Chloro-2-fluorophenyl)acetic acid (25.0 g, 133 mmol) was dissolved in MeOH (133 mL). Sulfuryl dichloride (9.67 mL, 133 mmol) was then added, and the reaction was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated in vacuo to give the title compound which was used without further purification. MS (m/z) = 203 $(M+H)^+$.

[0691] **Step B**: Preparation of Methyl 2-(4-chloro-2-fluorophenyl)-2-methylpropanoate

[0692] A 60% NaH dispersion in mineral oil (11.7 g, 292 mmol) was added to THF (266 mL). The mixture was then cooled to 0°C and methyl 2-(4-chloro-2-fluorophenyl)acetate (26.9 g, 133 mmol) and MeI (18.2 mL, 292 mmol) dissolved in ether were added dropwise via addition funnel. The reaction mixture was stirred at ambient temperature for 16 hours and then quenched dropwise with water. The resulting mixture was acidified with 3N HCl, diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (19.23 g) after flash chromatography. MS (m/z) = 231 $(M+H)^+$.

[0693] **Step C**: Preparation of 2-(4-Chloro-2-fluorophenyl)-2-methylpropanoic acid

[0694] Methyl 2-(4-chloro-2-fluorophenyl)-2-methylpropanoate (8.11 g, 35.2 mmol) was dissolved in EtOH (70.3 mL) in a vial. KOH (3.95 g, 70.3 mmol) was added, and the sealed vial was heated at 120°C for 2 hours. The

reaction mixture was then diluted with 75 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed with 75 mL of water, and separated. The aqueous layer was acidified to pH = 3 with 3N HCl and extracted 2 times with 100 mL of diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (6.46 g) as a light yellow solid. MS (m/z) = 217 $(M+H)^+$.

[0695] **Step D**: Preparation of Diethyl 2-(2-(4-chloro-2-fluorophenyl)-2-methylpropanoyl)malonate

[0696] To a mixture of diethyl malonate (5.01 mL, 33.1 mmol) and magnesium (0.805 g, 33.1 mmol), were added EtOH (11.6 mL) and CCl_4 (0.160 mL). THF (66.3 mL) was slowly added to the reaction, and the reaction was stirred at 70°C for 1 hour. The reaction was then allowed to cool and the acid chloride formed from 2-(4-chloro-2-fluorophenyl)-2-methylpropanoic acid (6.46 g, 29.8 mmol converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour and then concentrated) was added dropwise as an ether solution via addition funnel. The resulting reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was then quenched with 2N HCl, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (10.46 g) as a yellow oil. MS (m/z) = 359 $(M+H)^+$.

[0697] **Step E**: Preparation of Ethyl 6-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0698] To diethyl 2-(2-(4-chloro-2-fluorophenyl)-2-methylpropanoyl)malonate (2.20 g, 6.1 mmol), was added P_2O_5 (3.5 g, 25 mmol) in H_2SO_4 (3.3 mL) at 0°C. The reaction was then allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was poured into ice, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried

over Na_2SO_4, and concentrated in vacuo to give the title compound (0.75 g) which was used without further purification. MS (m/z) = 313 $(M+H)^+$.

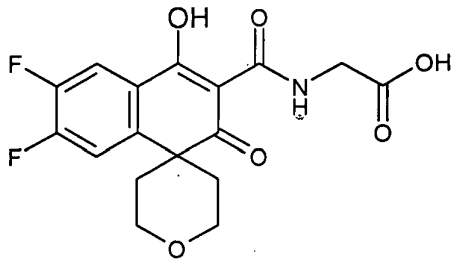
[0699] **Step F**: Preparation of 1,1-Dimethylethyl N-((6-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate

[0700] Ethyl 6-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.75 g, 2398 μmol) was dissolved in 1,4-dioxane (4797 μL) and N-ethyl-N-isopropylpropan-2-amine (1253 μL, 7195 μmol). tert-Butyl 2-aminoacetate hydrochloride (603 mg, 3597 μmol) was added, and the reaction was stirred at 80°C for 3 hours. The reaction was then diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 75 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (227 mg) as a white solid. MS (m/z) = 420$(M+Na)^+$.

[0701] **Step G**: Preparation of N-((6-Chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0702] 1,1-Dimethylethyl N-((6-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-yl)carbonyl)glycinate (227 mg, 571 μmol) was dissolved in TFA (2 mL) and stirred at ambient temperature for 30 minutes. The resulting mixture was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (219 mg, 112% yield) as a white solid. MS (m/z) = 342 $(M+H)^+$. Calculated for $C_{15}H_{13}ClFNO_5$ 341.05.

[0703] **Example 58.** N-((6,7-Difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0704] **Step A**: Preparation of 4-(3,4-Difluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0705] A mixture 2-(3,4-difluorophenyl)acetonitrile (25.00 g, 163 mmol) and 2-bromoethyl ether (22.8 mL, 163 mmol) in ether was added dropwise through an addition funnel to a mixture of sodium 2-methylpropan-2-olate (39.2 g, 408 mmol) in DMF (163 mL) at 0°C. The reaction was then allowed to warm to ambient temperature and stirred for 3 hours. The reaction mixture was quenched with 12N HCl, diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 100 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound which was used without further purification. MS (m/z) = 224 $(M+H)^+$.

[0706] **Step B**: Preparation of 4-(3,4-Difluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0707] 4-(3,4-Difluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile (21.96 g, 98.4 mmol) was suspended in H_2SO_4 (109 mL, 984 mmol) in a sealed vial and then heated to 160°C for 4 hours. The resulting reaction mixture was then cooled, diluted with 100 mL of EtOAc, added to a separation funnel, partitioned with 5N NaOH (aqueous), washed 2 times with 50 mL of 5N NaOH (aqueous), and separated. The aqueous layer was acidified to pH = 3 with concentrated HCl and extracted 3 times with 75 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (9.52 g) as a yellow oil which was used without further purification. MS (m/z) = 243 $(M+H)^+$.

[0708] **Step C**: Preparation of Diethyl 2-(4-(3,4-difluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0709] To diethyl malonate (11.6 mL, 76.5 mmol) and magnesium (1.86 g, 76.5 mmol), were added EtOH (26.7 mL, 459 mmol) and CCl_4 (0.369 mL). THF (76.5 mL) was slowly added to control the reaction, which was later heated to 70°C to consume all the magnesium. The reaction mixture was then cooled, and the acid chloride formed from 4-(3,4-difluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (12.36 g, 51.0 mmol; converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour and then concentrated) was added dropwise as an ether solution via addition funnel. After stirring for 30 minutes at ambient temperature, the reaction mixture was quenched with 5N HCl, diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 3 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (20.52 g) as a brown oil. MS (m/z) = 385 $(M+H)^+$.

[0710] **Step D**: Preparation of Ethyl 6,7-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0711] P_2O_5 (4.45 g, 31.3 mmol) was added to H_2SO_4 (4.17 mL, 78.3 mmol), the mixture was cooled to 0°C, and diethyl 2-(4-(3,4-difluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (3.01 g, 7.83 mmol) was added at 0°C. The reaction mixture was stirred for 4 hours and then poured into ice, diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound which was used without further purification. MS (m/z) = 339 $(M+H)^+$.

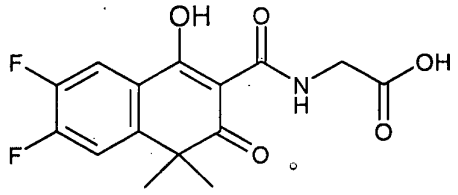
[0712] **Step E**: Preparation of 1,1-Dimethylethyl N-((6,7-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0713] Ethyl 6,7-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (1.06 g, 3133 μmol) was dissolved in 1,4-dioxane (3133 μL) and N-ethyl-N-isopropylpropan-2-amine (1637 μL, 9400 μmol). tert-Butyl 2-aminoacetate hydrochloride (788 mg, 4700 μmol) was added, and the reaction was placed in a microwave at 140°C for 10 minutes. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound as a white solid after purification via preparatory LC. MS (m/z) = 424 $(M+H)^+$.

[0714] **Step F**: Preparation of N-((6,7-Difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0715] 1,1-Dimethylethyl N-((6,7-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (152 mg, 359 μmol) was dissolved in TFA at ambient temperature for 30 minutes and then concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (115 mg) as a white solid. MS (m/z) = 368 $(M+H)^+$. Calculated for $C_{17}H_{15}F_2NO_6$ 367.09.

[0716] **Example 59.** N-((6,7-Difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0717] **Step A**: Preparation of 2-(3,4-Difluorophenyl)-2-methylpropanenitrile

[0718] 2-(3,4-Difluorophenyl)acetonitrile (25.0 g, 163 mmol) and MeI (25.4 mL, 408 mmol) were dissolved in DMF (163 mL) and added dropwise to a

suspension of sodium tert-butoxide (39.2 g, 408 mmol) in DMF at 0°C. The resulting reaction mixture was stirred at 0°C for 1 hour and then allowed to warm to ambient temperature for 1 hour. The reaction mixture was diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 3 times with 200 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (26.45 g) as a yellow oil.

[0719] **Step B**: Preparation of 2-(3,4-Difluorophenyl)-2-methylpropanoic acid

[0720] 9M H_2SO_4 (176 mL) was added to 2-(3,4-difluorophenyl)-2-methylpropanenitrile (19.15 g, 106 mmol). The resulting mixture was heated at 180°C for 2 hours and then was diluted with 100 mL of diethyl ether. The resulting mixture was added to a separatory funnel, and the organic phase was separated from the aqueous layer. The organic layer was partitioned with 5N NaOH (aqueous), and extracted 1 time with 50 mL of 5N NaOH (aqueous). The aqueous layers were acidified to pH = 2 with 3N HCl and extracted 2 times with 200 mL of diethyl ether, dried over Na_2SO_4, and concentrated in vacuo to give the title compound.

[0721] **Step C**: Preparation of Diethyl 2-(2-(3,4-difluorophenyl)-2-methylpropanoyl)malonate

[0722] EtOH (44.5 mL) and CCl_4 (0.614 mL) were added to a mixture of diethyl malonate (19.2 mL, 127 mmol) and magnesium (3.09 g, 127 mmol) at ambient temperature. THF (255 mL) was slowly added to control the temperature. The reaction mixture was then heated at 70°C for 1 hour. The acid chloride formed from 2-(3,4-difluorophenyl)-2-methylpropanoic acid (17.0 g, 84.9 mmol; converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour and then concentrated) was added dropwise as an ether solution via addition funnel to the cooling reaction mixture above, and the reaction was then stirred for 1 hour. The reaction mixture was diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated,

aqueous), washed 2 times 150 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (32.42 g) which was used without further purification. MS (m/z) = 343 $(M+H)^+$.

[0723] **Step D**: Preparation of Ethyl 6,7-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0724] P_2O_5 (26.9 g, 189 mmol) was added to concentrated H_2SO_4 (50.5 mL) at 0°C. Diethyl 2-(2-(3,4-difluorophenyl)-2-methylpropanoyl)malonate (32.42 g, 94.7 mmol) was added at 0°C, and the reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. The resulting reaction mixture was then poured into ice, diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 3 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound as a beige yellow amorphous solid which was used without further purification. MS (m/z) = 297 $(M+H)^+$.

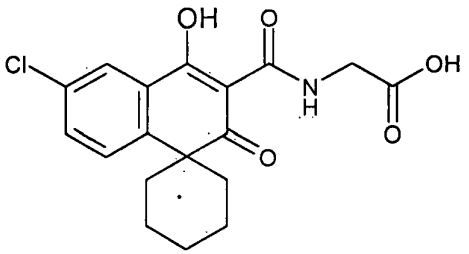
[0725] **Step E**: Preparation of 1,1-Dimethylethyl N-((6,7-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0726] To a mixture of ethyl 6,7-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (570 mg, 1924 µmol) in 1,4-dioxane (3848 µL) and N-ethyl-N-isopropylpropan-2-amine (1005 µL, 5772 µmol), was added tert-butyl 2-aminoacetate hydrochloride (484 mg, 2886 µmol). The reaction was then heated at 80°C for 3 hours. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (312 mg) as a white solid after flash chromatography. MS (m/z) = 404$(M+Na)^+$.

[0727] **Step F**: Preparation of N-((6,7-Difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0728] 1,1-Dimethylethyl N-((6,7-difluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (312 mg, 818 μmol) was dissolved in TFA (2 mL) at ambient temperature and reacted for 30 minutes. The mixture was then concentrated, precipitated with hexanes, filtered, and dried in a vacuum oven to give the title compound (228 mg, 85.7% yield) as a white solid. MS (m/z) = 326 $(M+H)^+$. Calculated for $C_{15}H_{13}F_2NO_5$ 325.08.

[0729] **Example 60.** N-((6'-Chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycine



[0730] **Step A**: Preparation of Diethyl 2-(1-(4-chlorophenyl)-cyclohexanecarbonyl)malonate

[0731] To diethyl malonate (23.7 mL, 157 mmol) and magnesium (3.82 g, 157 mmol) were added EtOH (54.9 mL, 942 mmol) and CCl_4 (0.758 mL, 7.85 mmol). THF (157 mL) was added to control the reaction temperature. The reaction mixture was then heated at 70°C for 1.5 hours and then cooled to ambient temperature. The acid chloride formed from 1-(4-chlorophenyl)cyclohexanecarboxylic acid (25.0 g, 105 mmol; converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour and then concentrated) was then added dropwise as an ether solution via addition funnel. The reaction mixture was stirred for 1 hour at ambient temperature and then quenched with 5N HCl, diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (43.8 g).

[0732] **Step B**: Preparation of Ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalene]-3'-carboxylate

[0733] Triflic acid (40.4 mL) was added dropwise via addition funnel to diethyl 2-(1-(4-chlorophenyl)cyclohexanecarbonyl)malonate (17.65 g, 46.3 mmol) at 0°C. The resulting mixture was stirred for 1 hour and then poured into a beaker of ice. The resulting mixture was diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (7.24 g) which was used without further purification. MS (m/z) = 335 $(M+H)^+$.

[0734] **Step C**: Preparation of 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate

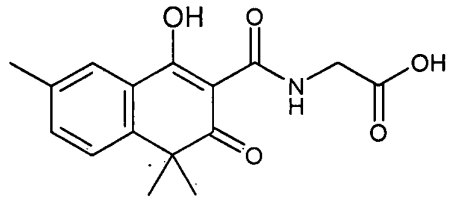
[0735] tert-Butyl 2-aminoacetate hydrochloride (901 mg, 5376 μmol) was added to a mixture of ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalene]-3'-carboxylate (1.20 g, 3584 μmol) in 1,4-dioxane (3584 μL) and N-ethyl-N-isopropylpropan-2-amine (1873 μL, 10753 μmol). The resulting mixture was heated at 80°C for 2 hours. The resulting mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (185 mg) as a light yellow solid after purification via preparatory HPLC. MS (m/z) = 364$(M+H-tBu)^+$.

[0736] **Step D**: Preparation of N-((6'-Chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycine

[0737] 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate (185 mg, 441 μmol) was dissolved in TFA (2 mL) at ambient temperature for 30 minutes. The reaction mixture was then concentrated, and the product was precipitated with hexanes, filtered, washed with ether, and dried in a vacuum oven to give

the title compound (119 mg) as a white solid. MS (m/z) = 364 $(M+H)^+$. Calculated for $C_{18}H_{18}ClNO_5$ 363.09.

[0738] **Example 61.** N-((6-Methyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0739] **Step A**: Preparation of 2-Methyl-2-p-tolylpropanenitrile

[0740] NaH (60% dispersion in oil, 14.2 g, 354 mmol) was added to THF (322 mL). The mixture was then cooled to 0°C, and an ether solution of p-tolylacetonitrile (21.12 g, 161 mmol) and MeI (22.1 mL, 354 mmol) was added dropwise via addition funnel. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. The reaction mixture was then quenched with water, acidified with 5N HCl, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (17.0 g) as an amber oil. MS (m/z) = 319 $(M+H)^+$ (dimer).

[0741] **Step B**: Preparation of 2-Methyl-2-p-tolylpropanoic acid

[0742] 9M H_2SO_4 (65.0 mL) was added to 2-methyl-2-p-tolylpropanenitrile (6.21 g, 39.0 mmol). The reaction mixture was then heated at 180°C in a sealed tube for 2 hours. The reaction mixture was cooled to ambient temperature, diluted with 100 mL of diethyl ether, added to a separation funnel, washed with 5N HCl, partitioned with 5N NaOH (aqueous), washed 2 times with 20 mL of 5N NaOH (aqueous), and separated before the aqueous layer was acidified to pH = 3 with 3N HCl and extracted 3 times with 75 mL of diethyl ether, dried over Na_2SO_4, and concentrated in vacuo to give the title

compound (5.27 g) as brownish yellow amorphous solid. MS (m/z) = 180 $(M+H)^+$.

[0743] **Step C**: Preparation of Diethyl 2-(2-methyl-2-p-tolylpropanoyl)malonate

[0744] To a mixture of magnesium (1.08 g, 44.3 mmol) and diethyl malonate (6.70 mL, 44.3 mmol) were added EtOH (15.5 mL, 266 mmol) and CCl_4 (0.21 mL) at ambient temperature. The reaction was controlled by slowly adding THF (44 mL). The reaction mixture was stirred at 70°C for 1 hour and then allowed to cool. The acid chloride formed from 2-methyl-2-p-tolylpropanoic acid (5.27 g, 29.6 mmol; converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour, and then concentrating) was added dropwise as an ether solution via addition funnel. The resulting mixture was stirred for 30 minutes at ambient temperature and then quenched with 5N HCl. The mixture was diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (9.24 g) as a brown oil which was used without further purification. MS (m/z) = 321 $(M+H)^+$.

[0745] **Step D**: Preparation of Ethyl 4-hydroxy-1,1,6-trimethyl-2-oxo-naphthalene-3-carboxylate

[0746] Concentrated H_2SO_4 (11.5 mL, 216 mmol) was added dropwise via addition funnel to stirred diethyl 2-(2-methyl-2-p-tolylpropanoyl)malonate (6.92 g, 21.6 mmol) at 0°C. The reaction mixture was stirred for 1.5 hours and then poured into a flask of ice, diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (3.05 g) as a brown oil which was used without further purification. MS (m/z) = 275 $(M+H)^+$.

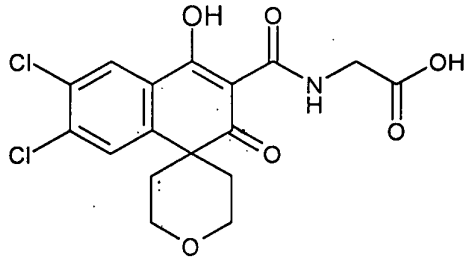
[0747] **Step E**: Preparation of 1,1-Dimethylethyl N-((6-methyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0748] Ethyl 4-hydroxy-1,1,6-trimethyl-2-oxo-naphthalene-3-carboxylate (750 mg, 2734 μmol) was dissolved in 1,4-dioxane (2734 μL) and N-ethyl-N-isopropylpropan-2-amine (1429 μL, 8202 μmol). tert-Butyl 2-aminoacetate hydrochloride (687 mg, 4101 μmol) was added, and the reaction was stirred at 80°C for 1 hour. The reaction mixture was cooled to ambient temperature, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (266 mg) as a white solid after flash chromatography. MS (m/z) = 304$(M+H-tBu)^+$.

[0749] **Step F**: Preparation of N-((6-Methyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0750] 1,1-Dimethylethyl N-((6-methyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (255 mg, 709 μmol) was dissolved in TFA (3 mL) at ambient temperature for 30 minutes. The reaction mixture was then concentrated, precipitated with hexanes, filtered, and dried in a vacuum oven to give the title compound (192 mg) as a white solid. MS (m/z) = 304 $(M+H)^+$. Calculated for $C_{16}H_{17}NO_5$ 303.11.

[0751] **Example 62.** N-((6,7-Dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0752] **Step A**: Preparation of 4-(3,4-Dichlorophenyl)-tetrahydro-2H-pyran-4-carbonitrile

[0753] 3,4-Dichlorophenylacetonitrile (10.00 g, 53.8 mmol) and bis(2-bromoethyl) ether (12.5 g, 53.8 mmol) were dissolved in ether and added dropwise via addition funnel to a suspension of NaH (60% dispersion in mineral oil; 6.45 g, 161 mmol) in 1-methylpyrrolidone (108 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 hour and was then allowed to warm to ambient temperature. The reaction was then quenched with water. 5N HCl was added, and the reaction mixture was diluted with 200 mL of diethyl ether, added to a separatory funnel, washed 2 times with 100 mL of ether, separated, dried over Na_2SO_4, and concentrated in vacuo to give the purified title compound (7.97 g) after flash chromatography.

[0754] **Step B**: Preparation of 4-(3,4-Dichlorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0755] 9M H_2SO_4 (43.7 mL) was added to 4-(3,4-dichlorophenyl)-tetrahydro-2H-pyran-4-carbonitrile (6.72 g, 26.2 mmol) in a vial. The sealed vial was heated to 180°C for 1 hour, and the reaction mixture was cooled to ambient temperature, diluted with 200 mL of diethyl ether, added to a separation funnel, partitioned with 5N NaOH (aqueous), washed 1 time with 75 mL of 5N NaOH (aqueous), and separated before the aqueous layer was acidified to pH = 4 with 3N HCl and extracted 3 times with 75 mL of diethyl ether, dried over Na_2SO_4, and concentrated in vacuo to give the title compound which was used without further purification.

[0756] **Step C**: Preparation of Diethyl 2-(4-(3,4-dichlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0757] To magnesium (0.868 g, 35.7 mmol) and diethyl malonate (5.39 mL, 35.7 mmol) were added EtOH (12.5 mL, 214 mmol) and CCl_4 (0.172 mL). THF (35.7 mL) was slowly added to keep the temperature down and control the reaction. The reaction mixture was then heated at 70°C for 1 hour and then

cooled to room temperature. Meanwhile, the acid chloride of 4-(3,4-dichlorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (6.55 g, 23.8 mmol) was formed by addition of thionyl chloride (20mL) followed by heating to 65°C for 1 hour. The mixture was cooled, concentrated and redissolved in ether (20mL). The resulting acid chloride solution was added dropwise via addition funnel to the magnesium enolate as prepared above. The reaction mixture was stirred for 1 hour and quenched with 5N HCl and then diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 3 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (3.94 g) as an off-white after flash chromatography. MS (m/z) = 417 $(M+H)^+$.

[0758] **Step D**: Preparation of Ethyl 6,7-dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0759] Concentrated H_2SO_4 (4203 µL) was added to solid diethyl 2-(4-(3,4-dichlorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (3.29 g, 7884 µmol) at ambient temperature. The reaction was heated at 50°C for 6 hours and then poured into a flask of ice, diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the purified title compound (375 mg) after flash chromatography as a pale yellow solid. MS (m/z) = 371 $(M+H)^+$.

[0760] **Step E**: Preparation of 1,1-Dimethylethyl N-((6,7-dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

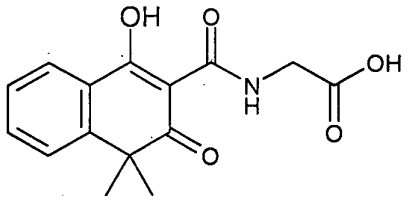
[0761] Ethyl 6,7-dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (550 mg, 1482 µmol) was dissolved in 1,4-dioxane (1482 µL), and N-ethyl-N-isopropylpropan-2-amine (774 µL, 4445 µmol). tert-Butyl 2-aminoacetate hydrochloride (373 mg, 2222 µmol) was added to the reaction, and the reaction was stirred at 80°C for 3 hours. The

reaction mixture was diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (350 mg) as a white solid after flash chromatography. MS (m/z) = 456 $(M+H)^+$.

[0762] **Step F**: Preparation of N-((6,7-Dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0763] 1,1-Dimethylethyl N-((6,7-dichloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (350 mg, 767 μmol) was dissolved in TFA (3 mL). The resulting mixture was stirred for 1 hour and then concentrated, precipitated with hexanes, sonicated, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (268 mg, 87.3% yield) as a white solid. MS (m/z) = 400 $(M+H)^+$. Calculated for $C_{17}H_{15}Cl_2NO_6$ 399.03.

[0764] **Example 63.** N-((4-Hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0765] **Step A**: Preparation of Diethyl 2-(2-methyl-2-phenylpropanoyl)malonate

[0766] EtOH (31.9 mL) and CCl_4 (0.441 mL) were added to magnesium (2.22 g, 91.3 mmol) and diethyl malonate (13.8 mL, 91.3 mmol) at ambient temperature. THF (91.3 mL) was added slowly to control the reaction and maintain the temperature under reflux. The reaction mixture was then heated to 70°C for 2 hours and cooled to room temperature. Meanwhile, the acid chloride of alpha,alpha-dimethylphenylacetic acid (10.0 g, 60.9 mmol) was formed by

addition of thionyl chloride (30mL) followed by heating to 65°C for 1 hour. The mixture was cooled, concentrated and redissolved in ether (20mL). The resulting acid chloride solution was added dropwise via addition funnel to the magnesium enolate as prepared above. The reaction mixture was stirred for 1 hour and then quenched with 1N HCl, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (22.11 g). MS (m/z) = 307 $(M+H)^+$.

[0767] **Step B**: Preparation of Ethyl 4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0768] Concentrated H_2SO_4 (38.5 mL) was added dropwise via addition funnel to diethyl 2-(2-methyl-2-phenylpropanoyl)malonate (22.1 g, 72.1 mmol) cooled to 0°C. The reaction mixture was stirred for 2 hours at 0°C and then poured into a flask containing ice, diluted with 400 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (10.82 g) as a white amorphous solid after flash chromatography. MS (m/z) = 261 $(M+H)^+$.

[0769] **Step C**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

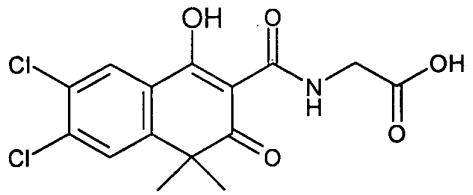
[0770] Ethyl 4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (425 mg, 1633 μmol) was dissolved in 1,4-dioxane (1633 μL) and N-ethyl-N-isopropylpropan-2-amine (853 μL, 4898 μmol). tert-Butyl 2-aminoacetate hydrochloride (411 mg, 2449 μmol) was added, and the mixture was heated at 80°C for 4 hours. The reaction mixture was then cooled, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title

compound (279 mg) as a white solid after purification via preparatory LC. MS (m/z) = 290(M+H-tBu)$^+$.

[0771] **Step D**: Preparation of N-((4-Hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0772] 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (270 mg, 782 μmol) was dissolved in TFA (2 mL) at ambient temperature. The mixture was then stirred for 30 minutes. The reaction mixture was concentrated, suspended in hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (215 mg) as a white solid. MS (m/z) = 290 (M+H)$^+$. Calculated for $C_{15}H_{15}NO_5$ 289.1.

[0773] **Example 64.** N-((6,7-Dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0774] **Step A**: Preparation of Methyl 2-(3,4-dichlorophenyl)acetate

[0775] 2-(3,4-Dichlorophenyl)acetic acid (25.0 g, 122 mmol) was dissolved in MeOH (122 mL) at ambient temperature. Sulfuryl dichloride (8.89 mL, 122 mmol) was then added, and the mixture was stirred for 2 hours. The reaction mixture was concentrated in vacuo to give the title compound as a light yellow oil which was used without further purification. MS (m/z) = 219 (M+H)$^+$.

[0776] **Step B**: Preparation of Methyl 2-(3,4-dichlorophenyl)-2-methylpropanoate

[0777] To NaH (60% in mineral oil) (10.7 g, 268 mmol) in THF (244 mL), was added dropwise through an addition funnel a mixture of methyl 2-

(3,4-dichlorophenyl)acetate (26.7 g, 122 mmol) and MeI (16.7 mL, 268 mmol) in ether at 0°C. The reaction mixture was warmed to ambient temperature and stirred for 4 hours and then quenched with water and acidified with 3N HCl. The reaction mixture was diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 3 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (22.03 g) as a brown oil after flash chromatography. MS (m/z) = 247 $(M+H)^+$.

[0778] **Step C**: Preparation of 2-(3,4-Dichlorophenyl)-2-methylpropanoic acid

[0779] To methyl 2-(3,4-dichlorophenyl)-2-methylpropanoate (22.03 g, 89.1 mmol) was added THF/water (4:1) (178 mL) and lithium hydroxide hydrate (22.4 g, 535 mmol). The reaction was then stirred at 50°C for 3 days. The reaction mixture was acidified with 3N HCl, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound which was used without further purification. MS (m/z) = 233 $(M+H)^+$.

[0780] **Step D**: Preparation of Diethyl 2-(2-(3,4-dichlorophenyl)-2-methylpropanoyl)malonate

[0781] To magnesium (3.23 g, 133 mmol) and diethyl malonate (20.1 mL, 133 mmol) were added EtOH (46.4 mL) and CCl_4 (0.641 mL) at ambient temperature. THF (133 mL) was slowly added to control the reaction and keep the temperature below reflux. After the Mg was visibly consumed, the reaction mixture was stirred at 70°C for 2 hours and cooled to room temperature. Meanwhile, 2-(3,4-dichlorophenyl)-2-methylpropanoyl chloride (22.4 g, 89.1 mmol) was prepared by heating to 65°C for 2 hours with thionyl chloride (50mL). The acid chloride solution was concentrated, dissolved in THF (20mL) and added dropwise to the magnesium enolate as prepared above. The resulting

reaction mixture was stirred at 70°C for 1 hour and then cooled, quenched with 3N HCl, diluted with 400 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (27.85 g) as a yellow oil after flash chromatography. MS (m/z) = 375 $(M+H)^+$.

[0782] **Step E**: Preparation of Ethyl 6,7-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0783] Concentrated H_2SO_4 (52.5 mL, 621 mmol) was added dropwise via an addition funnel to diethyl 2-(2-(3,4-dichlorophenyl)-2-methylpropanoyl)malonate (11.66 g, 31.1 mmol) cooled to 0°C. The reaction mixture was allowed to slowly warm to ambient temperature and then poured into a beaker of ice, diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (9.61 g) as a white amorphous solid. MS (m/z) = 329 $(M+H)^+$.

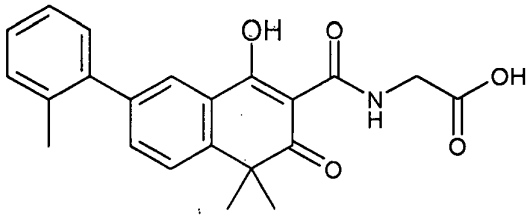
[0784] **Step F**: Preparation of 1,1-Dimethylethyl N-((6,7-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0785] Ethyl 6,7-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (325 mg, 987 μmol) was dissolved in 1,4-dioxane (987 μL) and N-ethyl-N-isopropylpropan-2-amine (516 μL, 2962 μmol). tert-Butyl 2-aminoacetate hydrochloride (248 mg, 1481 μmol) was added, and the reaction was stirred at 80°C for 4 hours. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 20 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (235 mg) as an off-white solid after purification via preparatory LC. MS (m/z) = 358$(M+H\text{-}tBu)^+$.

[0786] **Step G**: Preparation of N-((6,7-Dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0787] To 1,1-dimethylethyl N-((6,7-dichloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (235 mg, 567 μmol) was added TFA (2 mL) at ambient temperature. The mixture was stirred for 30 minutes and then concentrated, precipitated with ether, filtered, washed with ether, and dried in a vacuum oven to give the title compound (95 mg) as a white solid. MS (m/z) = 358 $(M+H)^+$. Calculated for $C_{15}H_{13}Cl_2NO_5$ 357.02.

[0788] **Example 65.** N-((6-(2-Methylphenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



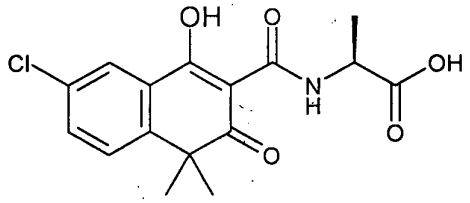
[0789] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-(2-methylphenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0790] To 1,1-dimethylethyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (250 mg, 658 μmol, Example 40 A-D) and o-tolylboronic acid (134 mg, 987 μmol), were added 1,4-dioxane (3291 μL), and K_2CO_3 in water (987 μL, 1975 μmol). The reaction was flushed with nitrogen for 10 minutes. Next, $Pd_2(dba)_3$ (60.3 mg, 65.8 μmol) and X-Phos (62.8 mg, 132 μmol) were added, and the reaction was heated at 110°C for 4 hours. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (160 mg) as a yellow oil. MS (m/z) = 380$(M+H-tBu)^+$.

[0791] **Step B**: Preparation of N-((6-(2-Methylphenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0792] 1,1-Dimethylethyl N-((6-(2-methylphenyl)-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (160 mg, 367 μmol) was dissolved in TFA (2 mL) at ambient temperature. The reaction was stirred for 30 minutes and then concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (57 mg) as a light yellow solid. MS (m/z) = 380 $(M+H)^+$. Calculated for $C_{22}H_{21}NO_5$ 379.14.

[0793] **Example 66.** N-((6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alanine



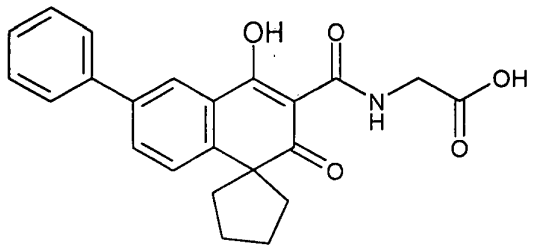
[0794] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alaninate

[0795] To ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (2.44 g, 8.28 mmol, see Example 2) and L-alanine t-butyl ester hydrochloride (2.26 g, 12.4 mmol), were added 1,4-dioxane (5.52 mL) and N-ethyl-N-isopropylpropan-2-amine (4.33 mL, 24.8 mmol). The reaction mixture was then heated in a microwave at 140°C for 10 minutes. The reaction mixture was diluted with 150 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 3 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (0.815 g) as a light yellow amorphous solid after flash chromatography. MS (m/z) = 338$(M+H-tBu)^+$.

