reduce gene expression. For PHD1, studies have suggested that inhibition of this protein could be therapeutically beneficial for treating skeletal muscle cell degeneration (U.S. Patent 7,858,593), for protection of myofibers against ischemia (Aragones et al. (2008) Nat. Genet. 40:170-180), for treatment of colitis and other forms of inflammatory bowel disease (Tambuwala et al. (2010) Gastroenterology 139:2093-2101, and for treatment of heart failure and anemia in patients with concomitant cardiac and renal disease (Bao et al. (2010) J. Cardiovasc. Pharmacol. 56:147-155).

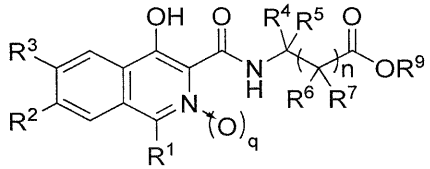
[0006] Numerous small molecule inhibitors for PHD proteins have been identified (for example, Arend, et al., U.S. Patent Nos. 7,323,475; 7,629,357; 7,863,292; and 7,928,120; and Deng, et al., U.S. Patent No. 7,696,223), however, few of these have been described as selective for inhibition of PHD1 in preference to the PHD2 and PHD3 isoforms. Inhibitors that are selective for PHD1 would be preferable for the therapeutic uses described above in order to minimize unwanted side effects that could occur from significant inhibition of PHD2 and PHD3. Murray et al. (J. Comb. Chem. 13:676-686 (2010)) describe some dipeptidyl-quinolone derivatives that were found to be about 10-fold more potent against PHD1 and PHD3 than against PHD2. Bao et al. (*supra*) describe a fluoroquinolone derivative that is selective for PHD1.

[0007] Given the potential therapeutic benefit of selectively inhibiting the activity of PHD1 in disorders such as muscle degeneration, colitis, IBD, and certain ischemias, there is a need for compounds that can achieve this selective inhibition. Compounds that selectively inhibit PHD1 are described herein.

SUMMARY

[0008] The present ~~invention~~ disclosure relates to novel compounds and compositions capable of inhibiting PHD1 enzyme activity selectively over other isoforms, for example, PHD2 and/or PHD3 enzymes.

[0009] ~~In one aspect, there~~There are provided compounds of Formula I:



I

wherein

n is 1, 2, or 3;

q is 0 or 1;

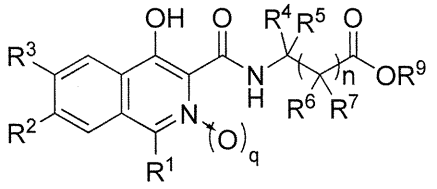
R^1 is hydrogen, cyano, C_1-C_4 alkyl, aryl, or heteroaryl;

R^9 is hydrogen or C_1-C_4 alkyl;

wherein said C_1-C_4 alkyl is optionally substituted with 1, 2, or 3 C_1-C_4 alkoxy, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, ester, tautomer or prodrug thereof.

[0009a] In an aspect, there is provided a compound of Formula I:



I

wherein

n is 1, 2, or 3;

q is 0 or 1;

R^1 is hydrogen, cyano, C_1-C_4 alkyl, aryl, or heteroaryl;

wherein said C_1-C_4 alkyl, aryl, or heteroaryl is optionally substituted with 1, 2, or 3 trifluoromethyl, C_1-C_4 alkyl, or halo;

one of R^2 or R^3 is -L-R^8 and the other is hydrogen;

R^4 and R^5 are independently hydrogen, halo, C_1-C_4 alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

wherein said C_1-C_4 alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1, 2, or 3 hydroxy, cyano, halo, nitro, acyl, amino, substituted amino, acylamino, sulfonyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, cycloalkyl, cycloalkyloxy, heterocyclyl, heterocyclyloxy, carboxyl, carboxyl ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, aryl, aryloxy, heteroaryloxy, alkylthio, cycloalkylthio, arylthio, heteroarylthio, heterocyclicthio, or heteroaryl;

each R^6 and R^7 are independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, substituted amino, acylamino, carboxyl, carboxyl ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, cycloalkyl, aryl, heterocyclyl, or heteroaryl, or R^6 and R^7 together with the carbon atom attached thereto, form a carbonyl;