[0796] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alanine

[0797] To 1,1-dimethylethyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-L-alaninate (320 mg, 812 μmol) was added TFA (2 mL) at ambient temperature. The mixture was stirred for 30 minutes and was then concentrated, precipitated with hexanes, filtered, washed, and dried in a vacuum oven to give the title compound (220 mg) as a white solid. MS (m/z) = 338 $(M+H)^+$. Calculated for $C_{16}H_{16}ClNO_5$ 337.07.

[0798] **Example 67.** N-((4'-Hydroxy-2'-oxo-6'-phenyl-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycine



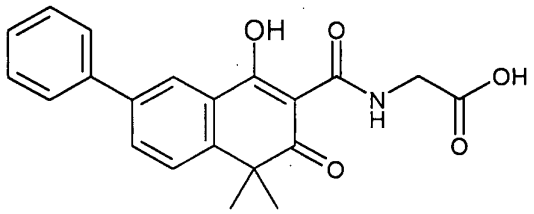
[0799] **Step A**: Preparation of 1,1-Dimethylethyl N-((4'-hydroxy-2'-oxo-6'-phenyl-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate

[0800] To 1,1-dimethylethyl N-((4'-hydroxy-2'-oxo-6'-chloro-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate (250 mg, 616 μmol, Example 25 A-B) and phenylboronic acid (113 mg, 924 μmol) were added 1,4-dioxane (3080 μL) and K_2CO_3 in water (924 μL, 1848 μmol). The reaction was then flushed with nitrogen for 10 minutes. $Pd_2(dba)_3$ (56.4 mg, 61.6 μmol) and X-Phos (58.7 mg, 123 μmol) were then added, and the reaction mixture was stirred at 110°C for 6 hours. The reaction mixture was diluted with 75 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (115 mg) as an oil after preparatory LC. MS (m/z) = 392(M+H-tBu)$^+$.

[0801] **Step B**: Preparation of N-((4'-Hydroxy-2'-oxo-6'-phenyl-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycine

[0802] 1,1-Dimethylethyl N-((4'-hydroxy-2'-oxo-6'-phenyl-spiro[cyclopentane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate (115 mg, 257 μmol) was dissolved in TFA (2 mL) at ambient temperature. The reaction was stirred for 30 minutes and was then concentrated to give an oil, dissolved in ether, concentrated again to give an amorphous solid, precipitated with ether, filtered, washed with ether, and dried in a vacuum oven to give the title compound (21 mg) as a white solid. MS (m/z) = 392 $(M+H)^+$. Calculated for the $C_{23}H_{21}NO_5$ 391.14.

[0803] **Example 68.** N-((6-Phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0804] **Step A**: Preparation of 1,1-Dimethylethyl N-((6-phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

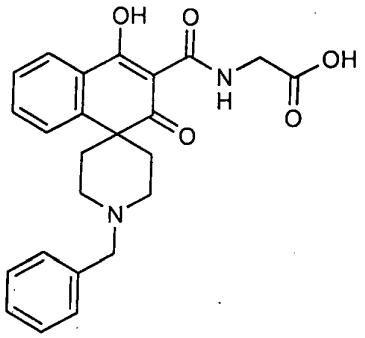
[0805] To 1,1-dimethylethyl N-((6-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (250 mg, 658 μmol, Example 40 A-D), phenylboronic acid (120 mg, 987 μmol), $Pd_2(dba)_3$ (60.3 mg, 65.8 μmol), and X-Phos (62.8 mg, 132 μmol), were added dioxane (3291 μL) and K_2CO_3 in water (987 μL, 1975 μmol). The reaction was then heated at 110°C for 6 hours. The resulting reaction mixture was cooled to ambient temperature, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the

title compound (190 mg) as an amber amorphous solid after purification via prep-LC. MS (m/z) = 444$(M+Na)^+$.

[0806] **Step B**: Preparation of N-((6-Phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0807] 1,1-Dimethylethyl N-((6-phenyl-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (190 mg, 451 μmol) was dissolved in TFA (2 mL) at ambient temperature. The resulting mixture was then stirred for 30 minutes. The reaction mixture was concentrated, precipitated with ether, filtered, washed with ether, and dried in a vacuum oven to give the title compound (57 mg) as a white solid. MS (m/z) = 366 $(M+H)^+$. Calculated for $C_{21}H_{19}NO_5$ 365.13.

[0808] **Example 69.** N-((4-Hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycine



[0809] **Step A**: Preparation of Ethyl 1-benzyl-4-(2-(2-(triethylsilyl)ethynyl)-phenyl)piperidine-4- carboxylate

[0810] At 0°C, n-BuLi (1.6N, 2 mL, 3.2 mmol, 1.6 eq.) was syringed into a solution of HNCy2 (615 mg, 3.4 mmol, 1.7 eq.) in toluene (6 mL) in a N_2-filled 40 mL vial equipped with a stirbar, an open-top cap and an I-Chem septum. The solution was warmed to room temperature, and ethyl 1-benzylpiperidine carboxylate (840 mg, 3.4 mmol, 1.7 eq.) was then syringed into the mixture.

[0811] $[PdBrP(t\text{-}Bu)_3]_2$ (15 mg, 0.02 mmol, 1%) was weighed into a separate 20 mL vial containing a stir bar. The vial was then capped with an I-Chem septum cap, and evacuated/refilled with N_2 (repeated twice). With N_2 needled into the vial, toluene (4 mL) was syringed in, followed by (2-(2-bromo-phenyl) ethynyl)triethylsilane (590 mg, 2.0 mmol). The needle was then removed from the vial, and the vial was heated at 100°C for 2 minutes with stirring. The vial was allowed to cool for about 1 minute. The whole solution was then pulled into a 10 mL syringe before it completely cooled. The solution was then syringed into the above vial containing the lithium/anion with N_2 needled in. The needle was removed. The whole solution was heated at 100°C and monitored using GC. No (2-(2-bromo-phenyl) ethynyl)triethylsilane remained after 20 minutes. The reaction was cooled to room temperature and filtered through a silica gel plug, eluted with EtOAc (30 mL). The resulting solution was concentrated, absorbed on silica gel and purified by silica flash chromatography (10-30% EtOAc/hexanes) to afford the title compound as a pale-yellow oil (533 mg). MS m/e = 462 $(M+H)^+$.

[0812] **Step B**: Preparation of Ethyl 1-benzyl-4-(2-ethynylphenyl)piperidine-4-carboxylate

[0813] To a solution of ethyl -1-benzyl-4-(2-(2-(triethylsilyl)ethynyl)phenyl)-piperidine-4-carboxylate (0.50 g, 1.1 mmol) and MeOH (10 mL), was added potassium t-butoxide (0.15 g, 1.3 mmol). The reaction mixture was heated at 40°C for 15 hours. The reaction mixture was then concentrated in vacuo and loaded on a silica gel column and purified by Isco HPLC (0-50 % EtOAc/hexane) to give the title compound as a viscous light yellow oil (0.22 g). MS m/e = 348 $(M+H)^+$.

[0814] **Step C**: Preparation of Ethyl 1-benzyl-4-(2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-4-carboxylate

[0815] n-Butyllithium (0.76 mL, 1.9 mmol) was added to a stirred solution of diisopropylamine(0.28 mL, 2.0 mmol) in THF (20 mL, 244 mmol) at

-78°C. The reaction mixture was then allowed to warm to ambient temperature for 5 minutes before it was cooled down to -78°C. Ethyl 1-benzyl-4-(2-ethynylphenyl)piperidine-4-carboxylate (0.22 g, 0.63 mmol) was then added dropwise as a solution in THF (20 mL, 244 mmol). After 15 minutes, ethyl chloroformate (0.19 mL, 2.0 mmol) in 5 mL of THF was added to the reaction. The resulting solution was allowed to warm to ambient temperature and then stirred for 30 minutes. MeOH (3 mL) was added, and the resulting mixture was concentrated in vacuo to give a bright-yellow oil. The residue was dissolved in DCM and purified by Isco HPLC (0-80% EtOAc/hexane) to give the title compound as a yellow oil (0.15 g). MS m/e = 420 $(M+H)^+$.

[0816] **Step D**: Preparation of Ethyl 4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-carboxylate

[0817] A solution of benzaldehyde oxime (0.05 g, 0.4 mmol) in dry DMF (5 mL, 65 mmol) was added to a stirred suspension of NaH (0.032 g, 0.4 mmol) in dry 1,4-dioxane (5 mL, 58 mmol) under a N_2 atmosphere at room temperature. After 0.5 hours, a solution of the ethyl 1-benzyl-4-(2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-4-carboxylate (0.15 g, 0.4 mmol) in dry DMF (5 mL, 65 mmol) was added, and the solution was stirred for 1 hour. The reaction mixture was concentrated in vacuo. The resulting residue was treated with water (0.5 mL). The crude product was purified by Isco HPLC (0-75% EtOAc/hexane then 10% MeOH/DCM) to afford the title compound as a white solid (0.035 g, 25%). MS m/e = 392 $(M+H)^+$.

[0818] **Step E**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycinate

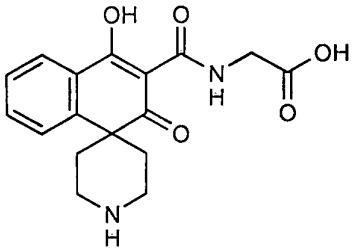
[0819] DIPEA (0.1 mL, 766 μmol) was added to a stirred mixture of ethyl 4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-carboxylate (30 mg, 77 μmol) and glycine tert-butyl ester hydrochloride (64 mg, 383 μmol) in 1,4-dioxane (3 mL). The reaction mixture

was then stirred at 100°C for 0.5 hours. The reaction mixture was concentrated in vacuo, and the residue was purified by Isco HPLC (0-50% EtOAc/hexane) to give the title compound as a light-yellow oil(30 mg, 82%). MS m/e = 477 $(M+H)^+$.

[0820] **Step F**: Preparation of N-((4-Hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycine

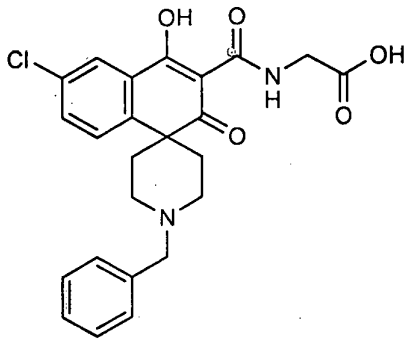
[0821] A solution of 1,1-dimethylethyl N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycinate (30 mg, 63 μmol) and TFA (3 mL) was stirred at room temperature. After 0.5 hours, the reaction was concentrated in vacuo. DCM was added, and the solution was concentrated in vacuo to give the title compound as an off-white solid (33 mg, 100%). MS m/e = 421 $(M+H)^+$. Calculated for $C_{24}H_{24}N_2O_5$ 420.46.

[0822] **Example 70.** N-((4-Hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycine



[0823] A solution of N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycine (8.0 mg, 15 μmol, See Example 69) and MeOH (2 mL) was hydrogenated over 10% Pd/C (0.02 mg, 0.2 μmol) at room temperature and 1 atm. After 3 hours, the reaction mixture was filtered and concentrated in vacuo to give the title compound as a white solid (4.3 mg). MS m/e = 331 $(M+H)^+$. Calculated for $C_{17}H_{18}N_2O_5$ 330.34.

[0824] **Example 71.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-N-benzyl-spiro[naphthalene-1,4'-piperidine]-3-yl)carbonyl)glycine



[0825] **Step A**: Preparation of 2-Bromo-5-chlorobenzenamine

[0826] A solution of 1-bromo-4-chloro-2-nitrobenzene (13.92 g, 58.87 mmol) in MeOH (300 mL) was treated with water (50 mL), ammonium chloride (22.99 g, 429.8 mmol), and iron powder (325 mesh, 16.44 g, 294.4 mmol). The suspension was stirred at 23°C. After 18 hours, the suspension was filtered through celite. The filter cake was washed with MeOH (500 mL). The combined filtrate/washings were concentrated, partitioned in EtOAc/water (500 mL/200 mL), and the organic layer was separated. The aqueous layer was washed with EtOAc (2 x 200 mL). The organic layers were combined, washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo affording 11.51 g of 2-bromo-5-chlorobenzenamine.

[0827] **Step B**: Preparation of 1-Bromo-4-chloro-2-iodobenzene

[0828] A suspension of 2-bromo-5-chlorobenzenamine (11.348 g, 54.963 mmol) in concentrated HCl (100 mL) was cooled to 0°C and treated dropwise over 20 minutes (using an addition funnel) with a solution of sodium nitrite (4.5506 g, 65.955 mmol) in water (20 mL). The reaction was stirred at 0°C for 75 minutes. A solution of potassium iodide (27.372 g, 164.89 mmol) in water (50 mL) was added, and the reaction was stirred at 23°C. After 1 hour, the reaction was heated to 70°C. After 18 hours, the reaction was diluted with EtOAc (500 mL) and washed with water (300 mL), 2N NaOH solution (300 mL), saturated sodium thiosulfate solution (300 mL) and brine (250 mL), dried

over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: hexane) affording 11.11 g of 1-bromo-4-chloro-2-iodobenzene.

[0829] **Step C**: Preparation of 3,3,3-Triethoxyprop-1-yne

[0830] A solution of trimethylsilylacetylene (29.4 mL, 20.8 mmol) in diethyl ether (100 mL, anhydrous) was cooled to 0°C in an oven-dried round bottomed flask under nitrogen. The solution was treated dropwise with butyllithium (2.5M solution in hexanes (83.2 mL, 208.0 mmol)). After 1 hour, the reaction mixture was cooled to -78°C.

[0831] A solution of tetraethyl orthocarbonate (21.8 mL, 104.0 mmol) in diethyl ether (50 mL) was added to a separate oven-dried round bottomed flask and cooled to 0°C under nitrogen. A solution of boron trifluoride diethyletherate (17.6 mL, 140.4 mmol) in diethyl ether (25 mL) was added to the tetraethyl orthocarbonate mixture in a dropwise fashion over 20 minutes (via an addition funnel). The white mixture was stirred at 0°C for 5 minutes, and then cooled to -78°C, followed by the addition of the TMS-acetylide solution via cannula.

[0832] After 1 hour, the reaction was removed from the dry ice-acetone bath and stirred at 23°C for 15 minutes. The reaction was then quenched with saturated aqueous K_2CO_3 solution (300 mL) and extracted with diethyl ether (2 x 300 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo affording trimethyl(3,3,3-triethoxyprop-1-ynyl)silane.

[0833] A solution of trimethyl(3,3,3-triethoxyprop-1-ynyl)silane (25 g, 102 mmol) in MeOH (400 mL) was treated with K_2CO_3 (14 g, 102 mmol). The reaction was stirred at 23°C. After 15 hours, the reaction was diluted with pentane (500 mL). The pentane layer was separated, and the MeOH layer was extracted with pentane (2 x 250 mL). The combined pentane layers were washed with water (200 mL), dried over $MgSO_4$, and concentrated (at 220 torr on rotary evaporator). The crude product was filtered through a silica gel plug using 10% diethyl ether/pentane as the eluant. The filtrate was then

concentrated (at 220 torr on rotary evaporator) affording 13.25 g of 3,3,3-triethoxyprop-1-yne.

[0834] **Step D**: Preparation of 1-Bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene

[0835] A suspension of 1-bromo-4-chloro-2-iodobenzene (2.5 g, 7.9 mmol), 3,3,3-triethoxyprop-1-yne (2.4 g, 13.9 mmol), copper(I) iodide, (455 mg, 2.3 mmol), and trans-dichlorobis(triphenylphosphine)palladium(II) (559 mg, 0.79 mmol) was treated with ACN (30 mL). The reaction was capped, evacuated under vacuum, backfilled with argon, and treated with TEA (9.9 mL, 71.6 mmol). The reaction was stirred at 23°C. After 2 hours, the reaction mixture was concentrated in vacuo to remove all solvents, diluted with EtOAc (250 mL) and washed with brine (150 mL), dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (eluant: 4% EtOAc/hexane + 1%TEA), affording 2.6 g of 1-bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene.

[0836] **Step E**: Preparation of Ethyl 1-benzyl-4-(4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)piperidine-4-carboxylate

[0837] In a glovebox, ethyl 1-benzylpiperidine-4-carboxylate (2.0 g, 8.1 mmol), LiNCy2 (1.55g, 8.3 mmol), and toluene (10 mL) were loaded sequentially into a 40 mL vial. In a separate vial, $Pd(OAc)_2$ (22 mg, 0.1 mmol), $P(t\text{-}Bu)_3$ (44 mg, 0.22 mmol), 1-bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene (1.5 g, 4.1 mmol), and toluene (10 mL) were loaded sequentially and were then heated at 100°C for 1 minute. The enolate solution in vial 1 was then added to the reaction mixture in vial 2 via a syringe. The combined mixture was heated at 100°C for 40 minutes. The reaction mixture was cooled to 23°C and passed through a short plug of silica gel eluting with EtOAc (20 mL). The filtrate was concentrated in vacuo and purified by silica gel chromatography (eluant: 5-20% EtOAc/hexane + 2%TEA), affording 833 mg

of ethyl 1-benzyl-4-(4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)piperidine-4-carboxylate.

[0838] **Step F**: Preparation of Ethyl 1-benzyl-4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-4-carboxylate

[0839] A solution of ethyl 1-benzyl-4-(4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)piperidine-4-carboxylate (820 mg, 1.5 mmol) and p-toluenesulfonic acid monohydrate (443 mg, 2.3 mmol) in EtOH (25 mL) and water (5 mL) was stirred at 23°C. After 30 minutes, the solvents were removed in vacuo, and the residue was diluted with EtOAc (200 mL) and washed with 10% HCl solution (100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo affording 620 mg of ethyl 1-benzyl-4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-4-carboxylate. MS m/e = 454.1 $(M+H)^+$.

[0840] **Step G**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-1'-(phenylmethyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate

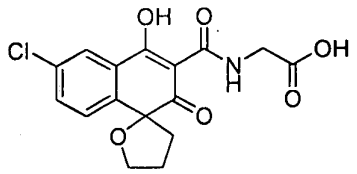
[0841] A suspension of NaH (60% dispersion in mineral oil (36 mg, 895 μmol)) in dioxane (5 mL) in an oven-dried round-bottomed flask was treated with a solution of (E)-benzaldehyde oxime (108 mg, 895 μmol) in DMF (4 mL) in a dropwise fashion. The reaction was stirred at 23°C under nitrogen. After 30 minutes, the reaction was cooled to 0°C, and was then treated with a solution of ethyl 1-benzyl-4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-4-carboxylate (325 mg, 716 μmol) in DMF (4 mL) which was added in a dropwise fashion over 10 minutes. After 1 hour, the solution was diluted with EtOAc (150 mL) and washed with a saturated $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 2-10% MeOH/DCM), affording the cyclized product, a solution of which (160 mg, 376 μmol) in 1,4-dioxane (7 mL) was treated with glycine tert-butyl ester hydrochloride (94.5 mg,

564 μmol) and DIPEA (131 μL, 751 μmol). The reaction was heated to 120°C. After 19 hours, the reaction was cooled to 23°C, diluted with EtOAc (50 mL) and washed with a saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (eluant: 0-5% MeOH/EtOAc + 1% TEA), affording 120 mg (62%, 2 steps) of 1,1-dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-1'-(phenylmethyl)-4H-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate. MS m/e = 512.2 $(M+H)^+$.

[0842] **Step H**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-1'-(phenylmethyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycine

[0843] A solution of 1,1-dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-1'-(phenylmethyl)-4H-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate (117 mg, 229 μmol) in TFA (1701 μL, 22896 μmol) was stirred at 23°C. After 25 minutes, the reaction was concentrated and the product was precipitated by addition of water (20 mL). The solid was collected by filtration, and the residue was washed with water (10 mL) and diethyl ether (5 mL), and dried under vacuum, affording 100 mg (77%) of N-((6-chloro-4-hydroxy-2-oxo-1'-(phenylmethyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycine as the trifluoroacetate salt. MS m/e = 455.2 $(M+H)^+$. Calculated for $C_{26}H_{24}ClF_3N_2O_7$ 454.13.

[0844] **Example 72.** N-((6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl)glycine



[0845] **Step A**: Preparation of Methyl tetrahydrofuran-2-carboxylate

[0846] To a mixture of methyl tetrahydrofuran-2-carboxylic acid (11.6 g, 100 mmol), MeOH (20 mL), and toluene (30 mL) was slowly added

concentrated H_2SO_4 (6 g). The resulting biphasic mixture was heated in a sealed pressure vessel for 1 hour at 95°C. The reaction was then cooled to 0°C and 7N NH_3 in MeOH was added until the pH reached between 7 and 9. Na_2SO_4 was then added, and the reaction was passed through short plug of silica gel, eluting with DCM. The resulting mixture was distilled at 64°C under vacuum to afford the product as a clear liquid.

[0847] **Step B**: Preparation of ((Dihydrofuran-2(3H)-ylidene)(methoxy)-methoxy)trimethylsilane

[0848] To a suspension of LDA (2.6g, 24.3 mmol) in THF (30 mL) at -78°C was slowly added methyl tetrahydrofuran-2-carboxylate (3.0 g, 23.0 mmol). The resulting mixture was stirred at -78°C for 20 minutes, and TMS chloride (2.6g, 24.3 mmol) was slowly added. The reaction was stirred for 1 hour at -78°C and then warmed to room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, avoiding contact with water. Hexanes (20 mL) was then added, and the mixture was passed through a short plug of celite, eluting with hexanes (10 mL). The solution was then concentrated, affording the crude product in good purity.

[0849] **Step C**: Preparation of 2-Bromo-5-chlorobenzenamine

[0850] A solution of 1-bromo-4-chloro-2-nitrobenzene (13.92 g, 58.87 mmol) in MeOH (300 mL) was treated with water (50 mL), ammonium chloride (22.99 g, 429.8 mmol) and iron powder (325 mesh, 16.44 g, 294.4 mmol). The suspension was stirred at 23°C. After 18 hours, the suspension was filtered through celite. The filter cake was washed with MeOH (500 mL). The combined filtrate/washings were concentrated, partitioned in EtOAc/water (500 mL/200 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 200 mL). The organic layers were combined, washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo affording 11.51 g of 2-bromo-5-chlorobenzenamine.

[0851] **Step D**: Preparation of 1-Bromo-4-chloro-2-iodobenzene

[0852] A suspension of 2-bromo-5-chlorobenzenamine (11.348 g, 54.963 mmol) in concentrated HCl (100 mL) was cooled to 0°C and treated dropwise (using an addition funnel) over 20 minutes with a solution of sodium nitrite (4.5506 g, 65.955 mmol) in water (20 mL). The reaction was stirred at 0°C for 75 minutes. A solution of potassium iodide (27.372 g, 164.89 mmol) in water (50 mL) was added, and the reaction was stirred at 23°C. After 1 hour, the reaction was heated to 70°C. After 18 hours, the reaction was diluted with EtOAc (500 mL) and washed with water (300 mL), a 2N NaOH solution (300 mL), saturated sodium thiosulfate solution (300 mL) and brine (250 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: hexane), affording 11.11 g of 1-bromo-4-chloro-2-iodobenzene.

[0853] **Step E**: Preparation of 3,3,3-Triethoxyprop-1-yne

[0854] A solution of trimethylsilylacetylene (29.4 mL, 20.8 mmol) in diethyl ether (100 mL, anhydrous) was cooled to 0°C in an oven-dried round bottomed flask under nitrogen. The solution was treated dropwise with butyllithium (2.5M solution in hexanes (83.2 mL, 208.0 mmol)). After 1 hour, the reaction mixture was cooled to -78°C.

[0855] A solution of tetraethyl orthocarbonate (21.8 mL, 104.0 mmol) in diethyl ether (50 mL) in a separate oven-dried round bottomed flask was cooled to 0°C under nitrogen. The solution was then treated dropwise over 20 minutes with a solution of boron trifluoride diethyletherate (17.6 mL, 140.4 mmol) in diethyl ether (25 mL). The white mixture was stirred at 0°C for 5 minutes, and then cooled to -78°C, followed by the addition of the TMS-acetylide solution via cannula.

[0856] After 1 hour, the reaction was removed from the dry ice-acetone bath and stirred at 23°C for 15 minutes. The reaction was then quenched with saturated aqueous K_2CO_3 solution (300 mL) and extracted with diethyl ether (2 x 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo affording trimethyl(3,3,3-triethoxyprop-1-ynyl)silane.

[0857] A solution of trimethyl(3,3,3-triethoxyprop-1-ynyl)silane (25 g, 102 mmol) in MeOH (400 mL), was treated with K_2CO_3 (14 g, 102 mmol). The reaction was stirred at 23°C. After 15 hours, the reaction was diluted with pentane (500 mL). The pentane layer was separated, and the MeOH layer was extracted with pentane (2 x 250 mL). The combined pentane layers were washed with water (200 mL), dried over $MgSO_4$, and concentrated (at 220 torr on rotary evaporator). The crude product was filtered through a silica gel plug using 10% diethyl ether/pentane as the eluant and concentrated (at 220 torr on rotary evaporator) affording 13.25 g of 3,3,3-triethoxyprop-1-yne.

[0858] **Step F**: Preparation of Ethyl 3-(2-bromo-5-chlorophenyl)propiolate

[0859] A suspension of 1-bromo-4-chloro-2-iodobenzene (5.4 g, 17.0 mmol), 3,3,3-triethoxyprop-1-yne (4.4 g, 25.6 mmol), copper(I) iodide (976 mg, 5.1 mmol), and trans-dichlorobis(triphenylphosphine)palladium(II) (1.19 g, 1.7 mmol) in ACN (60 mL) was degassed and backfilled with argon. The resulting mixture was treated with TEA (22.0 mL, 157.9 mmol). The reaction flask was capped with a septum and stirred at 23°C. After 90 minutes, the reaction was diluted with EtOAc (300 mL) and washed with water (150 mL). The aqueous layer was extracted with EtOAc (300 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated in vacuo, dissolved in EtOH (50 mL) and water (5 mL) and then treated with p-toluenesulfonic acid monohydrate (5 mg). After stirring at 23°C for 60 minutes, the solution was concentrated, dissolved in diethyl ether (300 mL) and washed with saturated $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo affording 2.7 g of ethyl 3-(2-bromo-5-chlorophenyl)propiolate.

[0860] **Step G**: Preparation of Methyl 2-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydrofuran-2-carboxylate

[0861] Ethyl 3-(2-bromo-5-chlorophenyl)propiolate (1.2g, 4.16 mmol), PdBr(Pt-Bu_3) dimer (32mg, 0.04mmol), and DMF (5mL) were loaded into a vial in a glove box, and the resulting mixture was stirred at 80°C for 4-5 minutes. This mixture was then transferred via syringe into a separate vial containing $ZnCl_2$ hydrate (0.84g), ((dihydrofuran-2(3H)-ylidene)(methoxy)methoxy)trimethylsilane (1.26g, 6.2 mmol), and DMF (5 mL). The combined mixture was then heated at 80°C for 40 minutes, at which time more of the Pd catalyst and ((dihydrofuran-2(3H)-ylidene)(methoxy)methoxy) trimethylsilane were added as necessary. Upon completion, the reaction mixture was cooled to room temperature and filtered through a silica gel plug, eluting with EtOAc (~30 mL). The combined solution was concentrated in vacuo. Purification by silica flash chromatography (5-10% EtOAc/hexanes) gave the desired phenyl carboxylate as a brown liquid.

[0862] **Step H**: Preparation of Ethyl 6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-carboxylate

[0863] To a suspension of NaH (74 mg, 1856 μmol) in 1,4-dioxane (11 mL, 1485 μmol) in a flame-dried flask was added dropwise (E)-benzaldehyde oxime (0.14 mL, 1856 μmol) in DMF (9.1 mL, 1485 μmol). The reaction was stirred for 30 minutes under argon and then cooled to -20°C. The reaction mixture was next treated dropwise with methyl 2-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydrofuran-2-carboxylate (500 mg, 1485 μmol) in DMF (9.109 mL, 1485 μmol). The reaction was maintained at -20°C. Upon completion of the reaction, EtOAc was added and the reaction was washed with 1M aqueous HCl, H_2O, and brine.

[0864] Purification by silica flash chromatography (0.5-3% MeOH/DCM) gave the desired ester. 1N aqueous NaOH was added to the pooled fractions, and the aqueous layer was acidified with concentrated HCl and extracted with EtOAc. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the pure ester as a white solid. MS m/e = 323.2 $(M+H)^+$.

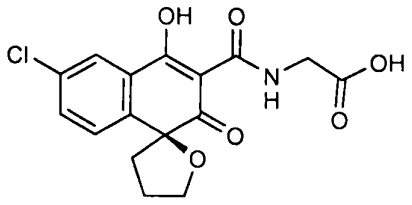
[0865] **Step I**: Preparation of 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl) glycinate

[0866] A mixture of tert-butyl 2-aminoacetate hydrochloride (399 mg, 2380 μmol) and ethyl 6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-carboxylate (256 mg, 793 μmol) in 1,4-dioxane (7932 μL, 793 μmol), was treated with DIPEA (829 μL, 4759 μmol) and warmed to 80°C. After 2 hours, the reaction was cooled to room temperature, diluted with EtOAc, washed with H_2O (2x) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the glycine ester as a white solid. MS m/e = 430.8 $(M+Na)^+$.

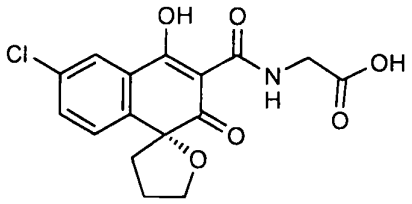
[0867] **Step J**: Preparation of N-((6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl)glycine

[0868] 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl) glycinate (323 mg, 793 μmol) was mixed with TFA (7930 μL, 793 μmol) and stirred for 30 minutes. The product was co-evaporated with DCM (5x) to give the title compound. MS m/e = 352.0 $(M+H)^+$. Calculated for $C_{16}H_{14}ClNO_6$ 351.05.

[0869] **Examples 73 and 74.** N-(((2S)-6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl)glycine and N-(((2R)-6'-Chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl)glycine

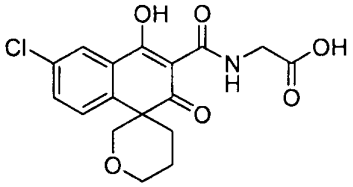


and



[0870] The title compounds were obtained by chiral separation of N-((6'-chloro-4'-hydroxy-2'-oxo-4,5-dihydro-spiro[furan-2,1'-naphthalen]-3'-yl)carbonyl)glycine (Example 72) into its two enantiomers using chiral HPLC. MS m/e = 352.0 $(M+H)^+$. Calculated for $C_{16}H_{14}ClNO_6$ 351.05.

[0871] **Example 75.** N-((6-Chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycine



[0872] **Step A**: Preparation of 1-Chloro-3-(chloromethoxy)propane.

[0873] Paraformaldehyde (18 g, 598 mmol) in DCM (239 mL, 598 mmol) was cooled to -10°C, and HCl gas (22 g, 598 mmol) was bubbled through the reaction until the solution became clear. 3-Chloropropan-1-ol (50 mL, 598 mmol) was then added dropwise, the HCl gas was discontinued, and the reaction was stirred for 10 minutes. The reaction was poured into a suspension of anhydrous K_2CO_3 in DCM (893 mL, 598 mmol) and stirred until bubbling ceased. The reaction was filtered and concentrated in vacuo to give the desired product as a clear liquid.

[0874] **Step B**: Preparation of 3-(4-Chlorophenyl)-tetrahydro-2H-pyran-3-carbonitrile

[0875] A mixture of 2-(4-chlorophenyl)acetonitrile (73 g, 483 mmol) and 1-chloro-3-(chloromethoxy)propane (69.1 g, 483 mmol) in ethoxyethane (242

mL, 483 mmol) was added dropwise to a mixture of NaH (57 g, 1437 mmol) in 1-methylpyrrolidin-2-one (1208 mL, 483 mmol) at -20°C. The reaction was stirred for 12 hours and then slowly quenched with H_2O. The reaction mixture was extracted with ether (5x), and the combined organic layers were washed with H_2O (3x) and brine (1x), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the desired nitrile as a yellow oil. MS m/e = 223.2 $(M+H)^+$.

[0876] **Step C**: Preparation of 3-(4-Chlorophenyl)-tetrahydrofuran-3-carboxylic acid

[0877] A solution of 3-(4-chlorophenyl)-tetrahydro-2H-pyran-3-carbonitrile (8.62g, 39 mmol), 9M H_2SO_4 (39 mL, 39 mmol), and 1,4-dioxane (8 mL, 39 mmol) was stirred at 100°C. Upon completion of the reaction, the reaction was cooled and extracted with EtOAc. The organic layer was washed with 2N aqueous NaOH. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc. This was repeated and the combined organic layers were then dried over Na_2SO_4, filtered, and concentrated in vacuo to give the desired acid as a light yellow solid. MS m/e = 263.2 $(M+Na)^+$.

[0878] **Step D**: Preparation of Diethyl 2-(3-(4-chlorophenyl)-tetrahydro-2H-pyran-3-carbonyl)malonate

[0879] 3-(4-Chlorophenyl)-tetrahydrofuran-3-carboxylic acid (2.73 g, 11 mmol) was dissolved in thionyl chloride (8 mL, 113 mmol) and heated at 70°C for 3 hours. The solution was cooled, concentrated under reduced pressure, and pumped down under high vacuum for 3 hours. In a flame-dried round-bottom flask, $MgCl_2$ (1 g, 11 mmol) was added to diethyl malonate (2 mL, 11 mmol) in ACN (23 mL, 11 mmol) and cooled to 0°C. The reaction was stirred for 15 minutes and then TEA (3 mL, 24 mmol) was slowly added. The resulting solution was allowed to warm to room temperature while stirring for 3 hours. The furan acid chloride was dissolved in ACN (10 mL, 11 mmol) and added to the malonate solution. The resulting mixture was stirred at 50°C for 12 hours. Upon completion, the reaction was concentrated and mixed with 1N aqueous

HCl and EtOAc. The aqueous layer was washed with EtOAc (2x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica flash chromatography (10-60% EtOAc/hexane) gave the desired malonate as a light yellow oil. MS m/e = 383.2 $(M+H)^+$.

[0880] **Step E**: Preparation of Ethyl 6-chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-carboxylate

[0881] A mixture of diethyl 2-(3-(4-chlorophenyl)-tetrahydro-2H-pyran-3-carbonyl)malonate (1.7771 g, 4642 µmol) in IPAc (3868 µL, 4642 µmol) was added to concentrated H_2SO_4 (11605 µL, 4642 µmol) at 0°C. The reaction was stirred at 0°C and then slowly warmed to room temperature. The reaction was poured over ice and extracted with EtOAc. The aqueous layer was washed with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica flash chromatography (1-5% MeOH/DCM) gave the desired naphthalenone as a white solid. MS m/e = 337.2 $(M+H)^+$.

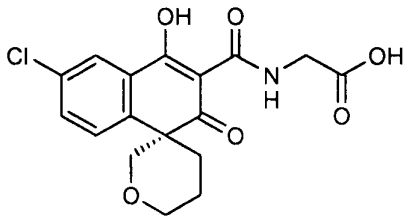
[0882] **Step F**: Preparation of 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycinate

[0883] To a solution of 1,1-dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycinate (85 mg, 252 µmol) in 1,4-dioxane (2524 µL, 252 µmol) was added DIPEA (132 µL, 757 µmol). The resulting reaction mixture was heated at 80°C for 3 hours. The reaction was then cooled, diluted with EtOAc, washed with water (2x) and brine, dried over Na_2SO_4, and concentrated in vacuo to give the desired glycine ester as a light yellow oil. MS m/e = 422.0 $(M+H)^+$.

[0884] **Step G**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycine

[0885] 1,1-Dimethylethyl N-((6-chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycinate (106 mg, 252 μmol) was mixed with TFA (6300 μL, 252 μmol) and stirred for 30 minutes. The product was co-evaporated with DCM (5x) to give the title compound. MS m/e = 366.0 $(M+H)^+$. Calculated for $C_{17}H_{16}ClNO_6$ 365.07.

[0886] **Examples 76 and 77.** N-(((1S)-6-Chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycine and N-(((1R)-6-Chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycine



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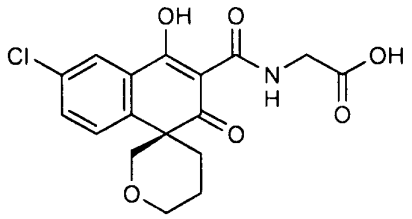
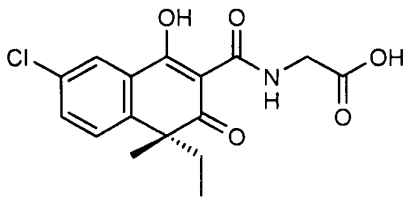


[0887] The title compounds were obtained by chiral separation of N-((6-chloro-4-hydroxy-2-oxo-5',6'-dihydro-spiro[naphthalene-1,3'-pyran]-3-yl)carbonyl)glycine (Example 75) into its separate enantiomers using chiral HPLC. MS m/e = 366.0 $(M+H)^+$. Calculated for $C_{17}H_{16}ClNO_6$ 365.07.

[0888] **Examples 78 and 79.** N-(((1R)-6-Chloro-4-hydroxy-1-ethyl-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine and N-(((1S)-6-Chloro-4-hydroxy-1-ethyl-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



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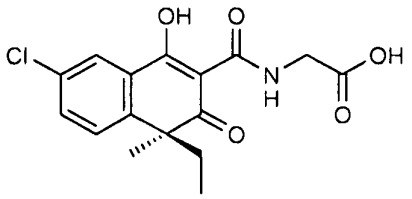
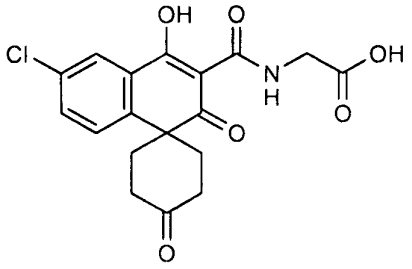


[0889] The title compounds were obtained by chiral separation of N-((6-chloro-1-ethyl-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine (Example 15) into its separate enantiomers using chiral HPLC. MS (m/z) = 338 $(M+H)^+$. Calculated for $C_{16}H_{16}ClNO_5$ 337.07.

[0890] **Example 80.** N-((6'-Chloro-4'-hydroxy-2',4-dioxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycine



[0891] **Step A**: Preparation of 1-Bromo-4-chloro-2-iodobenzene

[0892] A stirred mixture of copper(II) bromide (11 mL, 237 mmol) in 250 mL ACN at 0°C was slowly treated with tert-butyl nitrite (33 mL, 276 mmol). The mixture was then warmed to 65°C, and stirred for 30 minutes. The mixture was next treated dropwise with a mixture of 4-chloro-2-iodoaniline (50 g, 197 mmol) in 100 mL ACN. The resulting mixture was stirred for 1 hour. The mixture was cooled to room temperature and poured over 200 mL ice/10%HCl. The mixture was extracted with ether (3 x 100 mL). The

combined organic layers were washed with H_2O (2 x 100 mL), 1% ammonia water (2 x 100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 63 g brown oil as crude product. The crude product was purified by running it through a short silica plug eluting with 5% ether / hexane to give 54.2 g of the title compound as a yellow solid.

[0893] **Step B**: Preparation of 1-Bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene

[0894] A mixture of 1-bromo-4-chloro-2-iodobenzene (10 g, 32 mmol) in 100 mL degassed ACN and TEA (29 g, 284 mmol), was treated with 3,3,3-triethoxyprop-1-yne (6.0 g, 35 mmol), copper(I) iodide (0.60 g, 3.2 mmol), and dichlorobis(triphenylphosphine)palladium(II) (1.1 g, 1.6 mmol). The mixture was stirred at room temperature for 2 hours at room temperature (the mixture turned dark green after 5 minutes). TLC showed that all starting material was converted, and a new spot was produced. The mixture was concentrated in vacuo. The residue was diluted with 100 mL ether, washed with H_2O (2 x 20 mL), 5% ammonia water (2 x 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography pretreated with TEA and eluted with 0-15 % EtOAc/hexane to give 7.6 g of the product as a pale yellow oil. The oil solidified after it was stored in the refrigerator.

[0895] **Step C**: Preparation of Ethyl 4'-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-5,5-dimethyl-spiro[1,3-dioxane-2,1'-cyclohexane]-4'-carboxylate

[0896] A stirred mixture of dicyclohexylamine (5.5 g, 31 mmol) in 30 mL toluene at 0°C was treated with butyllithium (12 mL, 31 mmol) and stirred for 15 minutes at 0°C. The resulting mixture was treated with ethyl 5,5-dimethyl-spiro[1,3-dioxane-2,1'-cyclohexane]-4'-carboxylate (7.8 g, 31 mmol) and stirred at room temperature for 10 minutes.

[0897] To a different round-bottom flask was added 50 mL toluene and 1-bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene (9.2 g, 25 mmol). The flask was degassed by applying a vacuum and then filling it with nitrogen. The mixture was treated with $[PdBrP(t\text{-}Bu)_3]_2$ (0.84 g, 2.2 mmol) at room temperature. The reaction was then warmed to 85°C and quickly treated with above anion mixture (within 3 minutes). The mixture was stirred under nitrogen, warmed to 100°C, and stirred for 20 minutes. TLC showed a new spot. The resulting mixture was cooled to room temperature, filtered through a short silica plug, and washed with 500 mL 4:1 = hexane/EtOAc. The organic solution was concentrated in vacuo, diluted with 100 mL EtOAc, washed with 5 % HCl (20 mL), H_2O (3 x 20 mL), and brine 20 mL. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 0-15% EtOAc/hexane to give 3.68 g of the product as a yellow oil. MS (m/z) = 463 $(M+H)^+$.

[0898] **Step D**: Preparation of Ethyl 6"-chloro-4"-hydroxy-5,5-dimethyl-2"-oxo-dispiro[1,3-dioxane-2,1'-cyclohexane-4',1"-naphthalene]-3"-carboxylate

[0899] A stirred mixture of NaH (60% dispersion in mineral oil (0.39 mL, 9.3 mmol)) in 40 mL dioxane at room temperature, was treated with a mixture of (E)-benzaldehyde oxime (1.0 g, 8.6 mmol) in 40 mL DMF. The resulting mixture was stirred for 30 minutes. The mixture was then cooled to 0°C and treated with a mixture of ethyl 4'-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-5,5-dimethyl-spiro[1,3-dioxane-2,1'-cyclohexane]-4'-carboxylate (3.6 g, 7.8 mmol) in 30 mL DMF. The resulting mixture was stirred for 1 hour. The mixture was then carefully quenched with 10 mL H_2O and brought to a pH of 5 by addition of 10 % HCl. The mixture was extracted with ethyl ether (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography eluting with 20-30 % EtOAc to give 2.2 g of the product as a pale yellow solid. MS (m/z) = 435 $(M+H)^+$.

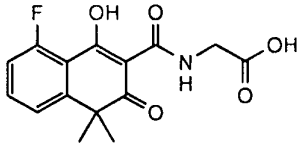
[0900] **Step E**: Preparation of 1,1-Dimethylethyl N-((6"-chloro-4"-hydroxy-5,5-dimethyl-2"-oxo-dispiro[1,3-dioxane-2,1'-cyclohexane-4',1"-naphthalen]-3"-yl)carbonyl)glycinate

[0901] A mixture of ethyl 6"-chloro-4"-hydroxy-5,5-dimethyl-2"-oxo-dispiro[1,3-dioxane-2,1'-cyclohexane-4',1"-naphthalene]-3"-carboxylate (69 mg, 159 μmol) and tert-butyl 2-aminoacetate hydrochloride (53 mg, 317 μmol) in 1.5 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (62 mg, 476 μmol). The mixture was warmed to 95°C and stirred for 2hours, M+1= 420. The mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography eluting with 10-20 % EtOAc/hexane to give 66 mg of the title compound as a white yellow solid. MS (m/z) = 520 $(M+H)^+$.

[0902] **Step F**: Preparation of N-((6'-Chloro-4'-hydroxy-2',4-dioxo-spiro[cyclohexane-1,1'-naphthalen]-3'-yl)carbonyl)glycine

[0903] A mixture of 1,1-dimethylethyl N-((6"-chloro-4"-hydroxy-5,5-dimethyl-2"-oxo-dispiro[1,3-dioxane-2,1'-cyclohexane-4',1"-naphthalen]-3"-yl)carbonyl)glycinate (18 mg, 35 μmol) in 1 mL TFA was stirred at room temperature for 30 minutes, M+1= 378. The mixture was concentrated in vacuo, and dried under high vacuum to give 11 mg of the product as an off-white solid. MS (m/z) = 378 $(M+H)^+$. Calculated for $C_{18}H_{16}ClNO_6$ 377.07.

[0904] **Example 81.** N-((5-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0905] **Step A**: Preparation of 3-Fluoro-2-iodobenzoic acid

[0906] Sodium nitrite (6.7 g, 97 mmol) in water (25 mL) was added to a solution of 2-amino-3-fluorobenzoic acid (10.0 g, 64 mmol) in DMSO (25 mL) and 30% H_2SO_4 (75mL) at 0°C. The mixture was stirred for 1 hour at 0°C and

then potassium iodide (27 g, 161 mmol) was added dropwise as a solution in water (25 mL). The ice bath was removed and the mixture was stirred at room temperature for 4 hours, and then partitioned between EtOAc and 2M sodium sulfite. The layers were mixed, separated, and the organic layer was washed with 2M sodium sulfite once and brine once, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 14.90 g of a yellow solid. MS m/e = 265 $(M-H)^+$.

[0907] **Step B**: Preparation of Ethyl 2-(3-fluoro-2-iodophenyl)acetate

[0908] A solution of 3-fluoro-2-iodobenzoic acid (14.90 g, 56.0 mmol) was stirred in thionyl chloride (150 mL) for 1 hour at reflux. The mixture was cooled to room temperature, and the excess thionyl chloride was removed in vacuo to give the corresponding acid chloride. Et_2O (20 mL) was added, and a solution of $TMSCHN_2$ (2.0M in Et_2O, 110 mL, 220 mmol) was added. The mixture was stirred for 4 hours, and the excess reagent was quenched by the addition of AcOH. The mixture was then partitioned between EtOAc (200 mL) and saturated $NaHCO_3$ solution. The layers were separated, and the organic layer was washed twice with saturated $NaHCO_3$, once with water, and once with brine once. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. This material was dissolved in EtOH (200 proof) and silver(I)oxide (2.60 g, 11.2 mmol) was added. The suspension was heated to 80°C for 30 minutes, cooled to room temperature, and filtered through celite. The filtrate was concentrated in vacuo, and the resulting oil was purified by flash chromatography to give 9.90 g of product as a yellow oil.

[0909] **Step C**: Preparation of Ethyl 2-(3-fluoro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)acetate

[0910] Bis(triphenylphosphine)palladium(II) chloride (456 mg, 0.649 mmol), cuprous iodide (371 mg, 1.95 mmol), and ethyl 2-(3-fluoro-2-iodophenyl)acetate (2.0 g, 6.49 mmol), were mixed in a 20 mL microwave tube. The tube was sealed, and ACN (12 mL) and TEA (6 mL) were added. The mixture was placed under argon atmosphere and 3,3,3-triethoxyprop-1-yne (1.68

g, 9.74 mmol) was added via syringe. The reaction was heated at 60°C for 16 hours, cooled to room temperature, and concentrated under vacuum. The residue was purified by flash chromatography to give 820 mg of ethyl 2-(3-fluoro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)acetate as a yellow oil.

[0911] **Step D**: Preparation of Ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate

[0912] Ethyl 2-(3-fluoro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)acetate (820 mg, 2.32 mmol) was added as a solution in DMF (6 mL) to a suspension of NaH (139 mg, 5.80 mmol) in DMF (4 mL) at 0°C. The mixture was stirred for 10 minutes, and MeI (0.58 mL, 9.28 mmol) was added via syringe. The ice bath was removed, and the mixture was stirred at room temperature for 1 hour, quenched with saturated $NaHCO_3$, and extracted with EtOAc (3x). This material was dissolved in EtOH (5 mL) and water (1 mL) and p-TSA (cat.) was added. The mixture was stirred for 30 minutes, quenched with saturated $NaHCO_3$, and extracted with EtOAc (3x). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified to give 452 mg ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate as a light yellow oil. MS m/e = 307 $(M+H)^+$.

[0913] **Step E**: Preparation of Ethyl 5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0914] A solution of (E)-Benzaldehyde oxime (214 mg, 1.76 mmol) in dry DMF (9 mL) was added to a suspension of NaH (42 mg, 1.76 mmol) in dry dioxane (9 mL). The mixture was stirred for 30 minutes at room temperature, cooled to 0°C, and a solution of ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate (450 mg, 1.4 mmol) in DMF (9 mL) was added. The mixture was stirred at 0°C for 3 hours and then warmed to room temperature and stirred for 1 hour. Water was added, and the mixture was extracted with EtOAc (2x). The aqueous layer was then made acidic with 2 mL 10% HCl. This was extracted with EtOAc (3x), and the combined organic

layers were dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by flash chromatography to give 226 mg ethyl 5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate as a colorless oil. MS m/e = 279 $(M+H)^+$.

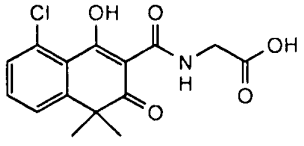
[0915] **Step F**: Preparation of 1,1-Dimethylethyl N-((5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0916] DIPEA (0.14 mL, 809 μmol, tert-butylglycine hydrochloride (136 mg, 809 μmol), and ethyl 5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (150 mg, 539 μmol) were heated to 75°C in dioxane (4 mL) for 3 hours. The resulting mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography to give 116 mg of 1,1-dimethylethyl N-((5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate as a white solid. MS m/e = 386 $(M+Na)^+$.

[0917] **Step G**: Preparation of N-((5-Fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0918] 1,1-Dimethylethyl N-((5-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (116 mg, 319 μmol) was stirred in TFA (5 mL) for 15 minutes. The solvent was then removed in vacuo, and the residue was partitioned between DCM and water. The DCM layer was removed, and the solvent was removed in vacuo to give the product as a light yellow solid. MS m/e = 308 $(M+H)^+$. Calculated for $C_{15}H_{14}FNO_5$ 307.09.

[0919] **Example 82.** N-((5-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0920] **Step A**: Preparation of 3-Chloro-2-iodobenzoic acid

[0921] A solution of sodium nitrite (4.82 g, 69.9 mmol) in water (25 mL) was added dropwise via addition funnel to a solution of 2-amino-3-chlorobenzoic acid (8.0 g, 46.6 mmol) in DMSO (25 mL) and 30% H_2SO_4 (75 mL) that had previously been cooled to 0°C. The mixture was stirred at 0°C for 1 hour, at which time a solution of potassium iodide (19.3 g, 117 mmol) in water (25 mL) was added via addition funnel. The ice bath was removed, and the mixture was stirred for 2 hours. EtOAc (200 mL) was added, and the mixture was washed with 2N sodium sulfite (3 x). The organic layer was then washed once with water and once with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 8.83 g of 3-chloro-2-iodobenzoic acid as a yellow solid.

[0922] **Step B**: Preparation of Ethyl 2-(3-chloro-2-iodophenyl)acetate

[0923] 3-Chloro-2-iodobenzoic acid (8.83 g, 31.3 mmol) was stirred in thionyl chloride (125 mL) at reflux for 2 hours. The mixture was cooled to room temperature, the thionyl chloride was removed under vacuum, and the residue was azeotroped once with toluene to give the acid chloride as a dark red solid. Trimethylsilyldiazomethane (2.0M in Et_2O, 124 mmol) was added to the acid chloride, and the mixture was stirred for 5 hours at room temperature. Excess reagent was destroyed by the addition of AcOH (until bubbling stopped), and the mixture was partitioned between EtOAc and saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with water once, brine once, dried over anhydrous $MgSO_4$ and concentrated in vacuo. This material was dissolved in absolute EtOH (250 mL) and silver (I) oxide (catalytic amount) was added. The mixture was heated at 80°C for 30 minutes, cooled to room temperature, and filtered through celite. The filtrate was concentrated and purified by flash chromatography to give 7.89 g of ethyl 2-(3-chloro-2-iodophenyl)acetate as an orange oil.

[0924] **Step C**: Preparation of Ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate

[0925] Cuprous iodide (CuI) (352 mg, 1.85 mmol), dichlorobis(triphenylphosphine)palladium(II) (432.5 mg, 0.62 mmol), and ethyl 2-(3-chloro-2-iodophenyl)acetate (2.0 g, 6.16 mmol) were mixed in a 20 mL microwave tube. ACN (14 mL) and TEA (4 mL) were added, the mixture was degassed and backfilled with argon, and 3,3,3-triethoxyprop-1-yne (1.27 g, 7.40 mmol) was added via syringe. The mixture was stirred for 18 hours at 45°C, cooled to room temperature, concentrated in vacuo, and the residue was flushed through a plug of silica gel with a 1:1 mixture of EtOAc and hexane. The eluent was concentrated in vacuo, dissolved in 20 mL dry DMF, and added to a suspension of NaH (370 mg, 15.4 mmol) in DMF (20 mL) that had previously been cooled to 0°C. The mixture was stirred for 10 minutes and MeI (1.15 mL, 18.5 mmol) was added via syringe. The mixture was stirred overnight at room temperature, quenched with aqueous NH_4Cl, and extracted with EtOAc (3 x). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. This material was dissolved in EtOH (15 mL) and water (2 mL). p-TSA (10 mg), was added and the mixture was stirred for 30 minutes. The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted with EtOAc three times. The extracts were dried over anhydrous $MgSO_4$ and concentrated to give a red oil, which was purified by flash chromatography to give 520 mg of ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate as a light yellow oil. MS m/e = 323 $(M+H)^+$.

[0926] **Step D**: Preparation of Ethyl 5-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0927] A solution of (E)-benzaldehyde oxime (234 mg, 1.93 mmol) in dry DMF (9 mL) was added to a suspension of NaH (46 mg, 1.93 mmol) in dioxane (9 mL) at room temperature. The mixture was stirred for 30 minutes and then cooled to 0°C. A solution of ethyl 3-(2-chloro-6-(1-ethoxy-2-methyl-1-oxopropan-2-yl)phenyl)propiolate (520 mg, 1.61 mmol) in dry DMF (9 mL) was added, and the mixture was stirred at 0°C for 3 hours and then at room temperature for 1 hour. The mixture was quenched with water and then washed

with EtOAc (2 x). The aqueous layer was made acidic with 10 % HCl and then extracted with EtOAc (2 x). The extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography to give 210 mg of ethyl 5-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate as a colorless oil. MS m/e = 295 $(M+H)^+$.

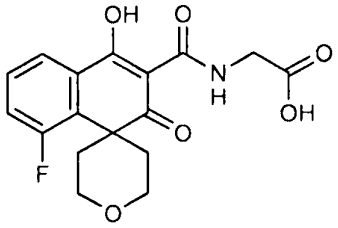
[0928] **Step E**: Preparation of tert-Butyl N-((5-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0929] Ethyl 5-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (210 mg, 713 µmol, 1.0 eq) and glycine tert-butyl ester hydrochloride (143 mg, 855 µmol, 1.20 eq) were mixed in dioxane (5 mL) in a round bottom flask. DIPEA (186 µL, 1069 µmol, 1.5 eq) was added via syringe, and the reaction was stirred at 75°C for 4 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a yellow solid. The crude product was purified by silica flash chromatography (0-50% DCM/hexane) to give the desired compound as a white solid (204 mg). MS m/e = 380 $(M+H)^+$.

[0930] **Step F**: Preparation of N-((5-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0931] tert-Butyl N-((5-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (204 mg, 537 µmol) was stirred in TFA (2 mL, 26924 µmol) for 25 minutes. Water was added. The resulting precipitate was filtered and washed with water to give a white solid (169 mg). MS m/e = 324 $(M+H)^+$. Calculated for $C_{15}H_{14}ClNO_5$ 323.06.

[0932] **Example 83.** N-((8-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[0933] **Step A**: Preparation of Methyl 2-(2-fluorophenyl)acetate

[0934] To a stirred solution of 2-fluorophenylacetic acid (9.6 g, 62 mmol) in MeOH (100 mL) was added concentrated HCl (0.7 mL, 19 mmol). The solution was heated at 68°C for 4 hours, and then the reaction was concentrated in vacuo to remove MeOH. The residue was dissolved in ether and then washed with saturated $NaHCO_3$ solution (1 x 50 mL). The organic extracts were separated, dried with Na_2SO_4, filtered and concentrated to give a yellow oil (10g). MS m/e = 169.0 $(M+H)^+$.

[0935] **Step B**: Preparation of Methyl 4-(2-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylate

[0936] To an ice-bath cooled, stirred solution of methyl 2-(2-fluorophenyl)acetate (3.4 g, 20 mmol) in THF (100 mL) was added NaH (1.8 g, 44 mmol). The reaction was stirred at 0°C for 10 minutes and then dichloroethyl ether (2.7 mL, 22 mmol) and tetrabutylammonium bromide (0.33 g, 1.0 mmol) were added sequentially. The yellow reaction mixture was stirred for 16 hours at room temperature and then quenched with a saturated ammonium chloride solution. The aqueous layer was extracted with EtOAc (3 x 60 mL), and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to afford a yellow oil. Purification by flash chromatography (100 % DCM) provided a pale yellow oil (2.5 g). MS m/e = 239.0 $(M+H)^+$.

[0937] **Step C**: Preparation of 4-(2-Fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid

[0938] A solution of methyl 4-(2-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylate (2.45 g, 10 mmol), water (10 mL, 555 mmol), EtOH (50 mL, 10

mmol) and KOH (2.3 g, 41 mmol) was placed in a sealed flask and then heated at 130°C for 10 hours. After cooling to room temperature, the reaction was concentrated to afford a yellow oil. The residue was diluted with water (100 mL) and extracted with DCM (120 mL). The separated aqueous phase was then acidified to pH = 1 and then extracted with EtOAc (3 x 10 mL). The organic later was dried (Na_2SO_4), filtered, and concentrated to afford a tan solid (1.9 g). MS m/e = 223.1 (M-1)-.

[0939] **Step D**: Preparation of Diethyl 2-(4-(2-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate

[0940] To a stirred solution of 4-(2-fluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (1.9 g, 8.5 mmol) in DCM (50 mL) and DMF (5 mL) was carefully added oxalyl chloride (0.79 mL, 8.9 mmol). Gas evolution was observed. The reaction was stirred at room temperature for 3 hours. In a separate flask was combined IPAc (1.0 mL, 8.7 mmol), diethyl malonate (1.6 mL, 11 mmol). and anhydrous $MgCl_2$ (1.0 g, 11 mmol). The resulting white slurry was stirred for 30 minutes, and then TEA (4.0 mL, 29 mmol) was added and the reaction was stirred for 2.5 hours. The reaction was chilled in an ice water bath for 10 minutes, and then the concentrated acid chloride oil was added via syringe over 10 minutes. The ice bath was removed, and the reaction was stirred for 16 hours at 50°C. After cooling to room temperature, the reaction was acidified with 5N HCl solution (100 mL). The aqueous layer was removed, and the organic layer was washed with saturated $NaHCO_3$ solution (150 mL). The aqueous layer was removed, and the organic extract was washed with water. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford a dark colored oil. The crude reaction mixture was used in the next step.

[0941] **Step E**: Preparation of Ethyl 8-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[0942] A flask containing H_2SO_4 (12 mL, 218 mmol) and P_2O_5 (12 g, 87 mmol) was cooled in an ice bath for 20 minutes under nitrogen, and then diethyl

2-(4-(2-fluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (8.0 g, 22 mmol) was added dropwise over 10 minutes. The reaction was stirred an additional 10 minutes at 0°C, and then was stirred at room temperature for 1 hour. The reaction was poured over ice and allowed to melt. The aqueous mixture was extracted with EtOAc (3 x 100 mL) and then the separated organic extracts were dried (Na_2SO_4), filtered and concentrated to provide an oil. Flash chromatography (20% EtOAc/hexane) afforded an oil (3.6 g). MS m/e = 321.0 $(M+H)^+$.

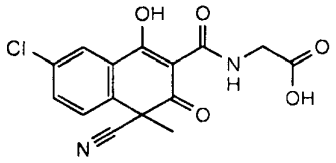
[0943] **Step F**: Preparation of 1,1-Dimethylethyl N-((8-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[0944] In a sealed flask was combined ethyl 8-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (1.8 g, 5.6 mmol), dioxane (75 mL), tert-butyl 2-aminoacetate hydrochloride (3.8 g, 22 mmol), and N-ethyl-N-isopropylpropan-2-amine (3.9 mL, 22 mmol). The flask was sealed and heated at 90°C for 10 hours. After cooling to room temperature, the reaction was concentrated to give a solid that was purified by flash chromatography (20% EtOAc/hexane) to afford a white solid (1.9 g). MS m/e = 406.1 $(M+H)^+$.

[0945] **Step G**: Preparation of N-((8-Fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[0946] In a flask was combined 1,1-dimethylethyl N-((8-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (1.7 g, 4.2 mmol) and TFA (50 mL). The reaction was stirred for 15 minutes and then concentrated to afford an oil. Water was added, affording a white precipitate that was filtered off and washed with water and ether. The solid was dried under vacuum at 50°C (1.4 g, 98%). MS m/e = 348 $(M-1)^-$. Calculated for $C_{17}H_{16}FNO_6$ 349.1.

[0947] **Example 84.** N-((6-Chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0948] **Step A**: Preparation of (4-Chloro-2-iodophenyl)methanol

[0949] 4-Chloro-2-iodobenzoic acid (5.0 g, 18 mmol) was dissolved in THF (40 mL) and cooled to 0°C. Borane-THF complex (1M in THF) (35 mL, 35 mmol) was added by syringe. The solution was allowed to warm to room temperature and stirred overnight. The reaction was monitored by LCMS and TLC. When the reaction was complete, water was added until gas evolution ceased and then the THF was removed under vacuum. EtOAc (100 mL) was added, and the organic layer was washed with water (3 x 50 mL), brine (3 x 50 mL), dried with $MgSO_4$, and concentrated in vacuo resulting in a white solid.

[0950] **Step B**: Preparation of 2-(4-Chloro-2-iodophenyl)acetonitrile

[0951] (4-Chloro-2-iodophenyl) methanol (4.67 g, 17 mmol) and PPh_3 (6 mL, 26 mmol) were stirred in Et_2O at 0°C. Diisopropyl azodicarboxylate (5 mL, 26 mmol) was added dropwise, and the reaction was stirred for 20 minutes (a white precipitate formed). A solution of acetone cyanohydrin (2 mL, 26 mmol) in diethyl ether (5 mL) was added dropwise to the reaction. The resulting solution was stirred for 5 minutes at 0°C and then allowed to warm to room temperature over two hours. The reaction was monitored by TLC and LCMS. The mixture was filtered, and the filtrate was concentrated in vacuo. Purification was done using silica flash chromatography with a gradient of 0-15% EtOAc/hexanes. MS m/e = 278 $(M+H)^+$.

[0952] **Step C**: Preparation of 2-(4-Chloro-2-iodophenyl)propanenitrile

[0953] 2-(4-Chloro-2-iodophenyl) acetonitrile (1.070 g, 3.9 mmol) was dissolved in THF (50 mL) and cooled to 0°C. Sodium tert-butoxide (0.74 g, 7.7

mmol) was added, and the solution was stirred for 10 minutes (the reaction color changed from colorless to orange.) MeI (0.24 mL, 3.9 mmol) was then added dropwise as a solution in THF (10 mL). The reaction was complete in ten minutes as determined by TLC. The crude residue was purified by silica flash chromatography using 0-15% EtOAc/hexanes. MS m/e = 292 $(M+H)^+$.

[0954] **Step D**: Preparation of 2-(4-Chloro-2-(2-(trimethylsilyl)ethynyl)phenyl)propanenitrile

[0955] 2-(4-Chloro-2-iodophenyl)propanenitrile (0.620 g, 2.13 mmol), (trimethylsilyl)acetylene (0.451 mL, 3.19 mmol), copper(I) iodide (0.0144 mL, 0.425 mmol), dichlorobis(triphenylphosphine)palladium (II) (0.149 g, 0.213 mmol), and TEA (20 mL) were stirred at 70°C for 3 hours. The reaction was monitored by LC-MS. The solution was filtered through a plug of Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica flash chromatography, 0-15% EtOAc/hexanes. MS m/e = 262 $(M+H)^+$.

[0956] **Step E**: Preparation of 2-(4-Chloro-2-ethynylphenyl)propanenitrile

[0957] To a solution of 2-(4-chloro-2-(2-(trimethylsilyl)ethynyl)phenyl)-propanenitrile (0.550 g, 2.1 mmol) in THF (25 mL) was added 5N NaOH (15 mL). After one hour, the reaction was complete as determined by LC-MS and TLC. The solution was acidified with 5N HCl until the pH was about 2. The solution was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water (2 x 30 mL) and brine (2 x 30 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting orange oil was purified using silica flash chromatography on the ISCO with 0-20% EtOAc/hexanes. MS m/e = 190 $(M+H)^+$.

[0958] **Step F**: Preparation of Ethyl 3-(5-chloro-2-(2-cyano-1-ethoxy-1-oxopropan-2-yl) phenyl)propiolate

[0959] n-Butyllithium (0.11 g, 1.7 mmol) was added to a stirred solution of diisopropylamine (0.24 mL, 1.7 mmol) in THF (20 mL) at -78°C. The reaction was allowed to warm to room temperature for 15 minutes and was then cooled back down to -78°C. A solution of 2-(4-chloro-2-ethynylphenyl)propanenitrile (0.322 g, 1.7 mmol) in THF (5mL) was then added dropwise to the reaction. After 20 minutes, a solution of ethyl chloroformate (0.16 mL, 1.7 mmol) in THF (5 mL) was added dropwise to the reaction mixture. The mixture was then allowed to warm to room temperature. After 15 minutes, the reaction was complete as determined by TLC and LC-MS. MeOH (2 mL) and water (35 mL) were added to the reaction mixture, and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with saturated NH_4Cl (3 x 35 mL), once with brine (35 mL), dried with $MgSO_4$, and concentrated in vacuo to afford a dark brown oil. The crude residue was purified by silica flash chromatography using a gradient of 0-20% EtOAc/hexanes. MS m/e = 334 $(M+H)^+$.

[0960] **Step G**: Preparation of Ethyl 6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate

[0961] A solution of benzaldehyde oxime (0.16 g, 1.3 mmol) in DMF (3 mL) was added dropwise to a stirred suspension of 60% NaH (0.033 mL, 1.3 mmol) in dry 1, 4-dioxane (5 mL) under a nitrogen atmosphere at room temperature. After 30 minutes, a solution of ethyl 3-(5-chloro-2-(2-cyano-1-ethoxy-1-oxopropan-2-yl) phenyl) propiolate (0.445 g, 1.3 mmol) in DMF (3 mL) was added dropwise. The reaction was monitored by LC-MS and, when complete, the solvent was removed. The residual brown oil was dissolved in DCM (50 mL), water (30 mL), and AcOH (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified using silica flash chromatography with a gradient of 10-50% EtOAc/hexanes. MS m/e = 306 $(M+H)^+$.