wherein said C_1-C_4 alkyl, C_1-C_4 alkoxy, cycloalkyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1, 2, or 3 hydroxy, cyano, halo, nitro, acyl, amino, substituted amino, acylamino, sulfonyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, cycloalkyl, cycloalkyloxy, heterocyclyl, heterocyclyloxy, carboxyl, carboxyl ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, aryl, aryloxy, heteroaryloxy, alkylthio, cycloalkylthio, arylthio, heteroarylthio, heterocyclicthio, or heteroaryl;

or wherein any of R^4 and R^5, R^6 and R^7, R^4 and R^6, or R^5 and R^7 groups, together with the carbon atom(s) attached thereto, join to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl group, each optionally substituted with 1 to 4 halogen, oxo, C_1-C_4 alkyl, C_1-C_4 alkoxy, carboxyl, carboxyl ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, or aryl;

R^8 is cycloalkyl, aryl, or heteroaryl;

wherein said cycloalkyl, aryl, or heteroaryl is optionally substituted with 1, 2, or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, or halo;

L is a covalent bond, C_1-C_4 alkylene, -O-, -S-, -SO-, -SO_2-, -NH-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -O-alkylene-, -NH-alkylene-, or -NHC(O)NH-alkylene; and

R^9 is hydrogen or C_1-C_4 alkyl;

wherein said C_1-C_4 alkyl is optionally substituted with 1, 2, or 3 C_1-C_4 alkoxy, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, ester, or tautomer thereof.

[0010] ~~The invention also provides~~In another aspect, there is provided pharmaceutical compositions comprising one or more compounds of Formula I and a pharmaceutically acceptable excipient. In some embodiments, the composition further comprises or is used in combination with at least one additional therapeutic agent.

[0011] The ~~invention~~ disclosure is also directed to methods and compositions capable of inhibiting PHD1 enzyme activity selectively over other isoforms, for example, PHD2 and/or PHD3 enzymes. Selective inhibition of PHD1 may be of particular benefit in treating skeletal muscle cell degeneration, colitis and other forms of inflammatory bowel disease, and heart failure in patients with concomitant cardiac and renal disease. In another aspect, there is provided a method of inhibiting PHD1 enzyme, the method comprising bringing into contact the PHD1 enzyme and an inhibitory-effective amount of a compound as defined above. In one embodiment, the method of the invention

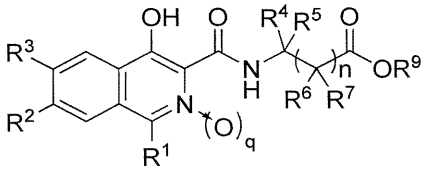
comprises administering to a patient in need a therapeutically effective amount of a compound of Formula I, or a pharmaceutical composition comprising one or more compounds of Formula I.

DETAILED DESCRIPTION

[0012] Before the present compositions and methods are described, it is to be understood that the invention is not limited to the particular compounds, compositions, methodologies, protocols, cell lines, assays, and reagents described, as these may vary. It is also to be understood that the terminology used herein is intended to describe particular embodiments of the present invention, and is in no way intended to limit the scope of the present invention as set forth in the appended claims.

1. Compounds

[0013] The invention is directed to compounds of Formula I:



I

wherein

n is 1, 2, or 3;

q is 0 or 1;

R^1 is hydrogen, cyano, C_1-C_4 alkyl, aryl, or heteroaryl;

ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, aryl, aryloxy, heteroaryloxy, alkylthio, cycloalkylthio, arylthio, heteroarylthio, heterocyclicthio, or heteroaryl;

or wherein any of R^4 and R^5, R^6 and R^7, R^4 and R^6, or R^5 and R^7 groups, together with the carbon atom(s) attached thereto, join to form a cycloalkyl, aryl, heterocyclyl, or heteroaryl group, each optionally substituted with 1 to 4 halogen, oxo, C_1-C_4 alkyl, C_1-C_4 alkoxy, carboxyl, carboxyl ester, carboxamide, oxycarbonylamino, aminocarbonyloxy, aminocarbonylamino, or aryl;

R^8 is cycloalkyl, aryl, or heteroaryl;

wherein said cycloalkyl, aryl, or heteroaryl is optionally substituted with 1, 2, or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, or halo;

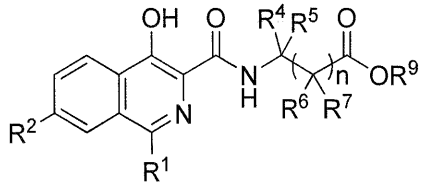
L is a covalent bond, C_1-C_4 alkylene, -O-, -S-, -SO-, -SO_2-, -NH-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -O-alkylene-, -NH-alkylene-, or -NHC(O)NH-alkylene; and

R^9 is hydrogen or C_1-C_4 alkyl;

wherein said C_1-C_4 alkyl is optionally substituted with 1, 2, or 3 C_1-C_4 alkoxy, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, ester, or tautomer ~~or prodrug~~ thereof.