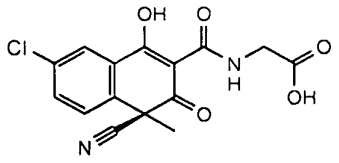
[0962] **Step H**: Preparation of 1,1-Dimethylethyl N((6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0963] Ethyl 6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalene-3-carboxylate (0.165 g, 0.54 mmol) was dissolved in 1, 4-dioxane (30 mL), and glycine tert-butyl ester hydrochloride (0.090 g, 0.54 mmol) and TEA (TEA) (0.11 mL, 0.81 mmol) were added. The reaction was stirred overnight at 70°C. The reaction was stirred for 18 hours. Another 0.5 equivalents of glycine and one equivalent of TEA were added, and the reaction was stirred at 105°C for 1 hour. The solvent was then removed, and the crude residue was dissolved in EtOAc and washed with water (3 x 25 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by silica flash chromatography using the 10-50% EtOAc/hexanes. MS m/e = 392 $(M+H)^+$.

[0964] **Step I**: Preparation of N((6-Chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0965] 1,1-Dimethylethyl N((6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.160 g, 0.41 mmol) was placed in a 25 mL round bottom flask and TFA (20 mL) was added. The mixture was stirred for 45 minutes. TFA was then removed under vacuum, and DCM was used to azeotrope off the remaining TFA (3 x) until the oil turned into a solid. MS m/e = 335 $(M+H)^+$. Calculated for $C_{15}H_{11}ClN_2O_5$ 334.04.

[0966] **Examples 85 and 86.** N-(((1R)-6-Chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine and N-(((1S)-6-Chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



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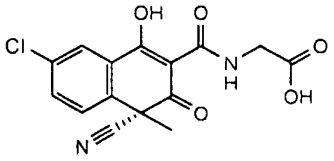
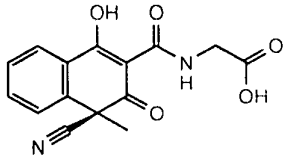


[0967] The title compounds were obtained by chiral separation N-((6-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine (Example 84) into its separate enantiomers using chiral HPLC. MS m/e = 335 $(M+H)^+$. Calculated for $C_{15}H_{11}ClN_2O_5$ 334.04.

[0968] **Examples 87 and 88.** N-(((1R)-1-Cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine and N-(((1S)-1-Cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



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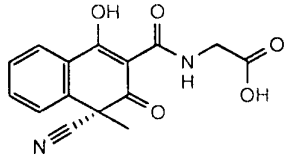
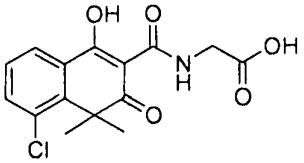


[0969] The title compounds were obtained by chiral separation of N-((1-cyano-4-hydroxy-1-methyl-2-oxo-naphthalen-3-yl)carbonyl)glycine (Example 28) into its separate enantiomers using chiral HPLC. MS (m/z) = 301 $(M+H)^+$. Calculated for $C_{15}H_{12}N_2O_5$ 300.07.

[0970] **Example 89.** N-((8-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0971] **Step A**: Preparation of Ethyl 2-(2-chlorophenyl)acetate

[0972] A solution of 2-chlorophenylacetic acid (10.12 g, 59.3 mmol) in EtOH (150 mL, 2576 mmol) in a 500 mL round bottom flask was treated with concentrated H_2SO_4 (0.700 mL, 8.28 mmol) and heated at 90°C for 16 hours. The solution was concentrated in vacuo, diluted with 1N NaOH(aq)(200 mL), and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with 1N NaOH(aq) (200 mL), water (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give ethyl 2-(2-chlorophenyl)acetate (11.344 g). MS m/e = 217 $(M+H)^+$.

[0973] **Step B**: Preparation of Ethyl 2-(2-chlorophenyl)-2-methylpropanoate

[0974] A suspension of NaH (60% dispersion in mineral oil (4.03 g, 101 mmol)) and ethyl 2-(2-chlorophenyl)acetate (5.00 g, 25.2 mmol)in DMF(100 mL) in a 500 mL round bottom flask was cooled to 0°C. A solution of MeI (4.70 mL, 75.5 mmol) in DMF(50 mL) was added, dropwise, and the mixture was stirred at 25°C for 18 hours. The reaction was quenched with 10% HCl(aq)(200 mL)and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 10% HCl(aq) (100 mL), water (100 mL), and brine (100 mL). The organic layer was then dried over $MgSO_4$, concentrated, and purified by flash column chromatography (silica, 0-50% DCM in hexane) to give ethyl 2-(2-chlorophenyl)-2-methylpropanoate (3.96 g). MS m/e = 227 $(M+H)^+$.

[0975] **Step C**: Preparation of 2-(2-Chlorophenyl)-2-methylpropanoic acid

[0976] A solution of ethyl 2-(2-chlorophenyl)-2-methylpropanoate (3.48 g, 15.4 mmol) and KOH (8.61 g, 154 mmol) in EtOH/water (1:1, 200 mL) was heated at 150°C in a sealed vessel for 2 hours. The solution was concentrated in vacuo, suspended in diethyl ether (200 mL), and extracted with 1N NaOH(aq)(3 x 100 mL). The aqueous solution was made acidic with concentrated HCl and

extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated, and dried in vacuo to give to give 2-(2-chlorophenyl)-2-methylpropanoic acid (2.578 g). MS m/e = 199 $(M+H)^+$.

[0977] **Step D**: Preparation of Diethyl 2-(2-(2-chlorophenyl)-2-methylpropanoyl)malonate

[0978] A solution of 2-(2-chlorophenyl)-2-methylpropanoic acid (2.55 g, 12.8 mmol) in thionyl chloride (50.0 mL, 685 mmol) was heated at 95°C for 2 hours. The solution was concentrated in vacuo, azeotroped using toluene (2x100 mL), and dried in vacuo to give the crude acid chloride. A mixture of diethyl malonate (1.94 mL, 12.8 mmol) and $MgCl_2$ (1.22 g, 12.8 mmol) in ACN (50 mL) was cooled to 0°C. TEA (3.75 mL, 27.0 mmol) was added slowly, and the mixture was stirred at 25°C for 2 hours. A solution of the acid chloride in ACN (50 mL) was added, and the mixture was heated at 50°C for 2 days. The solution was diluted with 10% HCl (aq)(200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 2N NaOH (aq) (3 x 200 mL) and then with brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (silica, 0-100% DCM in hexane) to give diethyl 2-(2-(2-chlorophenyl)-2-methylpropanoyl)malonate (3.25 g). MS m/e = 341 $(M+H)^+$.

[0979] **Step E**: Preparation of Ethyl 8-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[0980] P_2O_5 (19.0 g, 134 mmol) was treated with concentrated H_2SO_4 (17.1 mL, 308 mmol) at 0°C, and the resulting mixture was stirred for 30 minutes. Diethyl 2-(2-(2-chlorophenyl)-2-methylpropanoyl)malonate (1.500 g, 3.83 mmol) was added, and the mixture was stirred at 25°C for 1 hour. The solution was quenched with ice, and, on melting, was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated and dried in vacuo to give ethyl 8-chloro-4-

hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.320 g). MS m/e = 295 $(M+H)^+$.

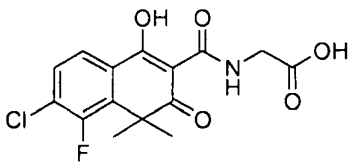
[0981] **Step F**: Preparation of 1,1-Dimethylethyl N-((8-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0982] A mixture of ethyl 8-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.320 g, 0.803 mmol), glycine tert-butyl ester hydrochloride (0.175 g, 1.04 mmol), DIEA (0.280 mL, 1.61 mmol), and 1,4-dioxane (12 mL) were heated at 120°C for 2 hours in a sealed vessel. The mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with water (30 mL) and then with brine (50 mL), dried over $MgSO_4$, and concentrated and dried in vacuo. The residue was purified by flash column chromatography (silica, 0-50% DCM in hexane) to give 1,1-dimethylethyl N-((8-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.214 g). MS m/e = 378 (M-H)-.

[0983] **Step G**: Preparation of N-((8-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0984] A solution of 1,1-dimethylethyl N-((8-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.162 g, 0.427 mmol) in TFA (5.00 mL, 67.3 mmol) was stirred at 25°C for 10 minutes. The solution was concentrated, azeotroped using DCM (2 x 100 mL), and dried in vacuo to give the title compound (0.138 g). MS m/e = 324 $(M+H)^+$. Calculated for $C_{15}H_{14}ClNO_5$ 323.06.

[0985] **Example 90.** N-((7-Chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[0986] **Step A**: Preparation of Ethyl 2-(3-chloro-2-fluorophenyl)acetate

[0987] A solution of 2-(3-chloro-2-fluorophenyl)acetic acid (2.56 g, 13.6 mmol) and thionyl chloride (100 mL, 1371 mmol) was stirred at 95°C for 2 hours in a 250 mL round bottom flask. The solution was concentrated, azeotroped in toluene, and dried in vacuo to give the crude acid chloride, which was then stirred in EtOH (150 mL, 2576 mmol) at 25°C for 16 hours. The solution was concentrated in vacuo, diluted with saturated $NaHCO_3$ (aq)(100 mL), and extracted with EtOAc (2x100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (aq) (100 mL), with water (100 mL), and then with brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica flash column chromatography (0-10% EtOAc in hexane) to give ethyl 2-(3-chloro-2-fluorophenyl)acetate (2.335 g, 79.4% yield). MS m/e = 217 $(M+H)^+$.

[0988] **Step B**: Preparation of 2-(3-Chloro-2-fluorophenyl)-2-methylpropanoic acid

[0989] A suspension of NaH (60% dispersion in mineral oil (1.28 g, 32.0 mmol)) in DMF(50 mL) in a 500 mL round bottom flask was cooled to 0°C. A solution of ethyl 2-(3-chloro-2-fluorophenyl)acetate (2.308 g, 10.7 mmol) in DMF(20 mL) was added dropwise, and the reaction was stirred for 5 minutes. A solution of MeI (1.66 mL, 26.6 mmol) in DMF(20 mL) was added, and the mixture was stirred at 25°C for 2 hours. The reaction was quenched with 10% HCl(aq)(200 mL), extracted with EtOAc (3 x 100 mL), washed with water (100 mL), and then washed with brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (silica, 0-50% DCM in hexane) to give an 11:1 mixture of ethyl 2-(3-chloro-2-fluorophenyl)-2-methylpropanoate and methyl 2-(3-chloro-2-fluorophenyl)-2-methylpropanoate. MS m/e = 245, 231 $(M+H)^+$.

[0990] The above mixture was treated with KOH (5.98 g, 107 mmol) in EtOH/water (2:1, 90 mL) and heated at 150°C in a sealed vessel for 3 hours. The solution was concentrated, diluted with diethyl ether (100 mL) and washed

with 1N NaOH(aq)(2x100 mL). The aqueous solution was acidified with concentrated HCl and extracted with EtOAc (3x100 mL). The combined organic layers were washed with water (100 mL) and then with brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give 2-(3-chloro-2-fluorophenyl)-2-methylpropanoic acid (1.907 g). MS m/e = 217 $(M+H)^+$.

[0991] **Step C**: Preparation of Diethyl 2-(2-(3-chloro-2-fluorophenyl)-2-methylpropanoyl)malonate

[0992] A mixture of 2-(3-chloro-2-fluorophenyl)-2-methylpropanoic acid (1.386 g, 6.40 mmol) and thionyl chloride (60.0 mL, 823 mmol) was stirred at 95°C for 2 hours. The reaction was concentrated in vacuo, azeotroped using DCM (2x100 mL), and dried in vacuo to give the crude acid chloride. A solution of diethyl malonate (0.967 mL, 6.40 mmol) and $MgCl_2$ (0.263 mL, 6.40 mmol) in ACN (40 mL) at 0°C, was treated dropwise with TEA (1.87 mL, 13.4 mmol), and the mixture was stirred at 25°C for 3 hours. A solution of the acid chloride in ACN (35 mL) was added, and the mixture was stirred at 50°C for 18 hours. The solution was concentrated in vacuo, diluted with 10% HCl(aq)(100 mL), and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, concentrated, and dried in vacuo. The residue was purified by flash column chromatography (silica, 0-100% DCM in hexane) to give 1.56 g of the title compound. MS m/e = 325 $(M+H)^+$.

[0993] **Step D**: Preparation of 1,1-Dimethylethyl N-((6 N-((7-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[0994] P_2O_5 (12.5 g, 88.1 mmol) was mixed with concentrated H_2SO_4 (11.2 mL, 81.3 mmol)at 0°C, and the resulting mixture was stirred for 30 minutes. Diethyl 2-(2-(3-chloro-2-fluorophenyl)-2-methylpropanoyl)malonate (1.00 g, 2.48 mmol) was added to the reaction, and the resulting mixture was stirred at 25°C for 1 hour. The resulting mixture was quenched with ice, and, on

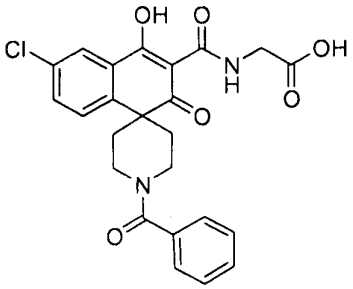
melting, was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated, and dried in vacuo to give crude ethyl 7-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.470 g). MS m/e = 313 $(M+H)^+$.

[0995] A portion of the above material (0.250 g) was treated with glycine tert-butyl ester hydrochloride (0.175 g, 1.04 mmol) and Hunig's base (0.277 mL, 1.59 mmol) in 1,4-dioxane (10 mL), and the mixture was heated at 120°C in a sealed vessel for 2 hours. The resulting mixture was diluted with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (silica, 0-50% DCM/hexane) to give the title compound (0.154 g). MS m/e = 396.5 (M-H)-.

[0996] **Step E**: Preparation of N-((7-Chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[0997] A solution of 1,1-dimethylethyl N-((6 N-((7-chloro-8-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.148 g, 0.372 mmol) in TFA (5.00 mL, 64.9 mmol) was stirred at 25°C for 15 minutes. The solution was concentrated, azeotroped using DCM (2 x 100 mL), and dried in vacuo to give the title compound (0.128 g). MS m/e = 342.4 $(M+H)^+$. Calculated for $C_{15}H_{13}ClFNO_5$ 341.05.

[0998] **Example 91.** N-((6-Chloro-4-hydroxy-2-oxo-1'-(phenylcarbonyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycine



[0999] **Step A**: Preparation of 2-Bromo-5-chlorobenzenamine

[01000] A solution of 1-bromo-4-chloro-2-nitrobenzene (13.92 g, 58.87 mmol) in MeOH (300 mL) was treated with water (50 mL), ammonium chloride (22.99 g, 429.8 mmol), and iron powder (325 mesh, 16.44 g, 294.4 mmol). The suspension was stirred at 23°C for 18 hours. The resulting suspension was filtered through celite. The filter cake was washed with MeOH (500 mL). The combined filtrate and washings were concentrated, and partitioned in EtOAc/water (500 mL/200 mL). The organic layer was separated. The aqueous layer was washed with EtOAc (2 x 200 mL). The organic layers were combined, washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo affording 11.51 g of 2-bromo-5-chlorobenzenamine.

[01001] **Step B**: Preparation of 1-Bromo-4-chloro-2-iodobenzene

[01002] A suspension of 2-bromo-5-chlorobenzenamine (11.348 g, 54.963 mmol) in concentrated HCl (100 mL) was cooled to 0°C and then treated in a dropwise fashion over 20 minutes using an addition funnel with a solution of sodium nitrite (4.5506 g, 65.955 mmol) in water (20 mL). The reaction was stirred at 0°C for 75 minutes. A solution of potassium iodide (27.372 g, 164.89 mmol) in water (50 mL) was added, and the reaction was stirred at 23°C. After 1 hour, the reaction was heated to 70°C. After 18 hours, the reaction was diluted with EtOAc (500 mL) and washed with water (300 mL), 2N NaOH solution (300 mL), saturated sodium thiosulfate solution (300 mL), and brine (250 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and

purified by silica gel chromatography (eluant: hexane) affording 11.11 g of 1-bromo-4-chloro-2-iodobenzene.

[01003] **Step C**: Preparation of 3,3,3-Triethoxyprop-1-yne

[01004] A solution of trimethylsilylacetylene (29.4 mL, 20.8 mmol) in diethyl ether (100 mL, anhydrous) was cooled to 0°C in an oven-dried round bottomed flask under nitrogen. Butyllithium (2.5 M solution in hexanes (83.2 mL, 208.0 mmol)) was then added dropwise to the reaction. After 1 hour, the reaction mixture was cooled to -78°C.

[01005] A solution of tetraethyl orthocarbonate (21.8 mL, 104.0 mmol) in diethyl ether (50 mL) in a separate oven-dried round bottomed flask was cooled to 0°C under nitrogen. The cooled mixture was treated dropwise with a solution of boron trifluoride diethyletherate (17.6 mL, 140.4 mmol) in diethyl ether (25 mL) over 20 minutes using an addition funnel. The white mixture was stirred at 0°C for 5 minutes, and then cooled to -78°C. The TMS-acetylide solution prepared in the previous paragraph was then added to the mixture at -78°C via cannula. After 1 hour, the reaction was removed from the dry ice-acetone bath and stirred at 23°C for 15 minutes. The mixture was then quenched with saturated aqueous K_2CO_3 solution (300 mL) and extracted with diethyl ether (2 x 300 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo affording trimethyl(3,3,3-triethoxyprop-1-ynyl)silane.

[01006] A solution of trimethyl(3,3,3-triethoxyprop-1-ynyl)silane (25 g, 102 mmol) in MeOH (400 mL) was treated with K_2CO_3 (14 g, 102 mmol). The reaction was stirred at 23°C. After 15 hours, the reaction was diluted with pentane (500 mL). The pentane layer was separated, and the MeOH layer was extracted with pentane (2 x 250 mL). The combined pentane layers were washed with water (200 mL), dried over $MgSO_4$, and concentrated (at 220 torr on rotary evaporator). The crude product was filtered through a silica gel plug, using 10% diethyl ether/pentane as the eluant, and concentrated (at 220 torr on rotary evaporator) affording 13.25 g of 3,3,3-triethoxyprop-1-yne.

[01007] **Step D**: Preparation of 1-Bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene

[01008] A suspension of 1-bromo-4-chloro-2-iodobenzene (2.5 g, 7.9 mmol), 3,3,3-triethoxyprop-1-yne (2.4 g, 13.9 mmol), copper(I) iodide, (455 mg, 2.3 mmol), and trans-dichlorobis(triphenylphosphine)palladium(II) (559 mg, 0.79 mmol) was treated with ACN (30 mL). The reaction was capped, evacuated under vacuum, backfilled with argon, and treated with TEA (9.9 mL, 71.6 mmol). The reaction was stirred at 23°C. After 2 hours, the reaction mixture was concentrated in vacuo to remove all solvents, diluted with EtOAc (250 mL), and washed with brine (150 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 4% EtOAc/hexane + 1%TEA) affording 2.6 g of 1-bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene.

[01009] **Step E**: Preparation of 1-tert-Butyl ethyl 4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-1,4-dicarboxylate

[01010] A solution of dicyclohexylamine (376 µL, 1.8 mmol) in toluene (4 mL) was cooled to 0°C under nitrogen and then treated with n-butyllithium (2.5M in hexanes (754 µL, 1.8 mmol)). After 20 minutes, 1-tert-butyl ethyl piperidine-1,4-dicarboxylate (398 µL, 1.6 mmol) was added, and the reaction was warmed to 23°C.

[01011] In a separate round-bottomed flask, 1-bromo-4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)benzene (487 mg, 1.3 µmol) and $[Pd(PtBu_3)Br]_2$ (105 mg, 135 µmol) were mixed. The reaction vessel was evacuated under vacuum and backfilled with argon. Toluene (5 mL) was added, and the mixture was heated to 50°C for 5 minutes and then transferred by syringe to the enolate solution. The aryl bromide-Pd flask was rinsed with toluene (1 mL) and added to the reaction mixture. The resulting mixture was heated at 50°C under nitrogen. After 90 minutes, the reaction was cooled to 23°C, diluted with EtOAc (100 mL), and washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel

chromatography (eluant: 4-6% EtOAc/hexane + 1% TEA) affording the desired coupled product 1-tert-butyl ethyl 4-(4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)piperidine-1,4-dicarboxylate. A solution of the 1-tert-butyl ethyl 4-(4-chloro-2-(3,3,3-triethoxyprop-1-ynyl)phenyl)piperidine-1,4-dicarboxylate in EtOH (10 mL) and water (2 mL) was treated with p-toluenesulfonic acid monohydrate (69.3 mg, 364 μmol). The reaction was stirred at 23°C for 30 minutes, and then diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (eluant: 12-16% EtOAc/hexane), affording 155 mg of 1-tert-butyl ethyl 4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-1,4-dicarboxylate. MS m/e = 486.1 $(M+Na)^+$.

[01012] **Step F**: Preparation of Methyl N-((6-chloro-4-hydroxy-2-oxo-1'-(tert-butoxycarbonyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate

[01013] A suspension of NaH (60% dispersion in mineral oil (17 mg, 423 μmol)) in dioxane (2.5 mL) was treated with a solution of (E)-benzaldehyde oxime (51 mg, 423 μmol) in DMF (1.5 mL). The reaction was stirred at 23°C under nitrogen. After 30 minutes, the reaction was cooled to 0°C and then a solution of 1-tert-butyl ethyl 4-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)piperidine-1,4-dicarboxylate (157 mg, 338 μmol) in DMF (3.5 mL) was added in a dropwise fashion over 10 minutes. After 1 hour, the reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (75 mL), water (75 mL) and brine (75 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (eluant: 1-8% MeOH/DCM), affording the cyclized product. The cyclized product was mixed with glycine methyl ester hydrochloride (28 mg, 220 μmol) and DIPEA (48 μL, 275 μmol) in 1,4-dioxane (4 mL) and heated to 95°C in a sealed vessel. After 18 hours, the reaction was cooled to 23°C, diluted with EtOAc (75 mL) and washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography

(eluant: 28-100% EtOAc/hexane) affording the title compound in 40 mg. MS m/e = 501.2 $(M+Na)^+$.

[01014] **Step G**: Preparation of Methyl N-((6-chloro-4-hydroxy-2-oxo-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate

[01015] A solution of methyl N-((6-chloro-4-hydroxy-2-oxo-1'-(tert-butoxycarbonyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate (333 mg, 695 µmol) in dioxane (10 mL) was treated with HCl (4.0M in 1,4-dioxane (1738 µL, 6953 µmol)). The reaction was stirred at 23°C. After 20 hours, the reaction was concentrated in vacuo affording 231 mg of the title compound as the hydrochloride salt. MS m/e = 379.2 $(M+H)^+$.

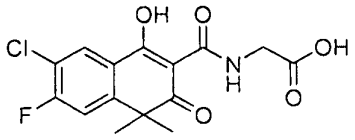
[01016] **Step H**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-1'-(phenylcarbonyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycine

[01017] A solution of the hydrochloride salt of methyl N-((6-chloro-4-hydroxy-2-oxo-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate (0.050 g, 0.12 mmol) and Hunig's base (0.024 mL, 0.14 mmol) in DMF/DMSO (2:1, 1.5 mL) was stirred at 25°C for 5 minutes. A mixture of benzoic acid (0.067 g, 0.54 mmol) and N-(3-dimethylaminopropyl)-n'-ethylcarbodiimide hydrochloride (0.13 g, 0.65 mmol) in DMF (1 mL) was added. The mixture was stirred at 60°C for 8 hours. The solution was diluted with EtOAc (20 mL), and washed with brine (2 x 25 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (silica, 0-1% MeOH in DCM)to give methyl N-((6-chloro-4-hydroxy-2-oxo-1'-(phenylcarbonyl)-spiro[naphthalene-1,4'-piperidin]-3-yl)carbonyl)glycinate. MS m/e = 483.5 $(M+H)^+$.

[01018] The ester was treated with lithium hydroxide hydrate (0.025 g, 0.60 mmol) in THF (1.4 mL) and water (0.6 mL) and stirred at 25°C for 30 minutes. The reaction was quenched with Dowex 50 (W X 8) acidic resin (prewashed with MeOH) to pH < 4.0 and filtered. The filtrate was concentrated

and azeotroped with toluene (2 x 5 mL), to give the title compound (0.017 g). MS m/e = 469.5 $(M+H)^+$. Calculated for $C_{24}H_{21}ClN_2O_6$ 468.11.

[01019] **Example 92.** N-((6-Chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[01020] **Step A**: Preparation of Methyl 2-(4-chloro-3-fluorophenyl)acetate

[01021] A solution of 2-(4-chloro-3-fluorophenyl)acetic acid (10.07 g, 53.4 mmol) and concentrated H_2SO_4 (0.297 mL, 5.34 mmol) in MeOH (200 mL, 4940 mmol) was stirred at 95°C for 17 hours in a 350 mL sealed vessel. The solution was concentrated in vacuo and then made basic with 1N NaOH(aq)(100 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL), washed with water (100 mL), and then washed with brine (75 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and dried in vacuo to give methyl 2-(4-chloro-3-fluorophenyl)acetate (10.80 g). MS m/e = 203.2 $(M+H)^+$.

[01022] **Step B**: Preparation of Methyl 2-(4-chloro-3-fluorophenyl)-2-methylpropanoate

[01023] A mixture of NaH (60% in mineral oil (1.78 g, 44.4 mmol)) in DMF (40 mL) in an oven dried 250 mL round bottom flask was cooled to 0°C, and a solution of methyl 2-(4-chloro-3-fluorophenyl)acetate (3.00 g, 14.8 mmol) in DMF (20) was added. After stirring for 10 minutes, a solution of MeI (3.69 mL, 59.2 mmol) in DMF (40 mL) was added dropwise. The mixture was stirred at 25°C for 4 hours. The reaction was quenched 10% HCl(aq)(150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (200 mL) and with brine (100 mL), dried over $MgSO_4$, concentrated, and dried in vacuo. The residue was purified by flash column chromatography

(silica, 0-30% DCM in hexane) to give methyl 2-(4-chloro-3-fluorophenyl)-2-methylpropanoate (3.007 g). MS m/e = 231.3 $(M+H)^+$.

[01024] **Step C**: Preparation of 2-(4-Chloro-3-fluorophenyl)-2-methylpropanoic acid

[01025] A solution of methyl 2-(4-chloro-3-fluorophenyl)-2-methylpropanoate (2.94 g, 12.7 mmol) and KOH (7.15 g, 127 mmol) in EtOH (90 mL) and water (30 mL) was stirred at 150°C in a sealed vessel for 3 hours. The solution was concentrated in vacuo, diluted with 10% HCl (aq)(150 mL), and extracted with EtOAc (2x100 mL). The combined organic layers were washed with water (2 x 100 mL) and then with brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give 2-(4-chloro-3-fluorophenyl)-2-methylpropanoic acid (2.63 g). MS m/e = 217.3 $(M+H)^+$.

[01026] **Step D**: Preparation of Diethyl 2-(2-(4-chloro-3-fluorophenyl)-2-methylpropanoyl)malonate

[01027] A solution of 2-(4-chloro-3-fluorophenyl)-2-methylpropanoic acid (2.05 g, 9.46 mmol) in thionyl chloride (40.0 mL, 548 mmol) in a 500 mL round bottom flask was stirred at 95°C for 2 hours. The reaction was concentrated in vacuo and azeotroped in toluene (50 mL) to give the crude acid chloride. A solution of diethyl malonate (1.43 mL, 9.46 mmol) in ACN (20 mL) was cooled to 0°C. $MgCl_2$ (0.901 g, 9.46 mmol) and then TEA (2.76 mL, 19.9 mmol) were added, and the mixture was stirred at 25°C for 2 hours. A solution of the acid chloride in ACN (30 mL) was added, and the mixture was stirred at 50°C for 16 hours. The reaction was cooled, diluted with water (75 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried in vacuo to give diethyl 2-(2-(4-chloro-3-fluorophenyl)-2-methylpropanoyl)malonate (2.95 g). MS m/e = 359.4 $(M+H)^+$.

[01028] **Step E**: Preparation of Ethyl 6-chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[01029] A suspension of P_2O_5 (33.0 g, 232 mmol) in concentrated H_2SO_4 (29.5 mL, 531 mmol) was cooled 0°C. At 0°C, the suspension was added to diethyl 2-(2-(4-chloro-3-fluorophenyl)-2-methylpropanoyl)malonate (2.90 g, 8.20 mmol), and the mixture was stirred at 25°C for 1 hour. The reaction was quenched with ice. On melting, it was extracted with EtOAc (3 x 100 mL), washed with water (150 mL), and then with brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the title compound (1.349 g, 52.6% yield) as a tan solid. MS m/e = 313.3 $(M+H)^+$.

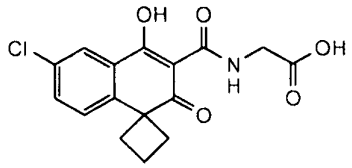
[01030] **Step F**: Preparation of 1,1-Dimethylethyl N-((6-chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

[01031] A solution of ethyl 6-chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (0.350 g, 1.12 mmol), glycine tert-butyl ester hydrochloride (0.244 g, 1.45 mmol), and Hunig's base (0.390 mL, 2.24 mmol) in 1,4-dioxane(15 mL) was heated at 120°C for 2 hours in a sealed vessel. The solution was diluted with water (50 mL), extracted with EtOAc (2 x 50 mL), washed with water (50 mL), and then washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica, 0-75% DCM in hexane) to give the title compound (0.305 g). MS m/e = 396.5 (M-H)-.

[01032] **Step G**: Preparation of N-((6-Chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[01033] A solution of 1,1-dimethylethyl N-((6-chloro-7-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (0.255 g, 0.641 mmol) in TFA (5.00 mL, 67.3 mmol) was stirred at 25°C for 10 minutes. The mixture was concentrated, azeotroped in DCM (2 x 50 mL), and dried in vacuo to give the title compound (0.220 g). MS m/e = 342.4 $(M+H)^+$. Calculated for $C_{15}H_{13}ClFNO_5$ 341.05.

[01034] **Example 93.** N-((6'-Chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-yl)carbonyl)glycine



[01035] **Step A**: Preparation of Ethyl 2-(4-chloro-2-iodophenyl)acetate

[01036] A catalytic amount of DMF (approximately 3 drops) was added to a stirred mixture of 4-chloro-2-iodobenzoic acid (24.47 g, 86.63 mmol) and oxalyl chloride (11.34 mL, 129.9 mmol) in DCM (100 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 2 hours and then concentrated in vacuo to give 4-chloro-2-iodobenzoyl chloride as a yellow oil that solidified upon standing (26.07 g).

[01037] 4-Chloro-2-iodobenzoyl chloride (23.05 g, 77 mmol) was dissolved in ether (100 mL). (Trimethylsilyl)diazomethane (2.0M in diethyl ether (115 mL, 230 mmol)) was added, and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with AcOH until nitrogen evolution stopped. The mixture was then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was separated and washed with saturated $NaHCO_3$ (2x), water (1x), and brine (1x), dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid (26.93 g).

[01038] The yellow solid (26.93 g, 87.9 mmol) prepared in the previous step was dissolved in EtOH (350 mL), and silver oxide (0.564 mL, 17.6 mmol) was added. The mixture was stirred at 80°C for 1 hour. The reaction mixture was then cooled to room temperature and filtered through celite. The filtrate was concentrated in vacuo to give a brown oil. The crude product was purified by silica flash chromatography (0-10% EtOAc/hexane) to give the desired compound as a yellow oil (20.79 g). MS (m/e) = 325.0 $(M+H)^+$.

[01039] **Step B**: Preparation of Ethyl 1-(4-chloro-2-iodophenyl)-cyclobutanecarboxylate

[01040] Ethyl 2-(4-chloro-2-iodophenyl)acetate (3.95 g, 12 mmol) was mixed in DMF (80 mL) in a round bottom flask. NaH (60% dispersion in mineral oil (0.54 g, 13 mmol)) was added, and the reaction mixture was stirred for 15 minutes under a nitrogen atmosphere. 1,3-dibromopropane (1.4 mL, 13 mmol, 1.1 eq) was added via syringe, and the reaction mixture was stirred for 2 hours. An additional 1.10 eq NaH (60% dispersion in mineral oil (0.54 g, 13 mmol)) was added, and the reaction was stirred for 3 hours. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give an orange oil. The crude product was purified by silica flash chromatography (0-30% DCM/hexane) to give the desired compound as a light yellow oil (2.01 g). MS (m/e) = 365.1 $(M+H)^+$.

[01041] **Step C**: Preparation of Ethyl 1-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)cyclobutanecarboxylate

[01042] Ethyl 1-(4-chloro-2-iodophenyl)cyclobutanecarboxylate (2.01 g, 5.51 mmol), copper(I) iodide (0.0560 mL, 1.65 mmol), and trans-dichlorobis(triphenylphosphine)palladium(II) (0.387 g, 0.551 mmol) were mixed in ACN (10 mL) and TEA (5 mL) in a round bottom flask. The flask was placed under a nitrogen atmosphere. 3,3,3-Triethoxyprop-1-yne (1.90 g, 11.0 mmol) was added via syringe, and the reaction was stirred for 16 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated in vacuo to give a black oil.

[01043] The black oil prepared in the previous step was suspended in EtOH (20 mL) and water (2 mL). The mixture was treated with p-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) and stirred for 30 minutes. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a black oil. The crude material was purified

by silica flash chromatography (0-100% DCM/hexane) to give the desired compound as a brown oil (0.80 g). MS (m/e) = 335.2 $(M+H)^+$.

[01044] **Step D**: Preparation of Ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-carboxylate

[01045] Benzaldehyde oxime (174 mg, 1434 μmol) in DMF (7 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil (57 mg, 1434 μmol)) in dioxane (7 mL) under a N_2 atmosphere. The mixture was stirred for approximately 30 minutes before being cooled to 0°C. Ethyl 1-(4-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)cyclobutanecarboxylate (400 mg, 1195 μmol) in DMF (7 mL) was added via syringe, and the reaction was stirred at 0°C for 1 hour. The reaction was quenched with water, and extracted with EtOAc. The aqueous layer was separated and brought to a pH of about 4 with 10% HCl and extracted again with EtOAc (2x). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give an orange oil. The crude oil was purified by silica flash chromatography (0-20% EtOAc/hexane) to give the desired compound as a white solid (155 mg). MS (m/e) = 307.1 $(M+H)^+$.

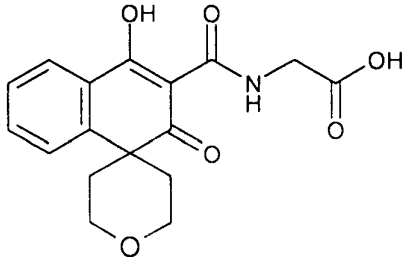
[01046] **Step E**: Preparation of 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate

[01047] A mixture of ethyl 6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-carboxylate (155 mg, 505 μmol) and glycine tert-butyl ester hydrochloride (102 mg, 606 μmol) were mixed in dioxane (4 mL). DIPEA (106 μL, 606 μmol) was added, and the reaction mixture was stirred at 75°C for 3.5 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting yellow solid was purified by silica flash chromatography (0-50% DCM/hexane) to give the desired compound as a white solid (151 mg). MS (m/e) = 336.1 $(M+H-tBu)^+$.

[01048] **Step F**: Preparation of N-((6'-Chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-yl)carbonyl)glycine

[01049] 1,1-Dimethylethyl N-((6'-chloro-4'-hydroxy-2'-oxo-spiro[cyclobutane-1,1'-naphthalen]-3'-yl)carbonyl)glycinate (151 mg, 385 μmol) was stirred in TFA (1 mL, 13462 μmol) for 20 minutes. Water was added. The resulting precipitate was filtered and washed with water to give the desired product as a white solid (87 mg). MS (m/e) = 336.1 $(M+H)^+$. Calculated for $C_{16}H_{15}ClO_4$ 335.06.

[01050] **Example 94.** N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[01051] **Step A**: Preparation of Methyl 4-phenyl-tetrahydro-2H-pyran-4-carboxylate

[01052] To NaH (60% dispersion in mineral oil (14.2 g, 355 mmol)) was added NMP (142 mL), and the mixture was cooled to 0°C. A solution of 1-bromo-2-(2-bromoethoxy)ethane (17.8 mL, 142 mmol) and methyl phenylacetate (20.00 mL, 142 mmol) in NMP was added dropwise, and the resulting reaction mixture was stirred at 0°C for 2 hours. The reaction was quenched with water, acidified to pH = 2 with concentrated HCl, extracted with 200 mL of diethyl ether, washed 2 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound after flash chromatography (15.40 g) as a white solid. MS m/e = 221 $(M+H)^+$.

[01053] **Step B**: Preparation of 4-Phenyl-tetrahydro-2H-pyran-4-carboxylic acid

[01054] Methyl 4-phenyl-tetrahydro-2H-pyran-4-carboxylate (15.4 g, 69.9 mmol) was dissolved in EtOH (100 mL). KOH (39.2 g, 699 mmol) was then

added. The reaction mixture was then heated at reflux for 2 hours and then cooled to ambient temperature, diluted with 150 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, and separated. The aqueous layer was acidified to a pH of 2 with concentrated HCl and extracted with $CHCl_3$ (3 x 100mL), dried over Na_2SO_4, and concentrated in vacuo to give the title compound (11.58 g) as a light yellow solid. MS m/e = 229 $(M+Na)^+$.

[01055] **Step C**: Preparation of Diethyl 2-(4-phenyl-tetrahydro-2H-pyran-4-carbonyl)malonate

[01056] To a solution of diethyl malonate (3.96 mL, 26.2 mmol) in ACN (52.4 mL) at 0°C was added $MgCl_2$ (2.74 g, 28.8 mmol) in one portion. TEA (7.30 mL, 52.4 mmol) was added dropwise, and the reaction mixture was allowed to warm to ambient temperature and stirred for 3 hours. 4-Phenyl-tetrahydro-2H-pyran-4-carboxylic acid (5.13 g, 24.9 mmol) was converted to the acid chloride by addition of thionyl chloride and reaction at 65°C for 1 hour. The resulting acid chloride solution was then concentrated in vacuo, dissolved in ACN, and added to the initial reaction mixture. The resulting mixture was stirred at ambient temperature for 2 hours and then diluted with 200 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 75 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound without further purification. MS m/e = 349 $(M+H)^+$.

[01057] **Step D**: Preparation of Ethyl 4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[01058] Diethyl 2-(4-phenyl-tetrahydro-2H-pyran-4-carbonyl)malonate (418 mg, 1200 µmol) was dissolved in a minimal amount of EtOAc and then cooled to 0°C. A slurry of P_2O_5 (681 mg) and H_2SO_4 (640 µL, 11998 µmol) (also at 0°C) was added to the mixture via spatula, and the reaction mixture was stirred for 3 hours. The reaction mixture was then poured into a beaker of ice, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with

water, washed with water (2 x 50mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound which was used without further purification. MS m/e = 303 $(M+H)^+$.

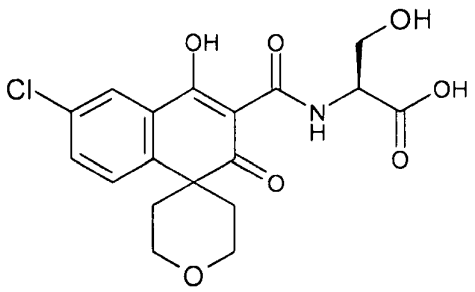
[01059] **Step E**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[01060] Ethyl 4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (450 mg, 1488 μmol) was dissolved in 1,4-dioxane (1488 μL) and N-ethyl-N-isopropylpropan-2-amine (778 μL, 4465 μmol). tert-Butyl 2-aminoacetate hydrochloride (374 mg, 2233 μmol) was added, and the mixture was heated at 80°C for 3 hours. The resulting mixture was then cooled to ambient temperature, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed with $NaHCO_3$ (saturated, aqueous)(2 x 75 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (270 mg) as a white solid. MS m/e = 388 $(M+H)^+$.

[01061] **Step F**: Preparation of N-((4-Hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.

[01062] 1,1-Dimethylethyl N-((4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (270 mg, 697 μmol) was reacted with TFA (2 mL) for 30 minutes and then concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (193 mg) as a white solid. MS m/e = 332 $(M+H)^+$. Calculated for $C_{17}H_{17}NO_6$ 331.11.

[01063] **Example 95.** N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-serine



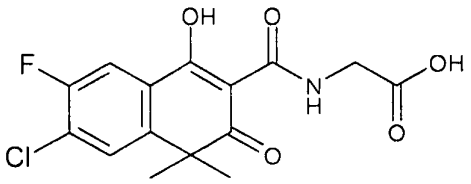
[01064] **Step A**: Preparation of Methyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-serinate

[01065] Ethyl 6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (287 mg, 852 μmol, Example 1 A-C) was dissolved in 1,4-dioxane (852 μL) and N-ethyl-N-isopropylpropan-2-amine (445 μL, 2557 μmol). L-Serine methyl ester hydrochloride (199 mg, 1278 μmol) was added, and the mixture was stirred at 80°C for 3 hours. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the 180 mg of the title compound as a white solid after flash chromatography. MS m/e = 410 $(M+H)^+$.

[01066] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-serine

[01067] Methyl N-((6-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)-L-serinate (180 mg, 439 μmol) was dissolved in THF (4392 μL). NaOH in water (4392 μL, 21961 μmol) was added, and the reaction was stirred at ambient temperature for 3 hours. The pH was adjusted to about 3, and the resulting mixture was diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with water, washed 2 times with 20 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (95 mg) after it was precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven. MS m/e = 396 $(M+H)^+$. Calculated for $C_{18}H_{18}NO_7$ 395.08.

[01068] **Example 96.** N-((7-Chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine



[01069] **Step A**: Preparation of 2-(3-Chloro-4-fluorophenyl)-2-methylpropanenitrile

[01070] NaH (60% dispersion in mineral oil, 13.3 g, 333 mmol) was suspended in DMF (151 mL, 151 mmol), cooled to 0°C, and then a solution of 3-chloro-4-fluorophenylacetonitrile (25.65 g, 151 mmol) and MeI (23.6 mL, 378 mmol) in DMF was added dropwise via addition funnel. The reaction mixture was slowly warmed to ambient temperature and stirred for 3 hours. The reaction mixture was quenched with water, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed with water (2 x 100 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (21.01 g) as a colorless oil after flash chromatography.

[01071] **Step B**: Preparation of 2-(3-Chloro-4-fluorophenyl)-2-methylpropanoic acid

[01072] 6M H_2SO_4 (45 mL) was added to 2-(3-chloro-4-fluorophenyl)-2-methylpropanenitrile (8.03 g, 40.6 mmol) in a sealed vial which was heated at 165°C for 2 hours. The reaction mixture was diluted with 100 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of 5N NaOH (aqueous), and separated. The aqueous layer was acidified to pH = 3 with 3N HCl and extracted with diethyl ether 3 x 75 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to give the title compound (7.73 g). MS m/e = 217 $(M+H)^+$.

[01073] **Step C**: Preparation of Diethyl 2-(2-(3-chloro-4-fluorophenyl)-2-methylpropanoyl)malonate

[01074] Diethyl malonate (5.68 mL, 37.6 mmol) was dissolved in ACN (75 mL) at 0°C. $MgCl_2$ (3.93 g, 41.3 mmol) was added to the reaction mixture in one portion and TEA (10.5 mL, 75.1 mmol) was added dropwise. 2-(3-chloro-4-fluorophenyl)-2-methylpropanoic acid (7.73 g, 35.7 mmol) was converted to the acid chloride by reaction with thionyl chloride at 65°C for 1 hour, and the resulting acid chloride was concentrated under reduced pressure. The acid chloride was then dissolved in ACN and added dropwise via addition funnel to the initial reaction mixture. The resulting mixture was stirred at ambient temperature for 2 hours and then quenched with water, acidified with 5N HCl, diluted with 100 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed with water (2 x 50 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (7.17 g) as a light yellow oil after flash chromatography. MS m/e = 359 $(M+H)^+$.

[01075] **Step D**: Preparation of Ethyl 7-chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate

[01076] P_2O_5 (1.43 g, 10.1 mmol) was suspended in H_2SO_4 (5.38 mL) and cooled to 0°C. Diethyl 2-(2-(3-chloro-4-fluorophenyl)-2-methylpropanoyl)malonate (3.62 g, 10.1 mmol) was added, and the reaction was stirred at 0°C for 1 hour. The reaction mixture was poured into ice, diluted with 150 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed with water (2 x 75 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to the title compound (1.46 g) as a white amorphous solid after flash chromatography. MS m/e = 313 $(M+H)^+$.

[01077] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate

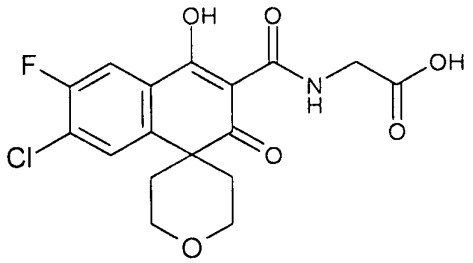
[01078] Ethyl 7-chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (820 mg, 2622 μmol) was dissolved in 1,4-dioxane

(5244 μL) and N-ethyl-N-isopropylpropan-2-amine (1370 μL, 7866 μmol). tert-Butyl 2-aminoacetate hydrochloride (659 mg, 3933 μmol) was added, and the reaction was stirred at 80°C for 3 hours. The reaction mixture was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (200 mg) as a white solid after flash chromatography. MS m/e = 420 $(M+Na)^+$.

[01079] **Step F**: Preparation of N-((7-Chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycine

[01080] 1,1-Dimethylethyl N-((7-chloro-6-fluoro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (200 mg, 503 μmol) was reacted with TFA (2 mL) at ambient temperature for 30 minutes. The mixture was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (139 mg) as a white solid. MS m/e = 342 $(M+H)^+$. Calculated for $C_{15}H_{13}NO_5$ 341.05.

[01081] **Example 97.** N-((7-Chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine



[01082] **Step A**: Preparation of 4-(3-Chloro-4-fluorophenyl)-tetrahydro-pyran-4-carbonitrile

[01083] NaH (60% in mineral oil, 14.3 g, 357 mmol) was suspended in NMP (143 mL) and cooled to 0°C. A solution of 1-chloro-2-(2-chloroethoxy)ethane (20.4 g, 143 mmol) and 3-chloro-4-

fluorophenylacetonitrile (24.23 g, 143 mmol) in ether was then added dropwise via addition funnel. The resulting reaction mixture was stirred at 0°C for 3 hours and then quenched with water, acidified with 5N HCl, diluted with 400 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 3 times with 100 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title (16.99 g) after flash chromatography. MS m/e = 240 $(M+H)^+$.

[01084] **Step B**: Preparation of 4-(3-Chloro-4-fluorophenyl)-tetrahydro-pyran-4-carboxylic acid

[01085] 6M H_2SO_4 (43.6 mL) was added to 4-(3-chloro-4-fluorophenyl)-tetrahydro-pyran-4-carbonitrile (9.40 g, 39.2 mmol) in a sealed vial which was then heated at 165°C for 4 hours. The reaction mixture was subsequently cooled to ambient temperature, diluted with 100 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 100 mL of 5N NaOH (aqueous), and separated. The aqueous layer was acidified to pH = 3 with 3N HCl and extracted 2 times with 75 mL of diethyl ether. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to give the title compound (5.61 g). MS m/e = 259 $(M+H)^+$.

[01086] **Step C**: Preparation of Diethyl 2-(4-(3-chloro-4-fluorophenyl)-tetrahydro-pyran-4-carbonyl)malonate

[01087] $MgCl_2$ (2.39 g, 25.1 mmol) was added to diethyl malonate (3.45 mL, 22.8 mmol) in ACN (45.7 mL) after cooling the reaction mixture to 0°C. TEA (6.36 mL, 45.7 mmol) was then added dropwise, and the reaction mixture was warmed to ambient temperature and stirred for 2 hours. 4-(3-Chloro-4-fluorophenyl)-tetrahydro-pyran-4-carboxylic acid (5.61 g, 21.7 mmol) was converted to the acid chloride by reaction with thionyl chloride at 70°C for 1 hour. The acid chloride reaction mixture was concentrated, dissolved in ACN, and added dropwise to the initial reaction mixture. The resulting mixture was stirred at ambient temperature for 2 hours and then quenched with water.

acidified with 5N HCl, diluted with 100 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed 2 times with 50 mL of water, separated, dried over Na_2SO_4, and concentrated in vacuo to give the title (3.87 g) after flash chromatography. MS m/e = 401 $(M+H)^+$.

[01088] **Step D**: Preparation of Ethyl 7-chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate

[01089] P_2O_5 (1.4 g) was suspended in H_2SO_4 (3.34 mL), and the mixture was cooled to 0°C. Diethyl 2-(4-(3-chloro-4-fluorophenyl)-tetrahydro-pyran-4-carbonyl)malonate (1.43 g, 3.57 mmol) was then added dropwise, and the resulting mixture was stirred for 1.5 hours. The reaction mixture was allowed to warm to ambient temperature and stirred for 5 hours. The reaction mixture was then poured into a beaker of ice, diluted with 200 mL of diethyl ether, added to a separatory funnel, partitioned with water, washed with water (2 x 75 mL), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (0.96 g) as a colorless oil after flash chromatography. MS m/e = 355 $(M+H)^+$.

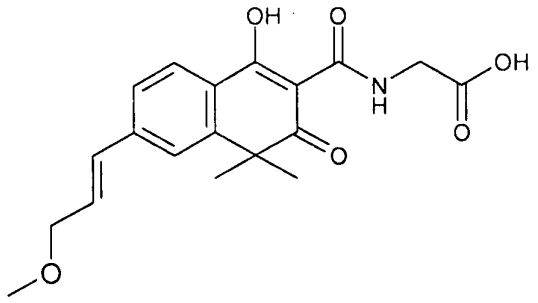
[01090] **Step E**: Preparation of 1,1-Dimethylethyl N-((7-chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate

[01091] Ethyl 7-chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (580 mg, 1635 μmol) was dissolved in 1,4-dioxane (3270 μL) and N-ethyl-N-isopropylpropan-2-amine (854 μL, 4905 μmol). tert-Butyl 2-aminoacetate hydrochloride (411 mg, 2452 μmol) was added, and the reaction was stirred at 80°C for 2 hours. The reaction was then diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 75 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title (30 mg) compound as a white solid after flash chromatography. MS m/e = 440 $(M+H)^+$.

[01092] **Step F**: Preparation of N-((7-Chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine

[01093] 1,1-Dimethylethyl N-((7-chloro-6-fluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (79 mg, 180 μmol) was reacted with TFA (2 mL) at ambient temperature for 30 minutes. The resulting mixture was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (49 mg) as an off-white solid. MS m/e = 384 $(M+H)^+$. Calculated for $C_{17}H_{15}NO_6$ 383.06.

[01094] **Example 98.** N-((4-Hydroxy-1,1-dimethyl-7-((1E)-3-(methyloxy)-1-propen-1-yl)-2-oxo-naphthalen-3-yl)carbonyl)glycine



[01095] **Step A**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-7-((1E)-3-(methyloxy)-1-propen-1-yl)-2-oxo-naphthalen-3-yl)carbonyl)glycinate

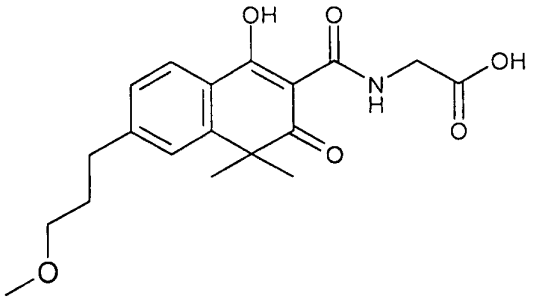
[01096] 1,1-Dimethylethyl N-((7-bromo-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)glycinate (500 mg, 1178 μmol, see Example 53) was dissolved in 1,4-dioxane (11785 μL). 2M K_2CO_3 in water (2357 μL, 4714 μmol), $Pd(Ph_3P)_4$ (136 mg, 118 μmol), and (E)-2-(3-methoxyprop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (300 μL, 1414 μmol) were added, and the reaction was stirred at 80°C for 2 hours. The reaction mixture was cooled to ambient temperature, diluted with 100 mL of EtOAc, added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 50

mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (385 mg) after flash chromatography. MS m/e = 438 $(M+Na)^+$.

[01097] **Step B**: Preparation of N-((4-Hydroxy-1,1-dimethyl-7-((1E)-3-(methyloxy)-1-propen-1-yl)-2-oxo-naphthalen-3-yl)carbonyl)glycine

[01098] 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-7-((1E)-3-(methyloxy)-1-propen-1-yl)-2-oxo-naphthalen-3-yl)carbonyl)glycinate (75 mg, 181 μmol) was dissolved in TFA (2 mL) at ambient temperature for 30 minutes before it was concentrated, precipitated with hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound (15 mg) as a yellow solid. MS m/e = 360 $(M+H)^+$. Calculated for $C_{19}H_{21}NO_6$ 359.14.

[01099] **Example 99.** N-((4-Hydroxy-1,1-dimethyl-7-(3-(methyloxy)propyl)-2-oxo-naphthalen-3-yl)carbonyl)glycine



[01100] **Step A**: Preparation of 1,1-Dimethylethyl N-((4-hydroxy-1,1-dimethyl-7-(3-(methyloxy)propyl)-2-oxo-naphthalen-3-yl)carbonyl)glycinate

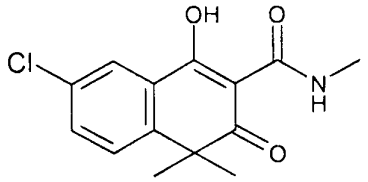
[01101] To a mixture of 1,1-dimethylethyl N-((4-hydroxy-1,1-dimethyl-7-((1E)-3-(methyloxy)-1-propen-1-yl)-2-oxo-naphthalen-3-yl)carbonyl)glycinate (245 mg, 590 μmol, Example 98 A) in EtOH (5897 μL), was added palladium (10 wt. % on activated carbon (62.8 mg, 590 μmol)) at ambient temperature. The mixture was placed under hydrogen gas using a balloon, and the reaction mixture was stirred for 1.5 hours before it was filtered through a pad of Celite,

washed with DCM, and concentrated to give the title compound (284 mg) as a light yellow oil. MS m/e = 440 $(M+Na)^+$.

[01102] **Step B**: Preparation of N-((4-Hydroxy-1,1-dimethyl-7-(3-(methyloxy)propyl)-2-oxo-naphthalen-3-yl)carbonyl)glycine

[01103] TFA (2 mL) was added to 1,1-dimethylethyl N-((4-hydroxy-1,1-dimethyl-7-(3-(methyloxy)propyl)-2-oxo-naphthalen-3-yl)carbonyl)glycinate (284 mg, 680 μmol) at ambient temperature, and the reaction was stirred for 30 minutes. The resulting mixture was concentrated to give the title compound (108 mg) as a light yellow amorphous solid after purification via preparatory LC. MS m/e = 362 $(M+H)^+$. Calculated for $C_{19}H_{23}NO_6$ 361.15.

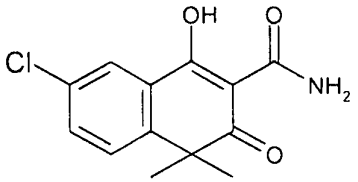
[01104] **Example 100.** 6-Chloro-4-hydroxy-N,1,1-trimethyl-2-oxo-naphthalene-3-carboxamide



[01105] **Step A:** Preparation of 6-Chloro-4-hydroxy-N,1,1-trimethyl-2-oxo-naphthalene-3-carboxamide

[01106] Ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (1.10 g, 3732 μmol, see Example 2) was dissolved in 2M methanamine in THF (9331 μL, 18661 μmol). The resulting mixture was stirred at 60°C for 16 hours and then diluted with 100 mL of EtOAc. The resulting mixture was added to a separatory funnel, partitioned with $NaHCO_3$ (saturated, aqueous), washed 2 times with 20 mL of $NaHCO_3$ (saturated, aqueous), separated, dried over Na_2SO_4 and concentrated in vacuo to give the title compound (131 mg) as a white solid after purification via preparatory LC. MS m/e = 280 $(M+H)^+$. Calculated for $C_{14}H_{14}ClNO_3$ 279.07.

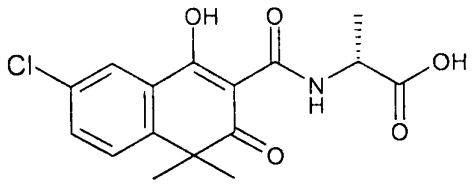
[01107] **Example 101.** 6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxamide



[01108] **Step A**: Preparation of 6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxamide

[01109] Ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (1.19 g, 4038 μmol, see Example 2) was dissolved in ammonia (0.5M in 1,4-dioxane (40376 μL, 20188 μmol)), and the resulting mixture was heated at 70°C for 16 hours. The reaction mixture was then concentrated, dissolved in MeOH and ammonium hydroxide, and stirred at ambient temperature for 16 hours. The reaction mixture was then heated at 80°C for 16 hours. The reaction mixture was concentrated, suspended in DCM, filtered, and washed with DCM. The mother liquor was purified via preparatory LC to give the title compound (31 mg) as an off-white solid. MS m/e = 266 $(M+H)^+$. Calculated for $C_{13}H_{12}ClNO_3$ 265.09.

[01110] **Example 102.** N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-D-alanine



[01111] **Step A**: Preparation of Methyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-D-alaninate

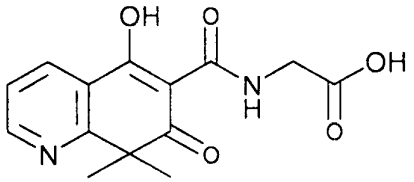
[01112] To ethyl 6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalene-3-carboxylate (100 mg, 339 μmol, see Example 2) and D-alanine methyl ester hydrochloride (71 mg, 509 μmol) was added 1,4-dioxane (339 μL) and N-ethyl-

N-isopropylpropan-2-amine (177 µL, 1018 µmol). The reaction was then heated at 80°C for 16 hours. The resulting reaction mixture was evaporated to give the title compound (78 mg) as an amorphous solid after purification via preparatory LC. MS m/e = 352 $(M+1)^+$.

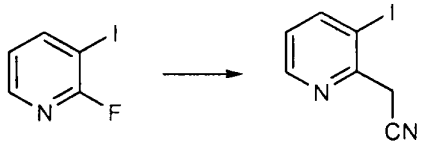
[01113] **Step B**: Preparation of N-((6-Chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-D-alanine

[01114] Methyl N-((6-chloro-4-hydroxy-1,1-dimethyl-2-oxo-naphthalen-3-yl)carbonyl)-D-alaninate (75 mg, 213 µmol) was dissolved in THF (2132 µL). 5N NaOH in water (2132 µL, 10660 µmol) was added at ambient temperature, and the reaction was stirred for 3 hours. The reaction mixture was acidified with 3N HCl, diluted with 50 mL of EtOAc, added to a separatory funnel, washed 2 times with 20 mL of brine (saturated, aqueous), separated, dried over Na_2SO_4, and concentrated to give the title compound as a white amorphous solid. MS m/e 338 $(M+H)^+$. Calculated for $C_{16}H_{16}ClNO_5$ 337.07.

[01115] **Example 103.** 2-(5-Hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxamido)acetic acid



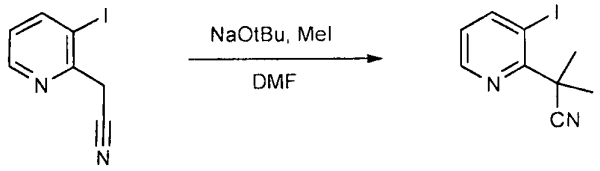
[01116] **Step A**: Preparation of 2-(3-Iodopyridin-2-yl)acetonitrile



[01117] To a solution of n-butyllithium (11 mL, 27 mmol) in dry THF (150 mL) at -78°C, was added dry ACN (2 mL, 29 mmol). The resulting mixture was stirred at -78°C for 45 minutes to generate a suspension of lithionitrile. 2-Fluoro-3-iodopyridine (5 g, 22 mmol) was added as a solution in

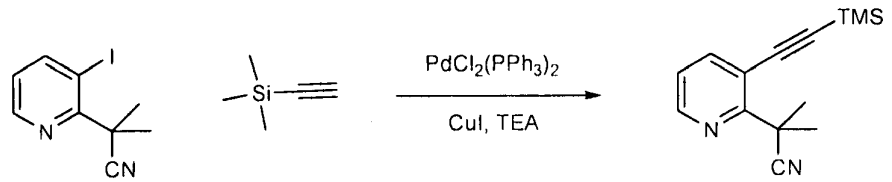
10 mL of THF, and the yellow mixture was allowed to warm slowly to room temperature. By the time that the temperature reached -19°C, the reaction had turned dark green. After 35 minutes (reaction temperature = -7°C), TLC (0-30% EtOAc/hexane) showed a new lower spot and a trace of starting material. LCMS showed the desired mass ($(M+H)^+ = 245$). The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed 3 times with saturated NH_4Cl and brine, and then dried over $MgSO_4$ and concentrated in vacuo to give a dark solid. The resulting product was purified by silica flash chromatography (0-50% EtOAc/hexane and then 10% MeOH/DCM) to give the title compound as a dark yellow solid (1.8 g, 33%). MS (m/z) = 245 $(M+H)^+$. Calculated for $C_7H_5IN_2$ 244.0.

[01118] **Step B**: Preparation of 2-(3-Iodopyridin-2-yl)-2-methylpropanenitrile



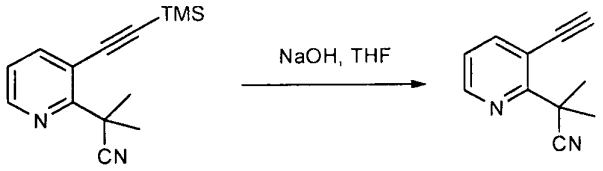
[01119] To a solution of 2-(3-iodopyridin-2-yl)acetonitrile (1.8 g, 7.4 mmol) and DMF (20 mL), was added sodium tert-butoxide (1.8 g, 18 mmol) and then MeI (1.0 mL, 16 mmol) at 0°C. The mixture was allowed to warm to room temperature. After 1.5 hours, LCMS showed complete reaction and the desired mass. The reaction was filtered through Celite and then concentrated in vacuo. The resulting product was extracted with EtOAc and washed with water and brine (3 x each) and then dried over $MgSO_4$ and concentrated in vacuo to give the crude product as a brown oil. The crude product was purified by silica flash chromatography (0-50% EtOAc/hexane) to give the title compound as a light-orange oil (1.8 g, 90%). MS (m/z) = 273 $(M+H)^+$. Calculated for $C_9H_9IN_2$ 272.1.

[01120] **Step C**: Preparation of 2-Methyl-2-(3-(2-(trimethylsilyl)ethynyl)pyridin-2-yl)propanenitrile



[01121] 2-(3-Iodopyridin-2-yl)-2-methylpropanenitrile (1.8 g, 6.6 mmol), cuprous iodide (0.045 mL, 1.3 mmol) and dichlorobis(triphenylphosphine)palladium (II) (0.46 g, 0.66 mmol) were dissolved in TEA (20 mL, 143 mmol). Ethynyltrimethylsilane (4.7 mL, 33 mmol) was added to the reaction mixture, and the reaction mixture was placed under an argon atmosphere. The reaction mixture was stirred and heated at 80°C. After 45 minutes, the reaction was >95% complete as determined by LCMS. The reaction was cooled to room temperature and then filtered through Celite to remove a dark solid. The filtrate was concentrated in vacuo and purified by silica flash chromatography (0-50% EtOAc/hexane) to give the title compound as a light-orange oil (1.6 g, 100%). MS (m/z) = 243 $(M+H)^+$. Calculated for $C_{14}H_{18}N_2Si$ 242.4.

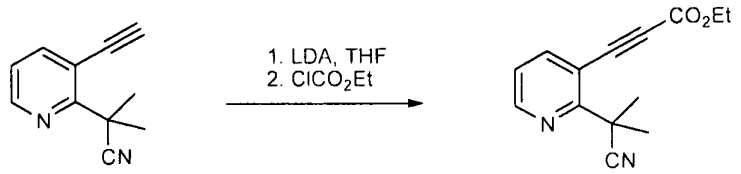
[01122] **Step D**: Preparation of 2-(3-Ethynylpyridin-2-yl)-2-methylpropanenitrile



[01123] To a solution of 2-methyl-2-(3-(2-(trimethylsilyl)ethynyl)pyridin-2-yl)propanenitrile (1.6 g, 6.6 mmol) and THF (20 mL, 244 mmol), was added NaOH (13 mL, 66 mmol). After 1.5 hours, TLC (30% EtOAc/hexane) showed complete reaction to provide a product with a lower spot. The reaction was acidified with 5N HCl (pH = 2) and then was extracted with EtOAc. The organic layer was washed with water and brine (3x each) and then dried over

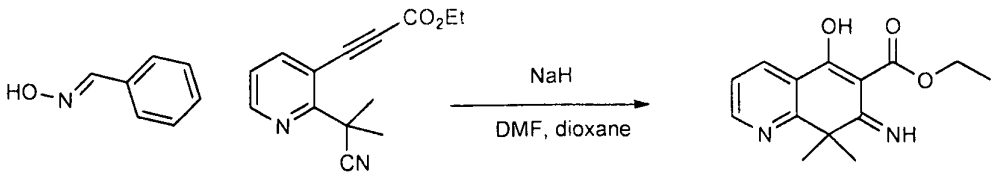
$MgSO_4$ and concentrated in vacuo to give a yellow oil. The crude product was purified by silica flash chromatography (0-75% EtOAc/hexane) to give the desired product as a light-orange crystalline solid (0.93 g, 83%). MS (m/z) = 171 $(M+H)^+$. Calculated for $C_{11}H_{10}N_2$ 170.2.