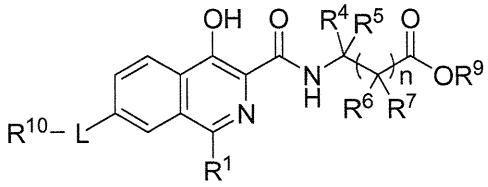
2. The compound of claim 1, wherein the compound of Formula I is represented by Formula II:



II

wherein n, R^1, R^2, R^4, R^5, R^6, R^7 and R^9 are as defined in claim 1.

3. The compound of claim 1, wherein the compound of Formula I is represented by Formula III:



III

wherein n, L, R^1, R^4, R^5, R^6, R^7 and R^9 are as defined in claim 1, and

17. The compound of claim 1, wherein L is -O- or -S-.

18. The compound of claim 1, wherein L is -O-.

19. The compound of claim 1, wherein L is -O-; R^9 is hydrogen; R^1 is hydrogen or cyano-; and R^8 is aryl.

20. The compound of claim 3, wherein L is -O-; R^9 is hydrogen; R^1 is hydrogen or cyano-; and R^{10} is aryl.

21. The compound of claim 1, wherein the compound is the trifluoroacetic acid salt thereof.

22. The compound of claim 1, wherein when n is 1 and each R^6 and R^7 are hydrogen, then R^1 is cyano.

23. ~~A~~ The compound of claim 1, selected from the group consisting of:
3-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-propionic acid,

3-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-2,2-dimethyl-propionic acid,

2-(S)-Hydroxy-3-[(4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-propionic acid,

4-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-butyric acid,

5-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-pentanoic acid,

3-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-methyl-butyric acid,

2-(S)-Hydroxy-4-[(4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-butyric acid,

4-[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-2,2-dimethyl-butyric acid,

2-(S)-Amino-3-[(4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-propionic acid,

3-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-propionic acid,

3-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-butyric acid,

1-{[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-cyclopropanecarboxylic acid,

1-{[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-cyclobutanecarboxylic acid,

1-{[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-cyclobutanecarboxylic acid,

4-{[(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-tetrahydro-pyran-4-carboxylic acid,

4-{[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-tetrahydro-pyran-4-carboxylic acid,

3-(S)-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-o-tolyl-propionic acid,

3-(S)-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-(4-cyano-phenyl)-propionic acid,

3-(4-Chloro-phenyl)-3-[(1-cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-propionic acid,

3-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-pyridin-3-yl-propionic acid,

3-(S)-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-pyridin-3-yl-propionic acid,

3-(R)-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-3-pyridin-3-yl-propionic acid,

3-{[1-Cyano-7-(2-fluoro-phenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-2-cyclopropyl-propionic acid,

3-{[1-Cyano-4-hydroxy-7-(pyridin-3-yloxy)-isoquinoline-3-carbonyl]-amino}-2-cyclopropyl-propionic acid tert-butyl ester, trifluoro-acetic acid salt,

3-{[1-Cyano-7-(4-fluoro-phenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-2-cyclopropyl-propionic acid,

3-{[1-Cyano-7-(2,6-difluoro-phenoxy)-4-hydroxy-isoquinoline-3-carbonyl]-amino}-2-cyclopropyl-propionic acid,

3-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-2-(4-fluoro-phenyl)-propionic acid,

3-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-2-(2-fluoro-phenyl)-propionic acid,

3-{[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-methyl}-5-methyl-hexanoic acid, and

4-[(1-Cyano-4-hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-pentanoic acid;

or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, ester, or tautomer ~~or prodrug~~ thereof.

24. A pharmaceutical composition comprising one or more compounds of claim 1, and a pharmaceutically acceptable excipient.

25. A method of inhibiting PHD1 enzyme, the method comprising bringing into contact the PHD1 enzyme and an inhibitory-effective amount of a compound of claim 1.