[01124] **Step E**: Preparation of Ethyl 3-(2-(2-cyanopropan-2-yl)pyridin-3-yl)propiolate



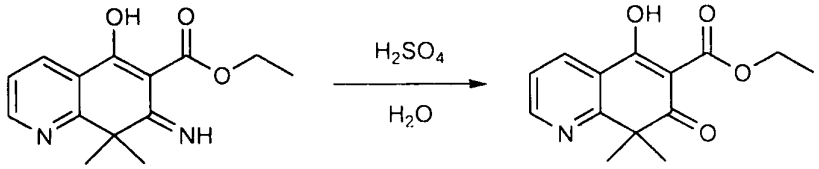
[01125] 2.5M n-butyllithium (6.6 mL, 16 mmol) was added to a stirred solution of diisopropylamine (2.4 mL, 17 mmol) in THF (20 mL) at -78°C. The reaction mixture was then allowed to warm to ambient temperature for 5 minutes before being cooled back down to -78°C. 2-(3-Ethynylpyridin-2-yl)-2-methylpropanenitrile (0.93 g, 5.5 mmol) was then added dropwise as a solution in THF (20 mL). After 15 minutes, ethyl chloroformate (1.7 mL, 17 mmol) in 5 mL of THF was added to the reaction. The resulting solution was allowed to warm to ambient temperature, and was then stirred for 15 minutes. TLC (30% EtOAc/hexane) showed complete reaction and a slightly lower spot than the starting material. 3 mL of MeOH was added at 8°C and then 3 mL of H_2O was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with water (3x), saturated NH_4Cl (3x) and brine (3x). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica flash chromatography (0-75% EtOAc/hexane) to give the title compound as a white crystalline solid (0.98g, 74%). MS (m/z) = 243 $(M+H)^+$. Calculated for $C_{14}H_{14}N_2O_2$ 242.3.

[01126] **Step F**: Preparation of Ethyl 5-hydroxy-7-imino-8,8-dimethyl-7,8-dihydroquinoline-6-carboxylate



[01127] A solution of benzaldehyde oxime (0.6 g, 5 mmol) in dry DMF (10 mL, 129 mmol) was added to a stirred suspension of 60% NaH (0.2 g, 5 mmol) in dry 1,4-dioxane (10 mL, 117 mmol) under a nitrogen atmosphere at room temperature. After 0.5 hours, a solution of the ethyl 3-(2-(2-cyanopropan-2-yl)pyridin-3-yl)propiolate (0.98 g, 4 mmol) in dry DMF (10 mL, 129 mmol) was added, and the solution was stirred for 30 minutes. The solvent was removed under vacuum, and water was added to the residue. The product was extracted with EtOAc. The organic layer was washed with water (3x) and then with saturated NH_4Cl and brine (3x each) and dried over $MgSO_4$. The resulting mixture was concentrated in vacuo to give a light-yellow crystalline solid/yellow oil. The yellow residue was washed with hexane providing the product as a yellow solid which was filtered off (0.65 g, 62%). MS (m/z) = 261 $(M+H)^+$. Calculated for $C_{14}H_{16}N_2O_3$ 260.3.

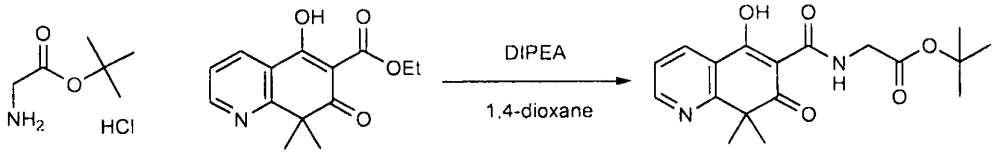
[01128] **Step G**: Preparation of Ethyl 5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxylate



[01129] To a mixture of ethyl 5-hydroxy-7-imino-8,8-dimethyl-7,8-dihydroquinoline-6-carboxylate (100 mg, 384 µmol) and water (3 mL, 166525 µmol), was added H_2SO_4 (0.02 mL, 384 µmol). The resulting mixture was then heated to 80°C. After 30 minutes, 0.1 mL of H_2SO_4 was added. After 90 minutes, the reaction was cooled to room temperature and extracted with EtOAc. The organic phase was washed with water and then with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated

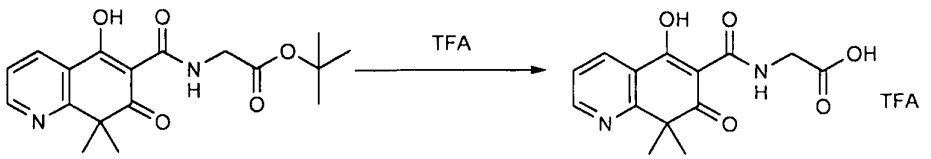
in vacuo to give a light-yellow solid. The aqueous layer was concentrated in vacuo to give a white solid/yellow liquid. The solid was washed with EtOH and a white solid was filtered away. The filtrate was concentrated in vacuo to give a yellow solid. The solid was washed with DCM and the supernatant was decanted off. The solid was dissolved in MeOH and concentrated in vacuo to give a light-yellow solid which was washed once more with DCM and the supernatant was decanted away. The solid was placed under high-vacuum to leave a light-yellow solid which was purified by silica flash chromatography (0-10% MeOH/DCM) to give the title compound as a white crystalline solid (24 mg, 24%). MS (m/z) = 262 $(M+H)^+$. Calculated for $C_{14}H_{15}NO_4$ 261.3.

[01130] **Step H**: Preparation of tert-Butyl 2-(5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxamido)acetate



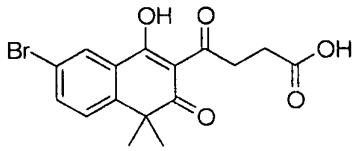
[01131] DIPEA (0.05 mL, 276 μmol) was added to a stirred mixture of ethyl 5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxylate (24 mg, 92 μmol) and glycine tert-butyl ester hydrochloride (38 mg, 230 μmol) in 1,4-dioxane (3 mL). The reaction mixture was then stirred at 75°C for 1.5 hours. The reaction mixture was concentrated, and the residue was purified by silica flash chromatography (0-75% EtOAc/hexane) to give the title compound as a crystalline white solid (15 mg, 47%). MS (m/z) = 347 $(M+H)^+$. Calculated for $C_{18}H_{22}N_2O_5$ 346.4.

[01132] **Step I**: Preparation of 2-(5-Hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxamido)acetic acid

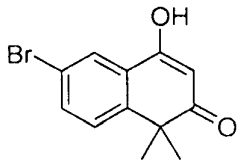


[01133] A solution of tert-butyl 2-(5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroquinoline-6-carboxamido)acetate (15 mg) and TFA (1 mL) was stirred at room temperature. After 20 minutes, LCMS showed that the reaction was complete. The reaction was concentrated in vacuo to give a yellow oil. The sample was lyophilized to give a white solid (10 mg, 60%). MS (m/z) = 291 $(M+H)^+$. Calculated for $C_{14}H_{14}N_2O_5$ 290.3.

[01134] **Example 104.** 4-(7-Bromo-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid

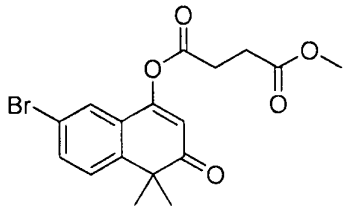


[01135] **Step A**: Preparation of 6-Bromo-4-hydroxy-1,1-dimethylnaphthalen-2(1H)-one



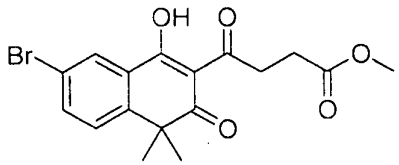
[01136] Concentrated aqueous HCl (36.5-37.5%, 10 mL) was added to a solution of ethyl 7-bromo-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalene-2-carboxylate (1.40 g, 4 mmol) in TFA (10 mL). The mixture was heated to 80°C for 18 hours. The solvent was then removed under reduced pressure, and the residue was rinsed with water and diethyl ether. The remaining solids were dried in vacuo at 50°C to afford the title compound in 70% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 7.98 (1 H, d, J = 1.9 Hz), 7.75 (1 H, dd, J = 2.0, 8.5 Hz), 7.67 (1 H, br. d, J ~ 8.0 Hz), 5.64 (1 H, s), 2.51 (6 H, m). MS (m/z not observed).

[01137] **Step B**: Preparation of 7-Bromo-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-1-yl methyl succinate



[01138] Methyl 4-chloro-4-oxobutyrate (0.107 mL, 0.873 mmol) was added to a solution of 6-bromo-4-hydroxy-1,1-dimethylnaphthalen-2(1H)-one (0.212 g, 0.794 mmol), TEA (0.121 mL, 0.873 mmol) in 1,2-dichloroethane (3 mL). The mixture was diluted with DCM, washed with water, washed with $NaHCO_3$, and dried over $MgSO_4$. The crude product was purified by flash chromatography using EtOAc/hexane to afford 7-bromo-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-1-yl methyl succinate in 85% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 7.74 (1 H, d, J = 2.0 Hz), 7.59 (1 H, dd, J = 8.4, 2.1 Hz), 7.36 (1 H, d, J = 8.5 Hz), 6.20 (1 H, s), 3.73 (3 H, s), 3.01 (2H, t, J = 6.0 Hz), 2.80 (2 H, t, J = 6.0 Hz), 1.48 (6 H, s). MS m/z: 381.

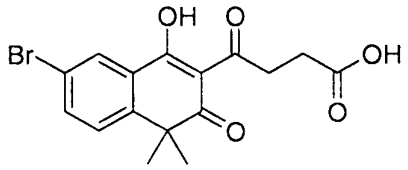
[01139] **Step C**: Preparation of Methyl 4-(7-bromo-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoate



[01140] A mixture of 7-bromo-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-1-yl methyl succinate (0.112 g, 0.29 mmol) and sodium acetate (0.024 g, 0.29 mmol) was heated at 160°C for 15 minutes. The mixture was cooled to room temperature, diluted with DCM, and washed with water. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography using EtOAc/hexane to afford the title

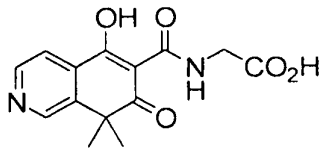
compound in 23% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 8.36-8.31 (1 H, m), 7.73-7.68 (1 H, m), 7.39-7.35 (1 H, m), 3.72, 3.71 (3 H, 2 s), 3.62, 3.49 (2 H, 2 t, $J \sim 6.4$ Hz), 2.74-2.68 (2 H, m), 1.64, 1.50 (6 H, 2 s). MS m/z: 383 (M^+).

[01141] **Step D**: Preparation of 4-(7-Bromo-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid



[01142] A solution of aqueous NaOH (5M, 2.0 mL) was added to a solution of methyl 4-(7-bromo-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoate (0.061 g, 0.16 mmol) in THF (1.5 mL). The mixture was stirred for 15 minutes at room temperature, diluted with DCM, and extracted with water. The water phase was acidified to pH = 1 using aqueous HCl (5M) and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated. The product was rinsed with diethyl ether and dried to afford the title compound in 31% yield. ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 12.19 (1 H, br. s.), 8.17, 8.16 (1 H, 2 s), 7.91-7.88 (1 H, m), 7.75-7.72 (1 H, m), 3.45-3.35 (2H, m, partially covered by HDO signal), 2.60-2.56 (2 H, m), 1.54 (6 H, br. s.). MS m/z: 368 (M^+).

[01143] **Example 105.** 2-(5-Hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxamido)acetic acid.



[01144] **Step A**: Preparation of ethyl 2-(3-fluoroisonicotinoyl)-4-methyl-3-oxopentanoate.

[01145] A mixture of ethyl isobutyrylacetate (2 mL, 10 mmol) in 20 mL ACN stirred at room temperature was treated with magnesium chloride (0.9 g,

10 mmol) in one portion and TEA (2 g, 22 mmol) drop wise. The mixture was stirred at room temperature for 2.5 hours.

[01146] A mixture of 3-fluoroisonicotinic acid (1.4 g, 10 mmol) in sulfuryl dichloride (12 g, 99 mmol) was refluxed for 2 hours until all solid was dissolved. The mixture was concentrated in vacuo. The residue was diluted with 30 mL ACN, and added to the above mixture drop wise. The mixture turned cloudy and was stirred at room temperature for 3.5 hours, M+1 = 282. The mixture was diluted with 200 mL ether, neutralized with 5N HCl to pH = 5, washed with H_2O (2 x 50 mL), brine 20 mL, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column eluting with 10-20% EtOAc/hexane to give 2.1 g of the intermediate as a pale orange yellow oil. MS m/e: $(M+H)^+$ 282.

[01147] **Step B**: Preparation of ethyl 5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxylate.

[01148] A mixture of potassium t-butoxide (0.34 g, 3.0 mmol) in 8 mL NMP stirred at room temperature was treated with a solution of ethyl 2-(3-fluoroisonicotinoyl)-4-methyl-3-oxopentanoate (0.28 g, 1.00 mmol) in 1 mL NMP drop wise. The dark red solution was stirred at room temperature for 15 hours, M+1= 262. There were two spots that had the MS = 262. The mixture was poured into 200 mL water. The mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried, and concentrated. The crude product was purified by column eluting with 10 - 50% EtOAc/hexane to give 0.2 g oil. MS m/e: $(M+H)^+$ 262.

[01149] **Step C**: Preparation of tert-butyl 2-(5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxamido)acetate.

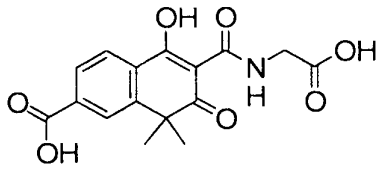
[01150] A mixture of ethyl 5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxylate (0.2 g, 0.8 mmol) and tert-butyl 2-aminoacetate hydrochloride (0.2 g, 0.9 mmol) in 1 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.4 mL, 2 mmol). The mixture was warmed to 100°C and stirred for 2.5 hours, M+1 = 347. The mixture was cooled to room temperature, diluted with 20 mL H_2O, and 100 mL EtOAc. The organic

layer was concentrated. The crude product was purified by column eluting with 10 - 20 % EtOAc/hexane to give 0.02 g of the product as an off-white solid. MS m/e: $(M+H)^+$ 347.

[01151] **Step D**: Preparation of 2-(5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxamido)acetic acid.

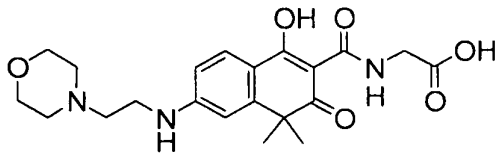
[01152] A mixture of tert-butyl 2-(5-hydroxy-8,8-dimethyl-7-oxo-7,8-dihydroisoquinoline-6-carboxamido)acetate (0.02 g, 0.06 mmol) in 2 mL TFA was stirred at room temperature for 1 hour, M+1= 291. The mixture was diluted with 10 mL water. The solution was concentrated and dried to give 0.018 g of the product as a pale yellow solid. MS m/e: $(M+H)^+$ 291.

[01153] **Example 106.** 6-((Carboxymethyl)carbamoyl)-7-hydroxy-8,8-dimethyl-5-oxo-5,8-dihydronaphthalene-2-carboxylic acid.



[01154] Tert-butyl 2-(7-bromo-2-hydroxy-1,1-dimethyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate (253 mg, 596 µmol, Example 53 A-E), trans-dichlorobis(triphenylphosphine)palladium (II) (21 mg, 30 µmol), and triphenylphosphine (16 mg, 60 µmol) were added to a vial, followed by water (32 µL, 1789 µmol) and n-tributylamine (1491 µL). The reaction mixture was placed under 4 atm of carbon monoxide at 90°C for 18 hours. The reaction mixture was diluted with 50 mL of EtOAc, washed 3 times with 50 mL of 5 N NaOH (aqueous), and separated. The aqueous layer was acidified to pH 2 with concentrated HCl and extracted 2 times with 50 mL of EtOAc, dried over sodium sulfate, and concentrated via rotovap to give the title compound. MS (ESI) m/z: Calculated; 333.3: Observed; 334.0.

[01155] **Example 107.** 2-(2-Hydroxy-1,1-dimethyl-7-(2-morpholinoethylamino)-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetic acid.



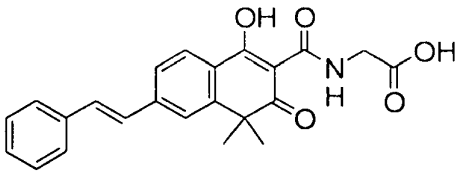
[01156] **Step A**: Preparation of tert-butyl 2-(2-hydroxy-1,1-dimethyl-7-(2-morpholinoethylamino)-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate.

[01157] Tert-butyl 2-(7-bromo-2-hydroxy-1,1-dimethyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate (125 mg, 295 μmol, Example 53 A-E), palladium acetate (7 mg, 29 μmol), racemic-2,2-bis(diphenylphosphino)-1,1-binaphthyl (18 mg, 29 μmol), and sodium tert-butoxide (42 mg, 442 μmol) were added to toluene (5892 μL) followed by 2-morpholinoethylamine (77 μL, 589 μmol). The reaction was then stirred at 110°C for 3 hours. The reaction mixture was diluted with 100 mL of EtOAc, washed 2 times with 50 mL of 3 N HCl (aqueous), and separated. The organic layer was dried over sodium sulfate and concentrated to give crude product which was purified via HPLC to give the title compound.

[01158] **Step B**: Preparation of 2-(2-hydroxy-1,1-dimethyl-7-(2-morpholinoethylamino)-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetic acid.

[01159] Tert-butyl 2-(2-hydroxy-1,1-dimethyl-7-(2-morpholinoethylamino)-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate (25 mg, 53 μmol) was dissolved in TFA (2 mL) at room temperature for 30 minutes and concentrated to give crude product. The crude product was purified via preparatory TLC to give the title compound. MS (ESI) m/z: Calculated; 417.5: Observed; 418.1.

[01160] **Example 108.** (E)-2-(2-Hydroxy-1,1-dimethyl-4-oxo-7-styryl-1,4-dihydronaphthalene-3-carboxamido)acetic acid.



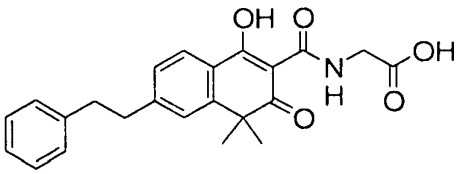
[01161] **Step A**: Preparation of (E)-tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-styryl-1,4-dihydronaphthalene-3-carboxamido)acetate.

[01162] Tert-butyl 2-(7-bromo-2-hydroxy-1,1-dimethyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate (360 mg, 848 μmol, Example 53 A-E) was dissolved in 1,4-dioxane (8485 μL) and then beta-styrylboronic acid pinacol ester (293 mg, 1273 μmol), potassium carbonate (2 M in water, 2121 μL, 4242 μmol) and tetrakis(triphenylphosphine)palladium (98.0 mg, 84.8 μmol) were added. The reaction was stirred at 80°C for 4 hours. The reaction mixture was diluted with 100 mL of EtOAc, washed 2 times with 50 mL of sodium bicarbonate (saturated, aqueous), separated, dried over sodium sulfate, and concentrated to give crude product. The title compound was obtained by flash chromatography.

[01163] **Step B**: Preparation of (E)-2-(2-hydroxy-1,1-dimethyl-4-oxo-7-styryl-1,4-dihydronaphthalene-3-carboxamido)acetic acid.

[01164] (E)-tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-styryl-1,4-dihydronaphthalene-3-carboxamido)acetate (120 mg, 268 μmol) was dissolved in TFA (2 mL) and stirred at room temperature for 30 minutes. The reaction mixture was concentrated, suspended in hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound. MS (ESI) m/z: Calculated; 391.4: Observed; 392.0.

[01165] **Example 109.** 2-(2-Hydroxy-1,1-dimethyl-4-oxo-7-phenethyl-1,4-dihydronaphthalene-3-carboxamido)acetic acid.



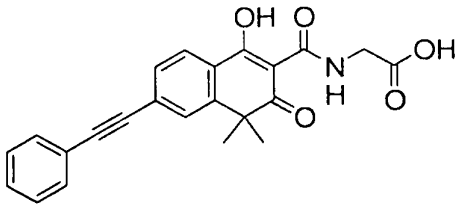
[01166] **Step A**: Preparation of tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-phenethyl-1,4-dihydronaphthalene-3-carboxamido)acetate.

[01167] (E)-tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-styryl-1,4-dihydronaphthalene-3-carboxamido)acetate (150 mg, 335 μmol, Example 108) was dissolved in EtOH (3352 μL). Palladium (10% on carbon, 35.7 mg, 335 μmol) was added, and the reaction mixture was placed under one atmosphere of hydrogen with a balloon for 2 hours. The reaction mixture was filtered through a pad of Celite, washed with DCM, and concentrated to give the title compound.

[01168] **Step B**: Preparation of 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-phenethyl-1,4-dihydronaphthalene-3-carboxamido)acetic acid.

[01169] Tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-phenethyl-1,4-dihydronaphthalene-3-carboxamido)acetate (130 mg, 289 μmol) was dissolved and stirred in TFA (2 mL) at ambient temperature for 30 minutes. The mixture was then concentrated to give the title compound. MS (ESI) m/z: Calculated; 393.4: Observed; 394.0

[01170] **Example 110.** 2-(2-Hydroxy-1,1-dimethyl-4-oxo-7-(2-phenylethynyl)-1,4-dihydronaphthalene-3-carboxamido)acetic acid.



[01171] **Step A**: Preparation of tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-(2-phenylethynyl)-1,4-dihydronaphthalene-3-carboxamido)acetate.

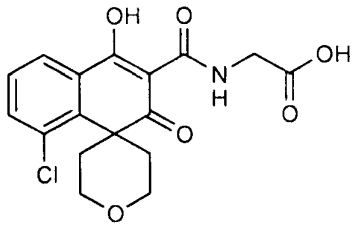
[01172] To a mixture of tert-butyl 2-(7-bromo-2-hydroxy-1,1-dimethyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetate (120 mg, 283 μmol,

Example 53 A-E), palladium dichloride bistriphenylphosphine (20 mg, 28 μmol), and copper(I) iodide (11 mg, 57 μmol) was added THF (1414 μL), *N*-ethyl-*N*-isopropylpropan-2-amine (148 μL, 848 μmol), and phenylacetylene (62 μL, 566 μmol). The reaction was heated at 80°C for 2 hours. The reaction mixture was diluted with 100 mL of EtOAc, washed 2 times with 75 mL of sodium bicarbonate (saturated, aqueous), separated, dried over sodium sulfate, and concentrated to give crude product which was purified via flash chromatography to give the title compound.

[01173] **Step B**: Preparation of 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-(2-phenylethynyl)-1,4-dihydronaphthalene-3-carboxamido)acetic acid.

[01174] Tert-butyl 2-(2-hydroxy-1,1-dimethyl-4-oxo-7-(2-phenylethynyl)-1,4-dihydronaphthalene-3-carboxamido)acetate (68 mg, 153 μmol) was dissolved and stirred in TFA (2 mL) at room temperature for 30 minutes. The reaction was concentrated, suspended in hexanes, filtered, washed with hexanes, and dried in a vacuum oven to give the title compound. MS (ESI) m/z: Calculated; 389.4: Observed; 390.0.

[01175] **Example 111.** N-((8-Chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.



[01176] **Step A**: Preparation of 2-(bromomethyl)-1-chloro-3-iodobenzene.

[01177] A mixture of 1-chloro-3-iodo-2-methylbenzene (11 g, 44 mmol) in 60 mL CCl_4 was stirred at 70°C and treated with 1-bromopyrrolidine-2,5-dione (12 g, 65 mmol) and dibenzoyl peroxide (1.1 g, 4.4 mmol) slowly. The resulting mixture was refluxed for 15 hours. The mixture was cooled to room temperature, filtered through a plug of Celite, and washed with 10%

EtOAc/hexane. The organic was concentrated and purified by column chromatography (0 - 10% EtOAc/hexane) to give 14 g pink solid.

[01178] **Step B**: Preparation of 2-(2-chloro-6-iodophenyl)acetonitrile.

[01179] A mixture of 2-(bromomethyl)-1-chloro-3-iodobenzene (14 g, 42 mmol) in 100 mL EtOH was treated with a solution of potassium cyanide (3.6 mL, 84 mmol) in 40 mL water. The mixture was refluxed for 2.5 hours. The mixture was cooled to room temperature and then concentrated. The residue was diluted with 200 mL EtOAc, washed with water (2x50 mL), saturated NaCl (50 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (20% EtOAc/hexane) to give 10.18 g pale yellow solid. MS m/e: $(M-1)^-$ 276.

[01180] **Step C**: Preparation of 2-(2-chloro-6-iodophenyl)acetic acid.

[01181] A mixture of 2-(2-chloro-6-iodophenyl)acetonitrile (10 g, 36 mmol) in 20 mL dioxane was treated with 25 mL 9M H_2SO_4. The mixture was stirred at 115°C for 2 hours. The mixture was transferred into a sealed tube and heated to 150°C and stirred for 2 hours. The mixture was then cooled to room temperature and diluted with 100 mL water. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over sodium sulfate, and concentrated to give crude product 10.3 g as pale yellow solid. MS m/e: $(M+H)^+$ 297.

[01182] **Step D**: Preparation of ethyl 2-(2-chloro-6-iodophenyl)acetate.

[01183] A mixture of 2-(2-chloro-6-iodophenyl)acetic acid (10 g, 34 mmol) in 100 mL EtOH was treated with 2 mL concentrated H_2SO_4, and refluxed for 15 hours. The resulting mixture was cooled to room temperature and concentrated. The residue was diluted with 200 mL EtOAc, washed with water (3 x 50 mL), saturated NaCl (20 mL), dried over sodium sulfate and concentrated. The crude mixture was purified by column chromatography (10-20% EtOAc/hexane) to give 9.5g of pale yellow oil. MS m/e: $(M+H)^+$ 324.

[01184] **Step E**: Preparation of ethyl 4-(2-bromoethoxy)-2-(2-chloro-6-iodophenyl)butanoate.

[01185] A mixture of ethyl 2-(2-chloro-6-iodophenyl)acetate (4.5 g, 14 mmol) in 12 mL DMF was stirred at room temperature and treated with sodium hydride (0.80 g, 35 mmol). The mixture turned to orange and was stirred for 10 minutes. The mixture was treated dropwise with 1-bromo-2-(2-bromoethoxy)ethane (4.2 g, 18 mmol) in 12 mL DMF. The resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was then warmed to 60°C and stirred for 2 hours. The mixture was cooled to room temperature and quenched carefully with 20 mL H_2O, extracted with ether (3 x 100 mL). The combined organic layers were washed with water (3x50 mL), 20 mL saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated to give 5.8 g of the crude product as a yellow oil. MS m/e: $(M+H)^+$ 475/477.

[01186] **Step F**: Preparation of ethyl 4-(2-chloro-6-(3,3,3-triethoxyprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01187] A mixture of ethyl 4-(2-bromoethoxy)-2-(2-chloro-6-iodophenyl)butanoate (5.8 g, 12 mmol) and TEA (15 mL, 110 mmol) in 24 mL ACN was degassed by vacuum and back filled with nitrogen 3 times. The mixture was treated with 3,3,3-triethoxyprop-1-yne (2.7 g, 16 mmol), dichlorobis(triphenylphosphine)palladium(ii) (0.17 g, 0.24 mmol) and copper(I) iodide (0.12 g, 0.61 mmol). The mixture was stirred at 55°C for 2 hours. The mixture was cooled to room temperature, diluted with 100 mL EtOAc, and washed with water (3 x 20 mL) and then with 20 mL saturated NaCl. The organic layers were dried and concentrated. The crude product was evaporated from 50 mL toluene and dissolved in 50 mL DMF. The mixture was treated with 0.7 g NaH. The mixture was stirred at room temperature for 15 hours. The mixture was quenched with 50 mL water and neutralized with 10% HCl to pH = 5. The mixture was then extracted with ether (3 x 100 mL). The combined organic layers were washed with water (3 x 20 mL) and saturated NaCl (20 mL), and then dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (10% EtOAc/hexane) to give 2.42 g yellow oil. MS m/e: $(M+H)^+$ 487.

[01188] **Step G**: Preparation of ethyl 4-(2-chloro-6-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01189] A mixture of ethyl 4-(2-chloro-6-(3,3,3-triethoxyprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate (2.42 g, 5.51 mmol) in 50 mL EtOH and 10 mL water was treated with 4-methylbenzenesulfonic acid hydrate (0.105 g, 0.551 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was diluted with 100 mL EtOAc, washed with 20 mL saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The concentrate was purified by column chromatography (20% EtOAc/hexane) to give 1.19 g pale yellow solid. MS m/e: $(M+H)^+$ 365.

[01190] **Step H:** Preparation of (Z)-ethyl 4-(2-chloro-6-(3-ethoxy-1-hydroxy-3-oxoprop-1-enyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01191] A mixture of lithium acetate (0.21 g, 3.2 mmol) in 5 mL TFA at room temperature was treated with ethyl 4-(2-chloro-6-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate (1.18 g, 3.2 mmol), and palladium(II) acetate (0.036 g, 0.16 mmol). The reaction was stirred at room temperature for 2 hours. The residue was diluted with 100 mL EtOAc, washed with water (3 x 20 mL), saturated NaCl (20 mL), dried over anhydrous sodium sulfate, and concentrated. The concentrate was purified by column chromatography (10 - 20% EtOAc/hexane) to give 0.38 g yellow oil. MS m/e: $(M+H)^+$ 383.

[01192] **Step I**: Preparation of ethyl 8-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate.

[01193] A mixture of (Z)-ethyl 4-(2-chloro-6-(3-ethoxy-1-hydroxy-3-oxoprop-1-enyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate (0.38 g, 0.99 mmol) in 5 mL EtOH was treated with NaOEt (freshly made from 0.1g Na and 5 mL EtOH), and stirred at 60°C for 2 hours. The mixture was cooled to room temperature and diluted with 100 mL EtOAc, neutralized with 5N HCl to pH = 5, washed with water (20 mL), saturated NaCl (20mL), dried over anhydrous sodium sulfate and concentrated. The concentrate was purified by column

chromatography (10 - 40% EtOAc/hexane) to give 0.27 g yellow solid. MS m/e: $(M+H)^+$ 337.

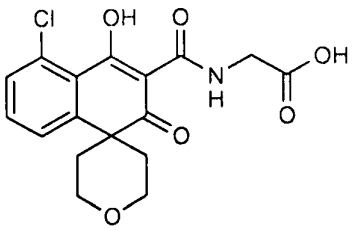
[01194] **Step J**: Preparation of t-butyl- N-((8-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate.

[01195] A mixture of ethyl 8-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.27 g, 0.80 mmol), and tert-butyl 2-aminoacetate hydrochloride (0.20 g, 1.2 mmol) in 1 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.26 g, 2.0 mmol). The mixture was warmed to 100°C and stirred for 2.5 hours. The mixture was then cooled to room temperature, diluted with 20 mL H_2O and 100 mL EtOAc. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. The concentrate was purified by column chromatography (10 - 20 % EtOAc/hexane) to give 0.13 g off-white solid. MS m/e: $(M+H)^+$ 422.

[01196] **Step K**: Preparation of N-((8-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.

[01197] A mixture of t-butyl- N-((8-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.13 g, 0.31 mmol) in 1.5 mL TFA was stirred at room temperature for 30 minutes. The mixture was diluted with 20 mL water, and a white solid precipitate formed. The solid was collected by filtration and washed with 20 mL water. The solid was dried under high vacuum to give 0.11 g off-white solid. MS m/e: $(M+H)^+$ 366.

[01198] **Example 112.** 7 N-((5-Chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.



[01199] **Step A**: Preparation of 1-(bromomethyl)-3-chloro-2-iodobenzene.

[01200] A mixture of 1-chloro-2-iodo-3-methylbenzene (7.5 g, 30 mmol) in 60 mL CCl_4 stirred at 70°C was treated with 1-bromopyrrolidine-2,5-dione (7.9 g, 45 mmol) and dibenzoyl peroxide (0.72 g, 3.0 mmol) slowly. The mixture was refluxed under a sunlight lamp for 15 hours. The mixture was cooled to room temperature, filtered through a plug of Celite, and rinsed with 10% EtOAc/hexane. The filtrate was concentrated and purified by column chromatography (0 - 10% EtOAc/hexane) to give 7.1 g pink oil.

[01201] **Step B**: Preparation of 2-(3-chloro-2-iodophenyl)acetonitrile.

[01202] A mixture of 1-(bromomethyl)-3-chloro-2-iodobenzene (7 g, 21 mmol) in 100 mL EtOH was treated with a solution of potassium cyanide (2 mL, 42 mmol) in 20 mL water. The mixture was refluxed for 2.5 hours. The mixture was cooled to room temperature and concentrated. The residue was diluted with 200 mL EtOAc, washed with water (2x50 mL), saturated NaCl (50 mL), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (20% EtOAc/hexane) to give 3.2 g pale yellow solid. MS m/e: $(M+H)^+$ 278.

[01203] **Step C**: Preparation of 2-(3-chloro-2-iodophenyl)acetic acid.

[01204] A mixture of 2-(3-chloro-2-iodophenyl)acetonitrile (3.2 g, 12 mmol) in 20 mL dioxane was treated with 25 mL 9M H_2SO_4. The mixture was stirred at 115°C for 2 hours, cooled to room temperature, and diluted with 100 mL water. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over anhydrous sodium sulfate, and concentrated to give crude product in 4g as pale yellow solid. MS m/e: $(M+H)^+$ 297.

[01205] **Step D**: Preparation of ethyl 2-(3-chloro-2-iodophenyl)acetate.

[01206] A mixture of 2-(3-chloro-2-iodophenyl)acetic acid (3.2 g, 11 mmol) in 50 mL EtOH was treated with 2 mL con. H_2SO_4, and refluxed for 2 hours. The mixture was cooled to room temperature, diluted with 200 mL EtOAc, washed with water (3 x 50 mL), saturated NaCl (20 mL), dried over

anhydrous sodium sulfate and concentrated. The concentrate was purified by column chromatography (10 - 20% EtOAc/hexane) to give 3.62 g pale yellow oil. MS m/e: $(M+H)^+$ 325.

[01207] **Step E**: Preparation of ethyl 4-(3-chloro-2-iodophenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01208] A mixture of ethyl 2-(3-chloro-2-iodophenyl)acetate (1.3 g, 4.0 mmol) in 6 mL DMF was stirred at room temperature and treated with sodium hydride (0.23 g, 10 mmol). The mixture turned orange, was stirred for 10 minutes, and was treated with 1-bromo-2-(2-bromoethoxy)ethane (1.2 g, 5.2 mmol) in 6 mL DMF dropwise. The mixture was then stirred at room temperature for 2.5 hours. The mixture was carefully quenched with 20 mL H_2O and extracted with ether (3 x 100 mL). The combined organic layers were washed with water (3x50 mL), 20 mL saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column eluting with (10 - 20% EtOAc/hexane) to give the title compound in 0.57 g. MS m/e: $(M+H)^+$ 395.

[01209] **Step F**: Preparation of ethyl 4-(3-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01210] A mixture of ethyl 4-(3-chloro-2-iodophenyl)-tetrahydro-2H-pyran-4-carboxylate (0.57 g, 1.4 mmol) and TEA (1.8 mL, 13 mmol) in 10 mL ACN was degassed by vacuum and back filled with nitrogen 3 times. The mixture was treated with 3,3,3-triethoxyprop-1-yne (0.37 g, 2.2 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.051 g, 0.072 mmol) and copper(I) iodide (0.028 g, 0.14 mmol) and stirred at 55°C for 2 hours. The mixture was cooled to room temperature and concentrated. The residue was diluted with 50 mL EtOH and 10 mL water. The mixture was treated with 4-methylbenzenesulfonic acid hydrate (0.105 g, 0.551 mmol) and stirred at room temperature for 2 hours. The mixture was diluted with 100 mL EtOAc, washed with 20 mL saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (10 - 25% EtOAc/hexane) to give 0.5 g yellow oil. MS m/e: $(M+H)^+$ 365.

[01211] **Step G**: Preparation of (Z)-ethyl 4-(3-chloro-2-(3-ethoxy-1-hydroxy-3-oxoprop-1-enyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate.

[01212] A mixture of ethyl 4-(3-chloro-2-(3-ethoxy-3-oxoprop-1-ynyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate (0.5 g, 1 mmol) in 1.5 mL TFA was stirred at room temperature and treated with lithium acetate (0.09 g, 1 mmol) and palladium(II) acetate (0.02 g, 0.07 mmol). The resulting solution was stirred at room temperature for 2 hours and concentrated. The residue was diluted with 100 mL EtOAc, washed with water (3 x 20 mL), 20 mL saturated NaCl, dried over anhydrous sodium sulfate, and concentrated. The concentrate was purified by column chromatography (10 - 20% EtOAc/hexane) to give 0.15 g of the product as a yellow oil. MS m/e: $(M+H)^+$ 383.

[01213] **Step H**: Preparation of ethyl 5-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate.

[01214] A mixture of (Z)-ethyl 4-(3-chloro-2-(3-ethoxy-1-hydroxy-3-oxoprop-1-enyl)phenyl)-tetrahydro-2H-pyran-4-carboxylate (0.14 g, 0.37 mmol) in 5 mL EtOH was treated with NaOEt (from 0.1g Na reacted with 5 mL EtOH). The mixture was stirred at room temperature for 2 hours, quenched with 20 mL water, and neutralized with 5N HCl to pH = 5. The mixture was extracted with EtOAc 3 x50 mL. The combined organic layers were washed with saturated NaCl (20 mL), dried over anhydrous sodium sulfate, and concentrated. The concentrate was purified by column chromatography (10-40% EtOAc/hexane) to give 67 mg white solid. MS m/e: $(M+H)^+$ 337.

[01215] **Step I**: Preparation of t-butyl-N-((5-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate.

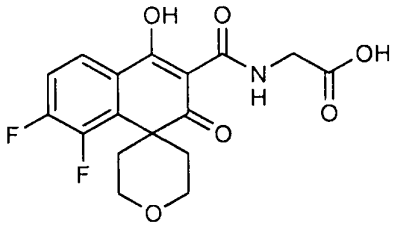
[01216] A mixture of ethyl 5-chloro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate (70 mg, 208 μmol) and tert-butyl 2-aminoacetate hydrochloride (52 mg, 312 μmol) in 1 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (81 mg, 624 μmol). The mixture was warmed to 95°C and stirred for 2.5 hours, cooled to room temperature, and then diluted with 20 mL H_2O and 100 mL EtOAc. The organic layers were separated, washed with 20 mL 1N HCl x 2, water 20 mL, saturated

NaCl 20 mL, dried over anhydrous sodium sulfate, and concentrated. The concentrate was purified by column chromatography (10 - 20 % EtOAc/hexane) to give 51 mg pale yellow solid. MS m/e: $(M+H)^+$ 366.

[01217] **Step J**: Preparation of N-((5-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.

[01218] A mixture of t-butyl-N-((5-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (51 mg, 121 μmol) in 1 mL TFA was stirred at room temperature for 30 minutes and diluted with 20 mL water. The solid was collected by filtration and washed with 20 mL water. The solid was then dried under high vacuum to give, 39 mg pale yellow solid. MS m/e: $(M+H)^+$ 366.

[01219] **Example 113.** N-((7,8-Difluoro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.



[01220] **Step A**: Preparation of 4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile.

[01221] A mixture of sodium hydride (2 mL, 88 mmol) in 120 mL NMP was stirred at 0°C and treated with a mixture of bis(2-bromoethyl) ether (9 mL, 40 mmol) and 2-(2,3-difluorophenyl)acetonitrile (6.12 g, 40 mmol) in 20 mL ether. The reaction was stirred at room temperature for 4 hours, carefully quenched with 20 mL H_2O, and neutralized to pH = 5 with concentrated HCl. The mixture was further diluted with 200 mL water, and the precipitate was collected by filtration. The solid was redissolved in 200 mL ether, washed with 20 mL saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated to give 6.55 g of the title compound as a white solid. MS m/e: $(M+H)^+$ 224.

[01222] **Step B**: Preparation of 4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid.

[01223] A mixture of 4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carbonitrile (7.8 g, 35 mmol) in 100 mL dioxane was treated with concentrated sulfuric acid (6.9 g, 70 mmol) 13 mL H_2O, and stirred at 160°C in a sealed tube for 2 hours. The mixture was treated with 20 mL water and stirred at 110°C for 15 hours. The mixture was then stirred at 160°C for another 5 hours. The resulting mixture was cooled to room temperature. The reaction was then diluted with water and extracted with EtOAc. The organic layer was extracted with 1M NaOH. Upon acidifying the aqueous phase with concentrated HCl, a precipitate formed. The precipitate was collected by filtration to give 6.2 g of the title compound as pale yellow solid. MS m/e: $(M+H)^+$ 243.

[01224] **Step C**: Preparation of diethyl 2-(4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate.

[01225] A mixture of diethyl malonate (4.2 g, 26 mmol) in 50 mL ACN was stirred at 0°C and treated with magnesium chloride (2.5 g, 26 mmol) in one portion and TEA (5.9 g, 58 mmol) dropwise. The mixture was stirred at room temperature for 2.5 hours. In a separate flask, a mixture of 4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carboxylic acid (6.4 g, 26 mmol) in sulfuryl dichloride (31 g, 264 mmol) was refluxed for 2 hours, then concentrated in vacuo. This residue was diluted with 30 mL ACN, and added to the malonate/magnesium chloride mixture dropwise. The resulting reaction was stirred at 50°C for 1.5 hours. The mixture was cooled to room temperature, diluted with 200 mL EtOAc, neutralized to pH= 5 with concentrated HCl, washed with H_2O (2 x 50 mL), saturated NaCl (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (10-20% EtOAc/hexane) to give the intermediate 3.3 g as pale yellow oil. MS m/e: $(M+H)^+$ 385.

[01226] **Step D**: Preparation of ethyl 7,8-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate.

[01227] To 10 mL concentrated H_2SO_4 stirred at 0°C was added diethyl 2-(4-(2,3-difluorophenyl)-tetrahydro-2H-pyran-4-carbonyl)malonate (3.3 g, 8.6 mmol) dropwise. The mixture was stirred at 0°C and allowed to warm to room temperature over 2 hours. The mixture was poured into 100 g crushed ice and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated NaCl (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography (20 % EtOAc/hexane) to give the title compound 0.23g as a pale yellow solid. MS m/e: $(M+H)^+$ 339.

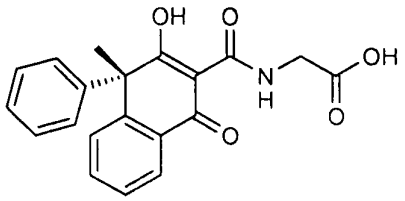
[01228] **Step E**: Preparation of t-butyl N-((7,8-difluoro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate.

[01229] A mixture of ethyl 7,8-difluoro-4-hydroxy-2-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-carboxylate (0.23 g, 0.68 mmol), tert-butyl 2-aminoacetate hydrochloride (0.14 g, 0.82 mmol) in 3 mL dioxane was treated with N-ethyl-N-isopropylpropan-2-amine (0.26 g, 2.0 mmol). The mixture was warmed to 120°C and stirred for 1.5 hours. The mixture was cooled to room temperature, diluted with 20 mL H_2O, and 100 mL EtOAc. The organic layer was separated, washed with 20 mL 1N HCl, saturated NH_4Cl, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (10 - 20 % EtOAc/hexane) to give 0.13 g white solid. MS m/e: $(M+H)^+$ 424.

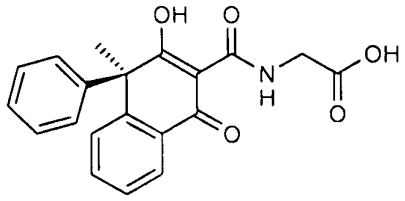
[01230] **Step F**: Preparation of (I) N-((7,8-difluoro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycine.

[01231] A mixture of t-butyl N-((7,8-difluoro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)carbonyl)glycinate (0.13 g, 0.3 mmol) in 3 mL TFA was stirred at room temperature for 1 hour. The mixture was diluted with 100 mL water and a white precipitate was formed to form a suspension. The suspension was stirred for 30 minutes at room temperature, filtered, and washed with 20 mL water. The solid was dried under vacuum at 45°C for 15 hours to give 0.09 g of the title compound as a white solid. MS m/e: $(M+H)^+$ 368.

[01232] **Example 114.** N-(((4S)-3-Hydroxy-4-methyl-1-oxo-4-phenyl-1,4-dihydro-2-naphthalenyl)carbonyl)glycine or N-(((4R)-3-Hydroxy-4-methyl-1-oxo-4-phenyl-1,4-dihydro-2-naphthalenyl)carbonyl)glycine.

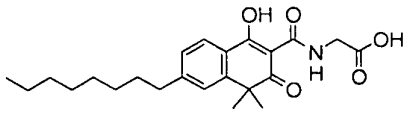
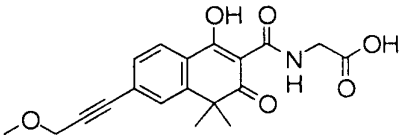
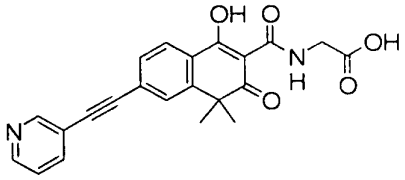


or

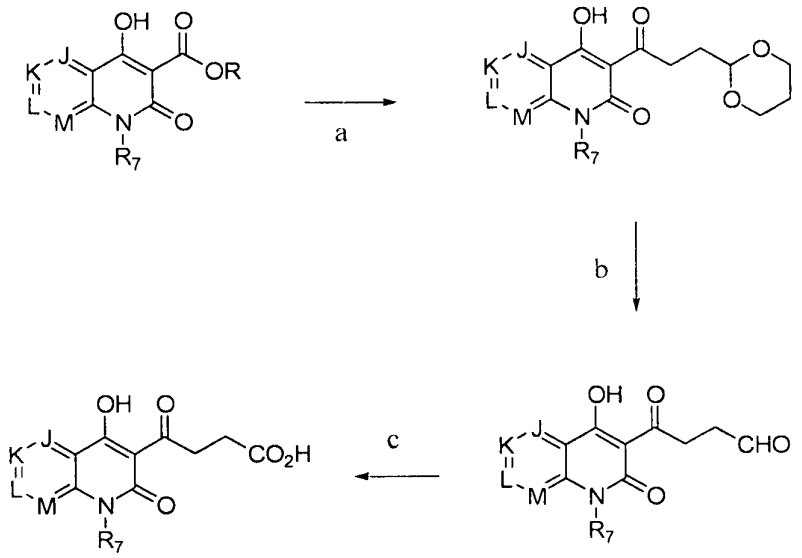


[01233] A mixture of one of the enantiomers of 2-(6-chloro-1-(4-chlorophenyl)-2-hydroxy-1-methyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetic acid (50 mg, 119 μmol, Example 29) and 50 mg 10% Pd-C in 10 mL MeOH was treated with sodium acetate (29 mg, 357 μmol). The mixture was stirred at room temperature under hydrogen for 4 hours, M+1= 352. The mixture was filtered through a short plug of silica gel and washed with 20 mL EtOAc. The organic layer was concentrated and purified by column eluting with 1:50:100 = AcOH/EtOAc/hexane to give 20 mg white solid. MS m/e: $(M+H)^+$ 352.

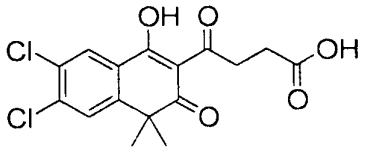
[01234] **Table 1.** The following table lists compounds which were prepared by the methods described in the referenced Examples.

Ex.	Structure	Name	MS H+	Synthetic Method
115		2-(2-hydroxy-1,1-dimethyl-7-octyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetic acid	402.3	Examples 108 and 109
116		2-(2-hydroxy-7-(3-methoxyprop-1-ynyl)-1,1-dimethyl-4-oxo-1,4-dihydronaphthalene-3-carboxamido)acetic acid	358.0	Example 110
117		2-(2-hydroxy-1,1-dimethyl-4-oxo-7-(2-(pyridin-3-yl)ethynyl)-1,4-dihydronaphthalene-3-carboxamido)acetic acid	391.1	Example 110

[01235] **Scheme 5.** General method for the preparation of the 4-Oxobutanoic acid side chain.



[01236] **Example 118**. 4-(6,7-Dichloro-3-hydroxy-4,4-dimethyl-1-oxo-1,4-dihydro-2-naphthalenyl)-4-oxobutanoic acid.



[01237] **Step A**: Preparation of 3-(3-(1,3-dioxan-2-yl)propanoyl)-6,7-dichloro-4-hydroxy-1,1-dimethylnaphthalen-2(1H)-one.

[01238] A mixture of ethyl 6,7-dichloro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalene-2-carboxylate (0.5 g, 2 mmol, Example 4 A-E) in 20 mL THF was stirred at room temperature and treated with sodium hydride (0.2 mL, 8 mmol). The resulting mixture was then stirred for 30 minutes. The mixture was then treated with 2-[2-(1,3-dioxanyl)]ethylmagnesium bromide (3 mL, 2 mmol) dropwise and stirred at room temperature for 2 hours. The mixture was quenched with water 10 mL at 0 °C, and neutralized with 2N HCl to pH= 5. The mixture was extracted with EtOAc 3 x 50 mL. The combined organic layers were washed with brine 20 mL, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography

eluting with 20% EtOAc/hexane to give 0.26 g pure product as white solid. MS m/e: 399 $(M+H)^+$.

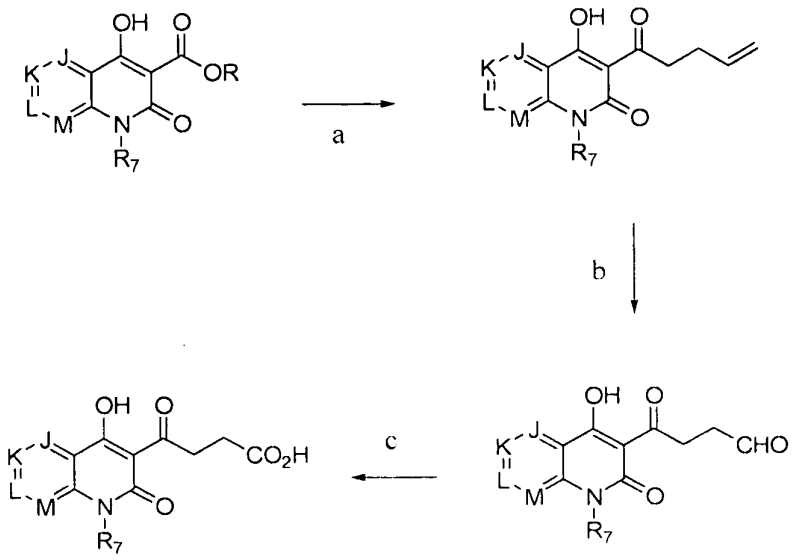
[01239] **Step B**: Preparation of 4-(6,7-dichloro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanal.

[01240] A mixture of 3-(3-(1,3-dioxan-2-yl)propanoyl)-6,7-dichloro-4-hydroxy-1,1-dimethylnaphthalen-2(1H)-one (0.26 g, 0.65 mmol) in 25 mL acetic acid /water (4:1) was warmed to 95°C and stirred for 1 hour. The mixture was treated with 10 mL water and stirred at 95°C for another 30 minutes. The reaction mixture was diluted with 20 mL water and cooled to room temperature. The resulting mixture was then diluted with 200 mL additional water. The precipitate that formed was filtered and washed with 20 mL H_2O. The crude precipitate was dissolved in 100 mL DCM, washed with 20 mL saturated NH_4Cl, dried over anhydrous Na_2SO_4, and concentrated to give 0.22 g of the product as a pale yellow solid. MS m/e: 341 $(M+H)^+$.

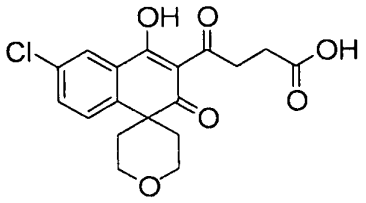
[01241] **Step C**: Preparation of 4-(6,7-dichloro-3-hydroxy-4,4-dimethyl-1-oxo-1,4-dihydro-2-naphthalenyl)-4-oxobutanoic acid.

[01242] A mixture of 4-(6,7-dichloro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanal (0.22 g, 0.64 mmol) in 6 mL DMF was stirred at room temperature and treated with oxone (0.36 mL, 0.64 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was quenched with 50 mL H_2O and adjusted to pH = 5 with concentrated HCl. The solid was collected by filtration and washed with 20 mL H_2O. The crude was dried under high vacuum to give 0.23 g white solid. MS m/e: 357 $(M+H)^+$. Calculated for $C_{16}H_{14}Cl_2O_5$: 356.

[01243] **Scheme 6.** General method for the preparation of the 4-Oxobutanoic acid side chain.



[01244] **Example 119.** 4-(6-Chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-4-oxobutanoic acid.



[01245] **Step A**: Preparation of 6-chloro-2-hydroxy-3-(4-pentenoyl)-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-4-one.

[01246] A mixture of ethyl 6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-spiro[naphthalene-1,4'-pyran]-3-carboxylate (2.53g, 8 mmol, Example 1 A-C) in 20 mL THF was stirred at room temperature and treated with sodium hydride (0.6 g, 15 mmol, 60% in oil). The resulting mixture was stirred for 10 minutes. The mixture was then treated with 3-butenylmagnesium bromide (15 mL, 8 mmol). After 5 minutes, the mixture was warmed to 60°C, and the reaction was stirred for another 0.5 hours. The mixture was cooled to 0°C, quenched with 20 mL saturated NH_4Cl, and 100 mL EtOAc was added. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column

chromatography eluting with 10 - 20 % EtOAc/hexane to give 2.17 g white solid. MS m/e: 347 $(M+H)^+$.

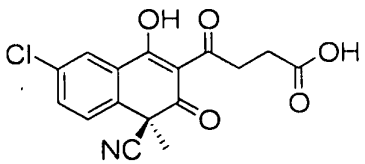
[01247] **Step B**: Preparation of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-4-oxobutanal.

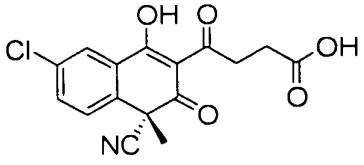
[01248] A mixture of 6-chloro-2-hydroxy-3-(4-pentenoyl)-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-4-one (0.65 g, 1.9 mmol) in 50 mL DCM was stirred at -78 °C and treated with O_3 until the solution remained blue. The mixture was stirred at -78 °C for 30 minutes and then treated with 1 mL dimethyl sulfide and stirred from -78°C to 0°C for 2 hours. The mixture was concentrated in vacuo and purified by column eluting with 40:100 = EtOAc/hexane to give the desired product. MS m/e: 349 $(M+H)^+$.

[01249] **Step C**: Preparation of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-4-oxobutanoic acid.

[01250] A mixture of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-4-oxobutanal (0.2g, 0.6 mmol) in 3 mL DMF was stirred at room temperature and treated with oxone (0.3 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was quenched with 10 mL H_2O and adjusted to pH = 5 with concentrated HCl. The solid was collected by filtration and washed with 10 mL H_2O. The crude product was dissolved in 50 mL EtOAc and washed with 20 mL H_2O and then with 20 mL brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 0.20 g white solid. MS m/e: 365 $(M+H)^+$. Calculated for $C_{18}H_{17}ClO_6$: 364.

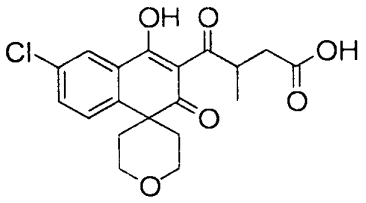
[01251] **Example 120.** Resolution of 4-(7-chloro-4-cyano-1-hydroxy-4-methyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid.





[01252] 4-(7-Chloro-4-cyano-1-hydroxy-4-methyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid (0.1g, prepared according to Example 123) was dissolved in dimethyoxy ethylenegycol (10mL) and separated on a chiralpack ADH (21x250mm, 5μm) column in ten 1mL injections (flow: 60mL/min, eluent: 50% MeOH in supercritical fluid and carbon dioxide). The first peak was concentrated and dried in vacuo to give the first enantiomer (35 mg). MS m/z 334 $(M+H)^+$. Calculated for $C_{16}H_{12}ClNO_5$: 333. The second peak was concentrated and dried in vacuo to give the other enantiomer (36 mg). MS m/z 334 $(M+H)^+$. Calculated for $C_{16}H_{12}ClNO_5$: 333.

[01253] **Example 121.** 4-(6-Chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-3-methyl-4-oxobutanoic acid.



[01254] **Step A**: Preparation of 3-(3-(1,3-dioxan-2-yl)propanoyl)-2-methyl-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-one.

[01255] A mixture of 6-chloro-2-hydroxy-3-(4-pentenoyl)-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-4-one (0.3 g, 0.7 mmol, see Example 119) in 20 mL THF stirred at 0°C was treated with lithium bis(trimethylsilyl)amide (1.0M solution in THF, 2 mL, 2 mmol). The mixture was stirred at 0°C for 1 hour and was then treated with methyl iodide (0.09 mL, 1 mmol). The resulting mixture was stirred at 0°C and allowed to warm to room temperature over 5 hours. The mixture was treated with another 1.0 mL LHMDS and 0.1 mL iodomethane and stirred at room temperature for 15 hours. The mixture was treated with another 1 mL LHMDS and stirred at room temperature for 2 additional hours. The mixture was quenched with 20 mL

water, adjusted pH = 5 with concentrated HCl, and extracted with EtOAc 3 x 50 mL. The combined organic layers were washed with brine (20 mL), dried, and concentrated. The crude product was purified by column chromatography eluting with 20 - 40% EtOAc/hexane to give 0.13 g of the product as a pale yellow solid. MS m/z 421 $(M+H)^+$.

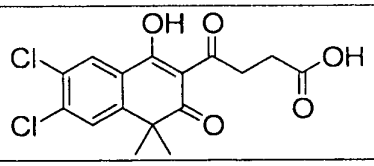
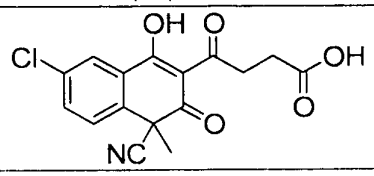
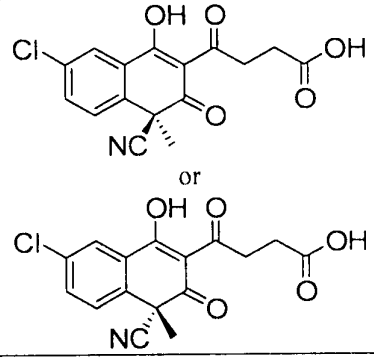
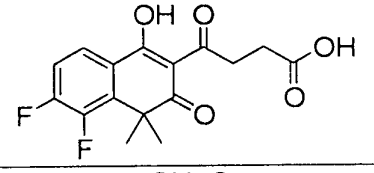
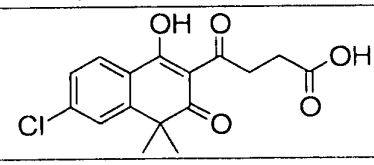
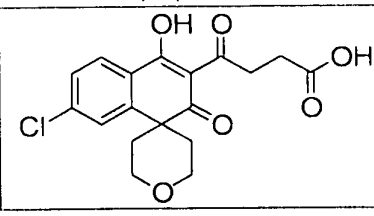
[01256] **Step B**: Preparation of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-3-methyl-4-oxobutanal.

[01257] A mixture of 3-(3-(1,3-dioxan-2-yl)propanoyl)-2-methyl-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-one (0.13 g, 0.3 mmol) in 20 mL 50% acetic acid / water was stirred at 95°C for 1 h. The mixture was cooled to room temperature and diluted with 100 mL water. The mixture was extracted with EtOAc 3x50 mL. The combined organic layers were washed with saturated $NaHCO_3$ 3 x 50 mL, brine 30 mL, dried over anhydrous Na_2SO_4, and concentrated to give 0.1 g of the product as a yellow solid. MS m/z 363 $(M+H)^+$.

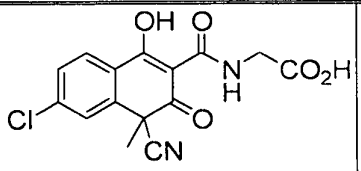
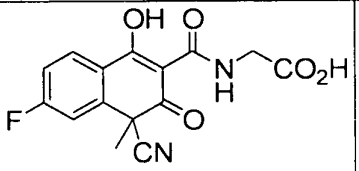
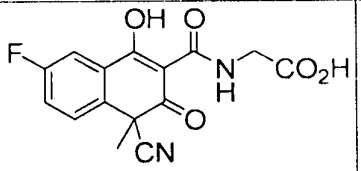
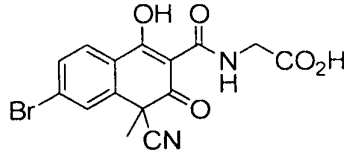
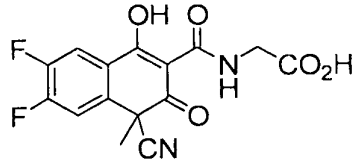
[01258] **Step C**: Preparation of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-3-methyl-4-oxobutanoic acid.

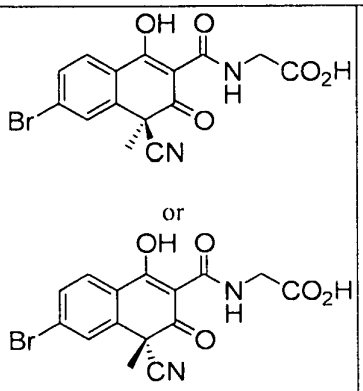
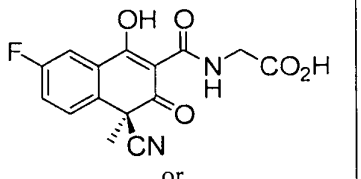
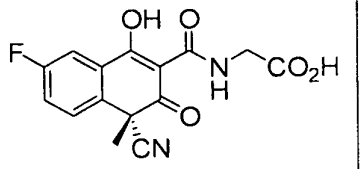
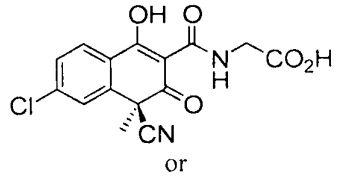
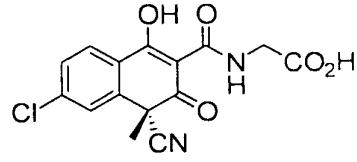
[01259] A mixture of 4-(6-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-3-methyl-4-oxobutanal (0.1 g, 0.3 mmol) in 2 mL DMF was stirred at room temperature and treated with oxone (0.2 mL, 0.3 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was quenched with 20 mL H_2O, and the pH was adjusted to pH = 5 with concentrated HCl. The precipitate that formed was collected by filtration and washed with 20 mL water. The product was dried under high vacuum to give 0.1g of the product as an off-white solid. MS m/z 379 $(M+H)^+$. Calculated for $C_{19}H_{19}ClO_6$: 378.

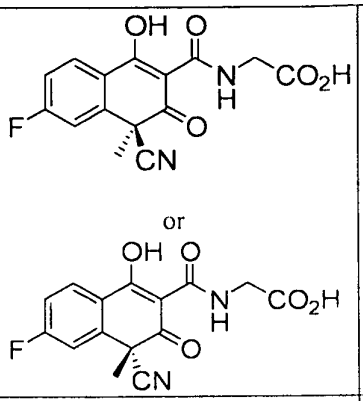
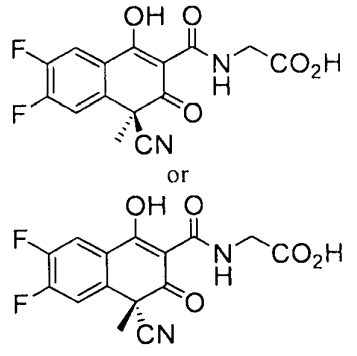
[01260] **Table 2.** The following table lists compounds which were prepared by the methods set forth in the Examples described above.

Ex	Structure	Name	MS (MH+)	Synthetic Method
122		4-(6,7-dichloro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid	357	Example 118
123		4-(7-chloro-4-cyano-3-hydroxy-4-methyl-1-oxo-1,4-dihydro-2-naphthalenyl)-4-oxobutanoic acid	334	Example 118
124		(R)-4-(7-chloro-4-cyano-1-hydroxy-4-methyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid or (S)-4-(7-chloro-4-cyano-1-hydroxy-4-methyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid	334	Example 120
125	Enantiomer of Example 124	Enantiomer of Example 124	334	Example 120
126		4-(5,6-difluoro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid	325	Example 118
127		4-(6-chloro-1-hydroxy-4,4-dimethyl-3-oxo-3,4-dihydronaphthalen-2-yl)-4-oxobutanoic acid	323	Example 118
128		4-(7-chloro-2-hydroxy-4-oxo-2',3',5',6'-tetrahydro-4H-spiro[naphthalene-1,4'-pyran]-3-yl)-4-oxobutanoic acid	365	Example 118

[01261] **Table 3.** The following table lists compounds which were prepared by the methods set forth in the Examples described above.

Ex	Structure	Name	MS (MH+)	Synthetic Method
129		2-(7-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	335.7	Example 84
130		2-(1-cyano-7-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	319.2	Example 84
131		2-(1-cyano-6-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	319.2	Example 84
132		2-(7-bromo-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	380.1	Example 84
133		2-(1-cyano-6,7-difluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	337.2	Example 84

134	 or	(R)-2-(7-bromo-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid or (S)-2-(7-bromo-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	380.1	Example 85
135	 or 	(R)-2-(1-cyano-6-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid or (S)-2-(1-cyano-6-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	319.2	Example 85
136	 or 	(R)-2-(7-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid or (S)-2-(7-chloro-1-cyano-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	335.7	Example 85

137		(R)-2-(1-cyano-7-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid or (S)-2-(1-cyano-7-fluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	319.2	Example 85
138	Enantiomer of Example 135	Enantiomer of Example 135	319.2	Example 86
139	Enantiomer of Example 134	Enantiomer of Example 134	380.1	Example 86
140	Enantiomer of Example 137	Enantiomer of Example 137	319.2	Example 86
141	Enantiomer of Example 136	Enantiomer of Example 136	335.7	Example 86
142		(R)-2-(1-cyano-6,7-difluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid or (S)-2-(1-cyano-6,7-difluoro-4-hydroxy-1-methyl-2-oxo-1,2-dihydronaphthalene-3-carboxamido)acetic acid	337.2	Example 85
143	Enantiomer of Example 142	Enantiomer of Example 142	337.2	Example 86

[01262] The following are examples of methods that may be used to quantitate HIF PHD activity and the inhibition of HIF PHD activity by compounds of the present invention.

Expression, Purification and Europium Labeling of VCB and Design of an Eu-VCB based TR-FRET Assay for the Detection of Hydroxyprolyl HIF1α Peptides

[01263] The VCB complex is defined as the Von Hippel-Lindau protein (pVHL), elongin B and elongin C heterotrimeric complex. VCB specifically binds to hydroxyproline residues of HIF1α, initiating polyubiquitinylation of HIF1α and its subsequent proteolytic destruction. In the absence of prolyl hydroxylase activity, VCB does not bind unmodified HIF1α. The VCB complex was expressed in *E.coli* and purified from the soluble fraction. The amino acid sequences of the three protein components are as follows:

VHL (Amino Acids 54-213)
MHHHHHHEAGRPRPVLRSVNSREPSQVIFCNRSPRVVLPVWLNFDGEPQ
PYPTLPPGTGRRIHSYRGHLWLFRDAGTHDGLLVNQTELFVPSLNVDGQ
PIFANITLPVYTLKERCLQVVRSLVKPENYRRLDIVRSLYEDLEDHPNVQ
KDLERLTQERIAHQRMGD (SEQ ID NO: 1)

ElonginB
MDVFLMIRRHKTTIFTDAKESSTVFELKRIVEGILKRPPDEQRLYKDDQL
LDDGKTLGECGFTSQTARPQAPATVGLAFRADDTFEALCIEPFSSPPELP
DVMKPQDSGSSANEQAVQ* (SEQ ID NO: 2)

ElonginC (Amino Acids 17-112)
MYVKLISSDGHEFIVKREHALTSGTIKAMLSGPGQFAENETNEVNFREIP
SHVLSKVCMYFTYKVRYTNSSTEIPEFPIAPEIALELLMAANFLDC (SEQ ID NO: 3)

The N-terminus of VHL contains a six histidine affinity tag for purification purposes.

[01264] A VCB-based assay allows a highly sensitive and direct measurement of enzymatic product formation (HIF1α protein or fragments

thereof containing a hydroxylated proline residue) and is suitable for high throughput screening.

[01265] For expression in *E.coli*, VHL 54-213 was cloned into pAMG21 (Plux promoter) between the NdeI-XhoI site. Immediately downstream of this is the ElonginC gene cloned into the XhoI site to SacII. There is a 13 bp spacer between the stop codon of VHL and the initiating codon of ElonginC. The expression plasmid pAMG21 is a 6118 base pair plasmid that was derived from the expression vector pCFM1656 (ATCC #69576), which in turn can be derived from the expression vector system described in US Patent No. 4,710,473. This design allows for chemical rather than thermal induction of protein expression by substitution of the promoter region, replacing a synthetic bacteriophage lambda pl promoter with a DNA segment containing the LuxR gene and the LuxPR promoter, and affords regulation of expression by the plasmid-encoded LuxR protein, thereby allowing any E.coli strain to serve as host.

[01266] ElonginB was cloned into pTA2 (pACYC184.1 based vector) under the control of a Lac promoter. Competent *E.coli* cells were transformed with the pAMG21-VHL-ElonginC construct. These *E.coli* cells were rendered competent again prior to transformation with the pTA2-elonginB construct to produce the final *E.coli* strain containing both plasmid constructs. Induction of protein expression was initiated by the addition of IPTG and N-(3-oxo-hexanoyl)-homoserine lactone (HSL) at 30°C.

[01267] Bacterial cells were lysed by a microfluidizer in aqueous buffer of pH 8.0 and the soluble fraction was separated by centrifugation. The soluble *E.coli* fraction was subjected to Nickel-NTA chelating chromatography to utilize the six histidine affinity tag located on the pVHL construct. The pooled fractions from the nickel column were applied to a Superdex 200 size exclusion chromatography (SEC) column. The protein eluted as a monomer on SEC, indicating that the three protein components formed a complex in solution. The fractions from the SEC column were pooled and applied to a Q Sepharose anion exchange column for final purification. The purified complex was visualized by

SDS-PAGE and the identities of the three protein components were confirmed by N-terminal amino acid sequencing.

[01268] Purified VCB was exchanged into 50 mM sodium carbonate buffer pH 9.2 and labeled with a europium chelate overnight. LANCE™ europium chelate (PerkinElmer, Inc; Eu-W1024 ITC chelate; catalog number is AD0013) was used to label the lysine residues of the VCB complex. The chelate contains an isothiocyanate reactive group that specifically labels proteins on lysine residues (there are fifteen lysine residues in the VCB protein complex). The resulting europylated VCB was purified by desalting columns and quantitated by standard means. The labeling yield was determined to be 6.6 europium groups per one VCB complex.

[01269] Two peptides were produced by SynPep, Inc.: a hydroxyproline modified peptide and an unmodified control peptide. VCB was expected to specifically bind to the hydroxyproline modified peptide (a mimic of enzymatic hydroxylation by prolyl hydroxylase). VCB was not expected to bind to the unmodified peptide. Both peptides were produced with a biotin group at the N-terminus to allow for binding by the streptavidin-labeled fluorescent acceptor allophycocyanin (streptavidin APC; Prozyme, Inc.).

[01270] The sequence of the custom synthesized HIF1α peptides (amino acids 556-575, with methionine residues replaced with alanine residues to prevent oxidation) were as follows:

(unmodified) Biotin-DLDLEALAPYIPADDDFQLR-$CONH_2$ (SEQ ID NO: 4)

(modified) Biotin-DLDLEALA[hyP]YIPADDDFQLR-$CONH_2$ (SEQ ID NO: 5)

[01271] The peptides were purchased from SynPep as lyophilized solids and were suspended in DMSO for experimental use. The peptides were quantitated according to their absorbance at 280 nm.

[01272] Experiments were conducted in 96 well Costar polystyrene plates. Biotinylated peptides and europylated VCB were suspended in the following buffer: 100 mM HEPES 7.5, 0.1M NaCl, 0.1% BSA and 0.05% Tween 20. The

reagents were allowed to reach equilibrium by shaking for 1 hour before the plates were read on the Discovery Instrument (Packard). The data output is the ratio of the 665nm and 620 nm emission signal resulting from the 320 nm excitation.

[01273] As shown in Figure 1, the specific interaction of europylated VCB with the hydroxyproline modified HIF1α peptide coupled to streptavidin APC generated a fluorescence signal detectable over the background signal. These results demonstrate a fluorescence signal generated by the specific interaction of Eu-VCB with hyp-HIF1α peptide. Each bar represents the data from a single well of a 96 well assay plate. The signal to background ratio was calculated from data from a control plate (unmodified peptide). Eu-VCB concentration was titrated across rows (nM) and streptavidin APC concentrations were titrated down columns. The peptide concentration was fixed at 100 nM.

Detection of Enzymatically Converted Hydroxyprolyl HIF-1α by HIF PHD2 and Inhibition of HIF PHD2 activity

[01274] Binding of the P564-HIF1α peptide to VCB was validated utilizing the homogeneous time-resolved FRET (TR-FRET) technology. A 17 amino acid (17aa) peptide with an N-terminally labeled biotin molecule corresponding to amino acid sequences 558 to 574 of the HIF1α protein was synthesized in-house (DLEMLAPYIPMDDDFQL (SEQ ID NO: 6)). A second 17aa peptide containing a hydroxylated proline at position 564 was chemically generated to mimic the PHD enzyme converted product form of the protein that is recognized by VCB. The assay was performed in a final volume of 100µL in buffer containing 50 mM Tris-HCl (pH 8), 100 mM NaCl, 0.05% heat inactivated FBS, 0.05% Tween-20, and 0.5% NaN_3. The optimal signal over background and the linear range of detection was determined by titrating the hydroxylated or unhydroxylated peptide at varied concentrations between 0 and 1µM with a titration of VCB-Eu at varying concentrations between 0 and 50 nM with 50 nM of streptavidin APC. The binding reagents were allowed to reach

equilibrium by shaking for 1 hour before it was read on the Discovery Instrument (Packard). The data output is the ratio of the 665nm and 620 nm emission signal resulting from the 320 nm excitation.

[01275] HIF PHD2 activity was detected by P564-HIF1α peptide and VCB binding in the TR-FRET format. HIF PHD2 was assayed at various concentrations between 0 and 400 nM with 3 μM HIF1α peptide in buffer containing 50 mM Tris-HCl (pH 7.5), 100 mM NaCl, 0.05% Tween 20, 2mM 2-oxoglutarate (2-OG), 2mM ascorbic acid and 100μM $FeCl_2$ in a final volume of 100μL. The time-course was determined by periodically transferring 2.5μL of the reaction into 250μL of 10x TR-FRET buffer containing 500 mM HEPES (pH 7.5), 1M NaCl, 1% BSA, and 0.5% Tween-20 to terminate the enzyme reaction. 15nM HIF-1α peptide from the terminated reaction was added to 35nM streptavidin-APC and 10 nM VCB-Eu to a final volume of 100μL in 10X TR-FRET buffer. The TR-FRET reagents were placed on a shaker for 1 hour before detection on the Discovery platform.

[01276] As demonstrated in Figures 2A and 2B, there was a dose dependent increase in TR-FRET signal resulting from binding of the hydroxylated-P564-HIF1α peptide to VCB-Eu compared to the unhydroxylated form of the peptide resulting in a 14 fold signal over noise ratio at 125 nM HIF1α peptide. VCB binding to the APC bound peptide permits a FRET transfer between the Eu and APC. The signal was linear to 2 nM peptide with 3.125 nM VCB, but increases to 62.5 nM peptide with 50 nM VCB resulting in a larger linear range.

[01277] TR-FRET detection utilizing Eu-labeled VCB is a practical system for determining HIF PHD2 catalytic activity. HIF PHD2 hydroxylation of the HIF1α peptide results in the increase affinity of VCB to the peptide and hence and increased FRET signal. As shown in Figures 3A and 3B, activity was verified with a fairly linear and an increasing TR-FRET signal over time. There was a dose dependant increase in initial rates with increasing HIF PHD2 enzyme concentration up to 400 nM. The initial rates were linear to 100 nM enzyme.

[01278] Inhibition of HIF PHD2 activity was quantified utilizing the TR-FRET technology. HIF PHD2 catalyzes a hydroxyl modification on the proline residue of the P564-HIF1α peptide substrate (Biotin-DLEMLAPYIPMDDDFQL (SEQ ID NO: 7)) resulting in recognition and binding of the europylated Von Hippel-Lindau protein (pVHL), elongin B and elongin C heterotrimeric (VCB-Eu) complex.

[01279] The PHD2 inhibition assay was executed by addition of freshly dissolved $FeCl_2$ to 178.57 μM (100 μM final concentration) in PHD2 Reaction Buffer containing 30 mM MES, pH 6, 10 mM NaCl, 0.25% Brij-35, 0.01% BSA, and 1% DMSO. 28 μL of the iron solution and 2 μL of inhibitor compounds serially diluted in 100% DMSO (5% DMSO final) were added to black polypropylene 96-well microtiter plates. To that, 10 μL of 10 nM PHD2 (2 nM final) was added to all wells of the plate except for the 8 wells of column 12 (LO control), and allowed to incubate at room temperature on the shaker for one hour. Column 6 was the HI control containing PHD2 enzyme and 5% DMSO vehicle, but no inhibitor compound. To initiate the PHD2 enzymatic reaction, 10 μL of a solution containing 500 nM P564-HIF1α peptide (100 nM final), 10 mM ascorbic acid (2 mM final), and 1.25 μM 2-oxoglutarate (α-ketoglutarate; 0.25 μM final) in PHD2 Reaction Buffer was added to all wells of the plate and allowed to incubate on the shaker at room temperature for one hour.

[01280] The reaction was terminated by addition of 25 μL TR-FRET Buffer (50 mM TRIS-HCl, pH 9, 100 mM NaCl, 0.05% BSA, and 0.5% Tween-20) containing 150 mM succinate (product inhibitor; 50 mM final), 75 nM streptavidin-APC (25 nM final), and 7.5 nM VCB-Eu (2.5 nM final). The TR-FRET detection reagents were placed on a shaker for 1 hour to reach binding equilibrium before reading on the Discovery platform (PerkinElmer). Europium is excited at 315nm and phosphoresces at 615nm with a large Stoke's shift. APC, in turn, emits at 655nm upon excitation at 615nm. The TR-FRET signal is measured as the ratio of the APC 655nm signal divided by the internal europium reference 615nm emission signal.

[01281] The POC (percentage of control) was determined by comparing the signal from hydroxylated peptide substrate in the enzyme reaction containing inhibitor compound with that from PHD2 enzyme with DMSO vehicle alone (HI control), and no enzyme (LO control). POC was calculated using the formula: % control (POC) = (cpd – average LO) / (average HI – average LO)*100. Data (consisting of POC and inhibitor concentration in μM) was fitted to a 4-parameter equation (y = A + ((B-A) / (1 + ((x/C)^D))), where A is the minimum y (POC) value, B is the maximum y (POC), C is the x (cpd concentration) at the point of inflection and D is the slope factor) using a Levenburg-Marquardt non-linear regression algorithm.

[01282] In certain embodiments, compounds of the present invention exhibit a HIF PHD inhibitory activity IC_{50} value of 40 μM or less. In additional embodiments, compounds of the present invention exhibit a HIF PHD inhibitory activity IC_{50} value of 10 μM or less and in further embodiments, compounds of the present invention exhibit a HIP PHD inhibitory activity IC_{50} value of 5 μM or less.

[01283] The following table includes PHD2 IC_{50} values obtained using the procedures set forth herein for various Examples compounds described herein.

Table 4.

Example	[a]PHD2 IC_{50} (nM)
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2	+++++
3	+++++
4	+++++
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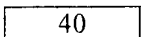
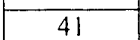
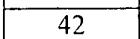
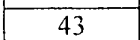
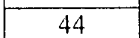
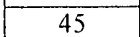
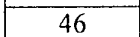
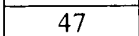
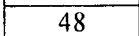
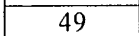
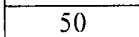
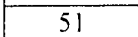
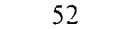
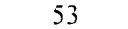
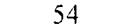
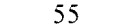
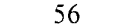
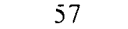
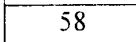
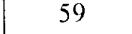
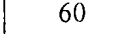
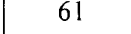
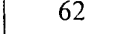
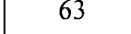
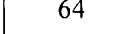
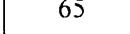
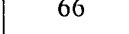
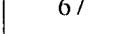
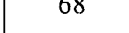
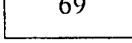
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
62	
63	
64	
65	
66	
67	
68	
69	

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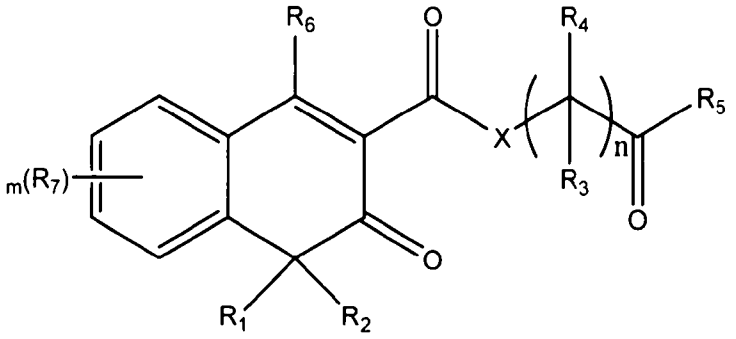
[a]IC_{50} value ranges
+ $IC_{50} > 10{,}000$ nM
++ 1000 nM $\leq IC_{50} \leq 10{,}000$ nM
+++ 500 nM $\leq IC_{50} \leq 1{,}000$ nM
++++ 100 nM $\leq IC_{50} \leq 500$ nM
+++++ $IC_{50} < 100$ nM

[01284] All publications and patent applications cited in this specification are hereby incorporated by reference herein in their entireties and for all purposes as if each individual publication or patent application were specifically and individually indicated as being incorporated by reference and as if each reference was fully set forth in its entirety. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

2007334323 16 Dec 2010

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. At least one compound of the Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

2. The at least one compound according to claim 1, wherein R_5 is OH.

3. The at least one compound according to claim 1, wherein R_6 is OH.

4. The at least one compound according to claim 1, wherein m is 1 to 4 and at least one instance of R_7 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group.

5. The at least one compound according to claim 1, wherein m is 1 to 4 and at least one instance of R_7 is independently selected from halo or a moiety substituted with at least one halo.

6. The at least one compound according to claim 1, wherein m is 0.

7. The at least one compound according to claim 1, wherein n is 1.

8. The at least one compound according to claim 1, wherein R_1 and R_2 are independently selected from CN, lower alkyl, aryl, or substituted aryl.

9. The at least one compound according to claim 1, wherein R_1 and R_2 are lower alkyl.

10. The at least one compound according to claim 1, wherein R_1 and R_2 join to form a spirocyclic ring system.

11. The at least one compound according to claim 1, wherein R_1 and R_2 join to form a heterocyclic spirocyclic ring system.

12. The at least one compound according to claim 1, wherein R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$.

13. The at least one compound according to claim 1, wherein R_1 is CN.

14. The at least one compound according to claim 1, wherein m is 1.

15. The at least one compound according to claim 1, wherein X is NH, n is 1, R_3 and R_4 are independently selected from H, lower alkyl or substituted lower alkyl, and R_6 is OH.

16. The at least one compound according to claim 15, wherein R_5 is OH.

17. The at least one compound according to claim 1, wherein X is $-(CR_bR_c)-$.

18. The at least one compound according to claim 17, wherein X is $-CH_2-$.

19. The at least one compound according to claim 1, wherein X is $-NR_a-$.

20. The at least one compound according to claim 19, wherein X is –NH-.

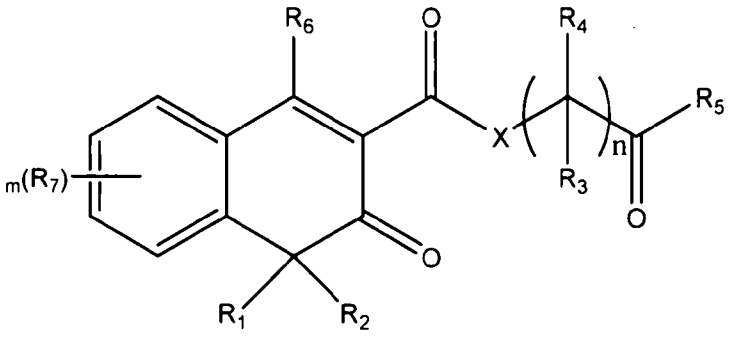
21. The at least one compound according to claim 1, wherein R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

22. The at least one compound according to claim 21, wherein R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl.

23. The at least one compound according to claim 22, wherein R_4 is a methyl group.

24. The at least one compound according to claim 21, wherein n is 1.

25. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a therapeutically effective amount of at least one compound of Formula I:



I

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

m is 0 to 4;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$ wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is chosen from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7, if present, is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)OR_8$, OR_8, SR_8, SO_2R_8, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, alkoxycarbonyl, substituted alkoxycarbonyl, haloalkyl, perhaloalkyl, or -Y-R_9, wherein:

Y is selected from $-N(R_{10})-Z-$ or $-Z-N(R_{10})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_9 is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

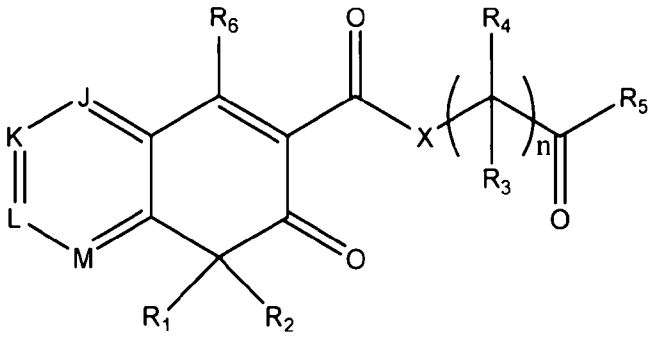
R_{10} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

26. The pharmaceutical composition of claim 25, wherein the at least one compound is present in an amount effective for the treatment of at least one disease selected from ischemia, anemia, wound healing, auto- transplantation, allo- transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

27. At least one compound of the Formula II:



II

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

28. The at least one compound according to claim 27, wherein each of J, K, L, and M is CR_7.

29. The at least one compound according to claim 27, wherein one of J, K, L, and M is N, and the other three of J, K, L, and M are CR_7.

30. The at least one compound according to claim 29, wherein M is N, and J, K, and L are CR_7.

31. The at least one compound according to any one of claims 27-30, wherein R_5 is OH.

32. The at least one compound according to any one of claims 27-31, wherein R_6 is OH.

33. The at least one compound according to any one of claims 27-32, wherein at least one instance of R_7 is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl group.

34. The at least one compound according to claim 27, wherein at least one instance of R_7 is chosen from a halo or a moiety substituted with at least one halo.

35. The at least one compound according to any one of claims 27-34, wherein n is 1.

36. The at least one compound according to any one of claims 27-35, wherein R_1 and R_2 are independently chosen from CN, lower alkyl, aryl, or substituted aryl.

37. The at least one compound according to claim 36, wherein R_1 and R_2 are lower alkyl.

38. The at least one compound according to any one of claims 27-35, wherein R_1 and R_2 join to form a spirocyclic ring system.

39. The at least one compound according to claim 38, wherein R_1 and R_2 join to form a heterocyclic spirocyclic ring system.

40. The at least one compound according to claim 39, wherein R_1 and R_2 join to form the group $-CH_2-CH_2-O-CH_2-CH_2-$.

41. The at least one compound according to any one of claims 27-35, wherein R_1 is CN.

42. The at least one compound according to any one of claims 27-41, wherein X is $-(CR_dR_d)-$.

43. The at least one compound according to claim 42, wherein X is $-CH_2-$.

44. The at least one compound according to any one of claims 27-41, wherein X is $-NR_a-$.

45. The at least one compound according to claim 44, wherein X is –NH-.

46. The at least one compound according to any one of claims 27-45, wherein R_3 and R_4 are independently selected from H and lower alkyl.

47. The at least one compound according to claim 46, wherein R_3 and R_4 are independently selected from H and methyl.

48. The at least one compound according to claim 46, wherein R_3 and R_4 are both H.

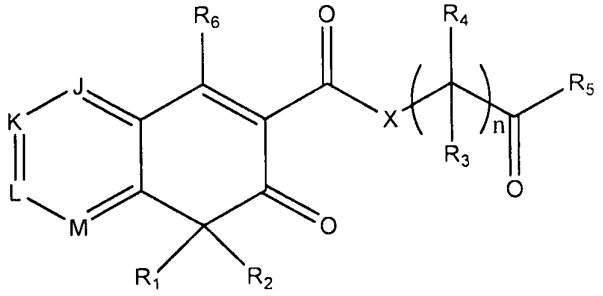
49. The at least one compound according to claim 27, wherein R_3 is selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl and R_4 is selected from lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

50. The at least one compound according to claim 49, wherein R_4 is a C_1-C_4 alkyl or a substituted C_1-C_4 alkyl.

51. The at least one compound according to claim 50, wherein R_4 is a methyl group.

52. The at least one compound according to claim 49, wherein n is 1.

53. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient, and a therapeutically effective amount of at least one compound of Formula II:



II

a pharmaceutically acceptable salt thereof, a tautomer thereof, or a pharmaceutically acceptable salt of the tautomer; or a solvate thereof, or a mixture of any of the foregoing, wherein:

J, K, L, and M are independently selected from CR_7 or N, wherein 0, 1, or 2 of J, K, L, and M are N;

n is 1 to 6;

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R_1 and R_2 are independently selected from halogen, CN, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R_1 and R_2 can join to form a spirocyclic ring system that may be substituted with one or more substituents;

X is selected from $-NR_a-$, -O-, -S-, or $-(CR_bR_c)-$, wherein R_a is selected from H or lower alkyl;

R_3 and R_4 are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_3 and R_4 can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring;

R_5 is selected from OH, SH, NH_2, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, or sulfanyl;

R_6 is selected from H, OH, SH, NH_2, $NHSO_2R_8$, or sulfonyl;

each R_7 is independently selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, NR_dR_e, $C(O)R_8$, $C(O)OR_9$, OR_9, SR_9, SO_2R_9, CN, NO_2, halo, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, haloalkyl, perhaloalkyl, or $-Y-R_{10}$, wherein:

Y is selected from $-N(R_{11})-Z-$ or $-Z-N(R_{11})-$;

Z is selected from C(O), SO_2, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, or substituted alkynylene;

R_8 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R_9 is selected from H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl;

R_{10} is selected from H, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_{11} is selected from H, lower alkyl, or substituted lower alkyl;

R_b and R_c are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_b and R_c can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring; and

R_d and R_e are independently selected from H, lower alkyl, substituted lower alkyl, lower haloalkyl, or substituted lower haloalkyl, or R_d and R_e can join together to form a 3 to 6 membered ring or a substituted 3 to 6 membered ring.

54. The pharmaceutical composition of claim 53, wherein the at least one compound is present in an amount effective for the treatment of at least one disease selected from ischemia, anemia, wound healing, auto-transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

55. A method of increasing or stabilizing HIF levels or activity in a subject, comprising administering to the subject the at least one compound according to any one of claims 1-24 or 27-52.

56. A method of treating a condition where it is desired to modulate HIF activity, comprising administering to a subject the at least one compound according to claim any one of claims 1-24 or 27-52.

57. A method according to claim 56, wherein said condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

58. A method of treating a hypoxic or ischemic related disorder in a subject, comprising administering to a subject the at least one compound according to any one of claims 1-24 or 27-52.

59. A method of modulating the amount of HIF in a cell, comprising contacting the cell with the at least one compound according to any one of claims 1-24 or 27-52.

60. A method of inhibiting HIF hydroxylation in a subject, comprising administering to the subject the at least one compound according to any one of claims 1-24 or 27-52.

61. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament.

62. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament for increasing or stabilizing HIF levels or activity in a subject.

63. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament for treating a condition where it is desired to modulate HIF activity.

64. The use of claim 63, wherein the condition is selected from at least one of ischemia, anemia, wound healing, auto- transplantation, allo-transplantation, xeno-transplantation, systemic high blood pressure, thalassemia, diabetes, cancer, or an inflammatory disorder.

65. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament for treating a hypoxic or ischemic related disorder in a subject.

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66. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a composition for modulating the amount of HIF in a cell.

67. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the modulation of the amount of HIF in a cell.

68. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament for modulating angiogenesis in a subject.

69. The use of the at least one compound according to any one of claims 1-24 or 27-52, in the preparation of a medicament for inhibiting HIF hydroxylation in a subject.

70. A method for modulating angiogenesis in a subject comprising administering the at least one compound according to any one of claims 1-24 or 27-52 to a subject.

71. At least one compound of the Formula I; a pharmaceutical composition; at least one compound of the Formula II; a method of increasing or stabilizing HIF levels or activity; a method of treating a condition where it is decided to modulate HIF activity; a method of treating hypoxic or ischemic related disorder; a method of modulating the amount of HIF in a cell; a method of inhibiting HIF hydroxylation; use of at least one compound; or a method for modulating angiogenesis in a subject, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

FIG. 1

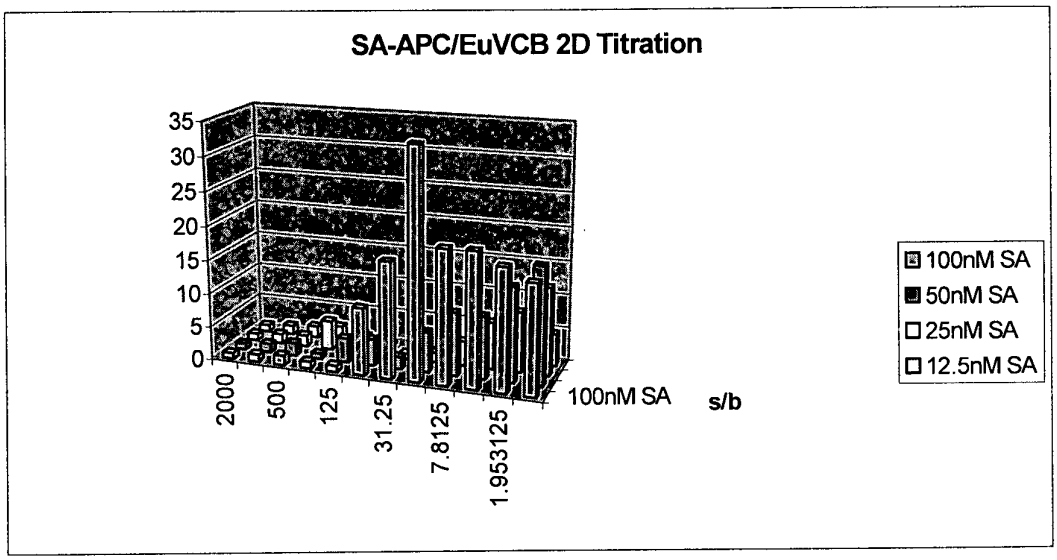

SA-APC/EuVCB 2D Titration
35
30
25
20
15
10
5
0
2000
500
125
31.25
7.8125
1.953125
100nM SA
s/b
100nM SA
50nM SA
25nM SA
12.5nM SA

FIG. 2A

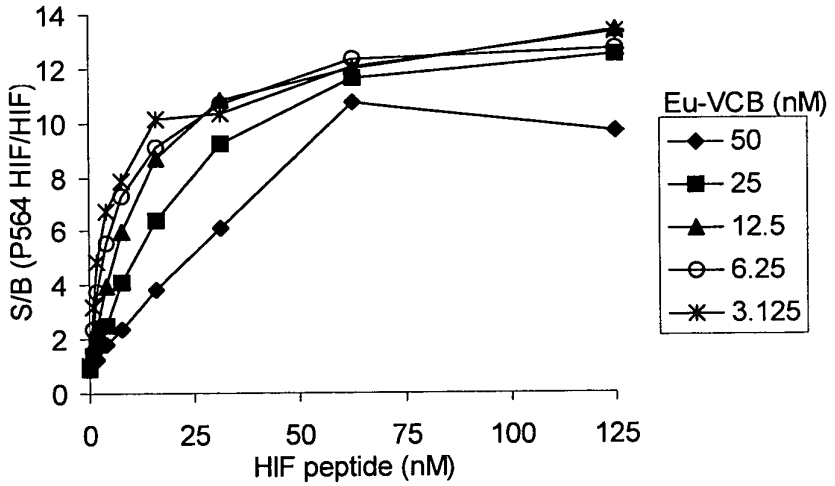

S/B (P564 HIF/HIF)
HIF peptide (nM)
Eu-VCB (nM)
50
25
12.5
6.25
3.125

FIG 2B

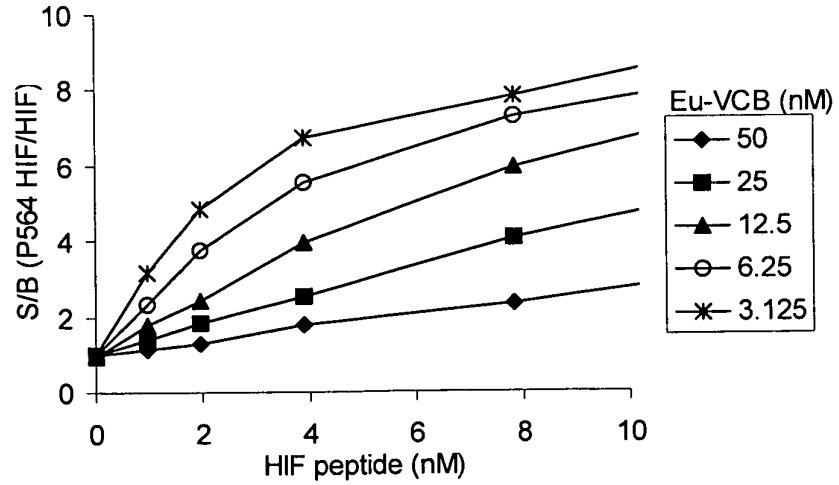

S/B (P564 HIF/HIF)
HIF peptide (nM)
Eu-VCB (nM)
50
25
12.5
6.25
3.125

FIG. 3A

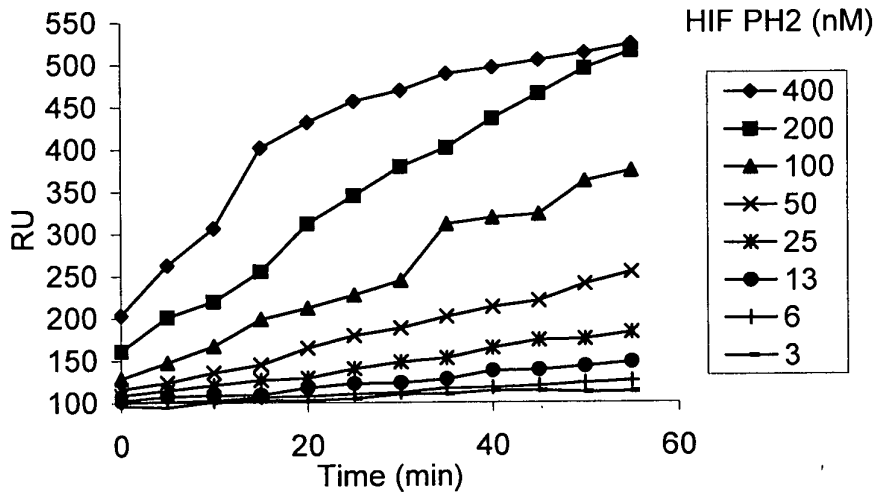
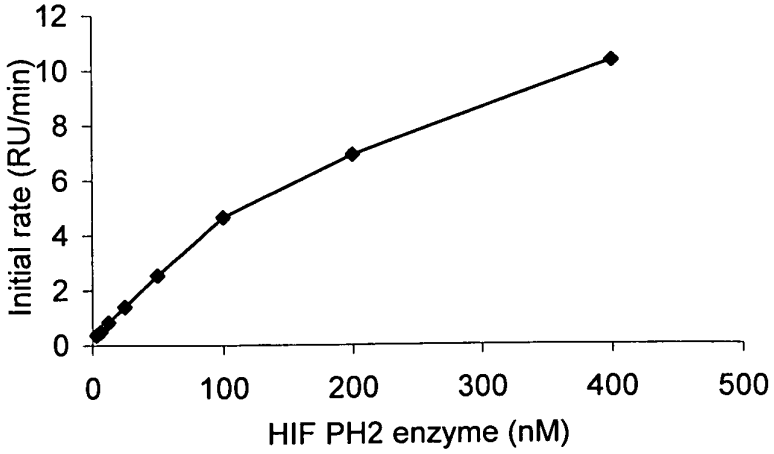

HIF PH2 (nM)
400
200
100
50
25
13
6
3
RU
550
500
450
400
350
300
250
200
150
100
0
20
40
60
Time (min)

FIG. 3B


Initial rate (RU/min)
12
10
8
6
4
2
0
0
100
200
300
400
500
HIF PH2 enzyme (nM)