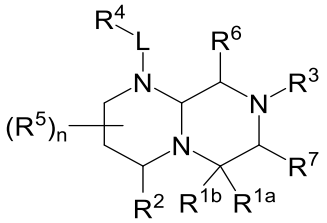
[0004] Although progress has been made in this field, there remains a need for improved compounds and methods for treatment of HGF-modulated diseases. Accordingly, in one aspect, provided herein are compounds which modulate HGF for use in treating neurodegenerative diseases.

SUMMARY

[0005] Described herein, in certain examples, are compounds and compositions thereof for modulating hepatocyte growth factor (HGF) for treatment of diseases. Nonlimiting exemplary examples include:

[0006] Example 1. A method of treating mild cognitive impairment in a subject in need thereof, comprising administering an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

L is a direct bond, -C(=O)-, -$(CR^aR^b)_m$-C(=O)-, -C(=O)-$(CR^aR^b)_m$-, or -$(CR^aR^b)_m$-;

each R^a and R^b is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R^{1a} and R^{1b} are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, or C_6-C_{10} arylalkyl;

R^2 is H, oxo, or thioxo;

R^3 is C_2-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_{12} cycloalkyl, C_3-C_6 cycloalkylalkyl, C_6-C_{10} arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl,

wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

R^4 is C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl,

wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

each R^5 is independently C_1-C_6 alkyl, oxo, or halo;

R^6 is H, C_1-C_6 alkyl, or oxo;
R^7 is H or oxo;
m is 1 or 2; and
n is an integer from 0 to 3;
wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkylalkyl, C_6-C_{10} aryl, C_6-C_{10} arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclylalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, -(C=O)NH_2, nitro, -SO_2(C_1-C_6 alkyl), and -CO_2H.

[0007] Example 2. The method of example 1, wherein L is -C(=O)- or -$(CR^aR^b)_m$-.

[0008] Example 3. The method of example 1 or 2, wherein L is a -C(=O)-.

[0009] Example 4. The method of example 1 or 2, wherein L is -$(CR^aR^b)_m$-.

[0010] Example 5. The method of example 4, wherein R^a and R^b are each H, and m is 1.

[0011] Example 6. The method of any one of examples 1-5, wherein R^{1a} and R^{1b} are each independently H; C_1-C_6 alkyl optionally substituted with 1-3 substituents selected from halo, -CO_2H, and -C(=O)NH_2; C_1-C_6 alkoxy; halo; or C_6-C_{10} arylalkyl optionally substituted by 1-3 substituents selected from halo and amino.

[0012] Example 7. The method of example 6, wherein R^{1a} and R^{1b} are each independently H, methyl, fluoro, 2-methylbutyl, -CH_2F, methoxy, -CH_2CO_2H, -CH_2C(=O)NH_2, benzyl, or 4-aminobenzyl.

[0013] Example 8. The method of example 6, wherein R^{1a} and R^{1b} are each independently H or C_1-C_3 alkyl.

[0014] Example 9. The method of example 8, wherein R^{1a} is methyl and R^{1b} is H.

[0015] Example 10. The method of example 8, wherein R^{1a} and R^{1b} are each H.

[0016] Example 11. The method of any one of examples 1-10, wherein R^2 is H.

[0017] Example 12. The method of any one of examples 1-10, wherein R^2 is thioxo.

[0018] Example 13. The method of any one of examples 1-10, wherein R^2 is oxo.

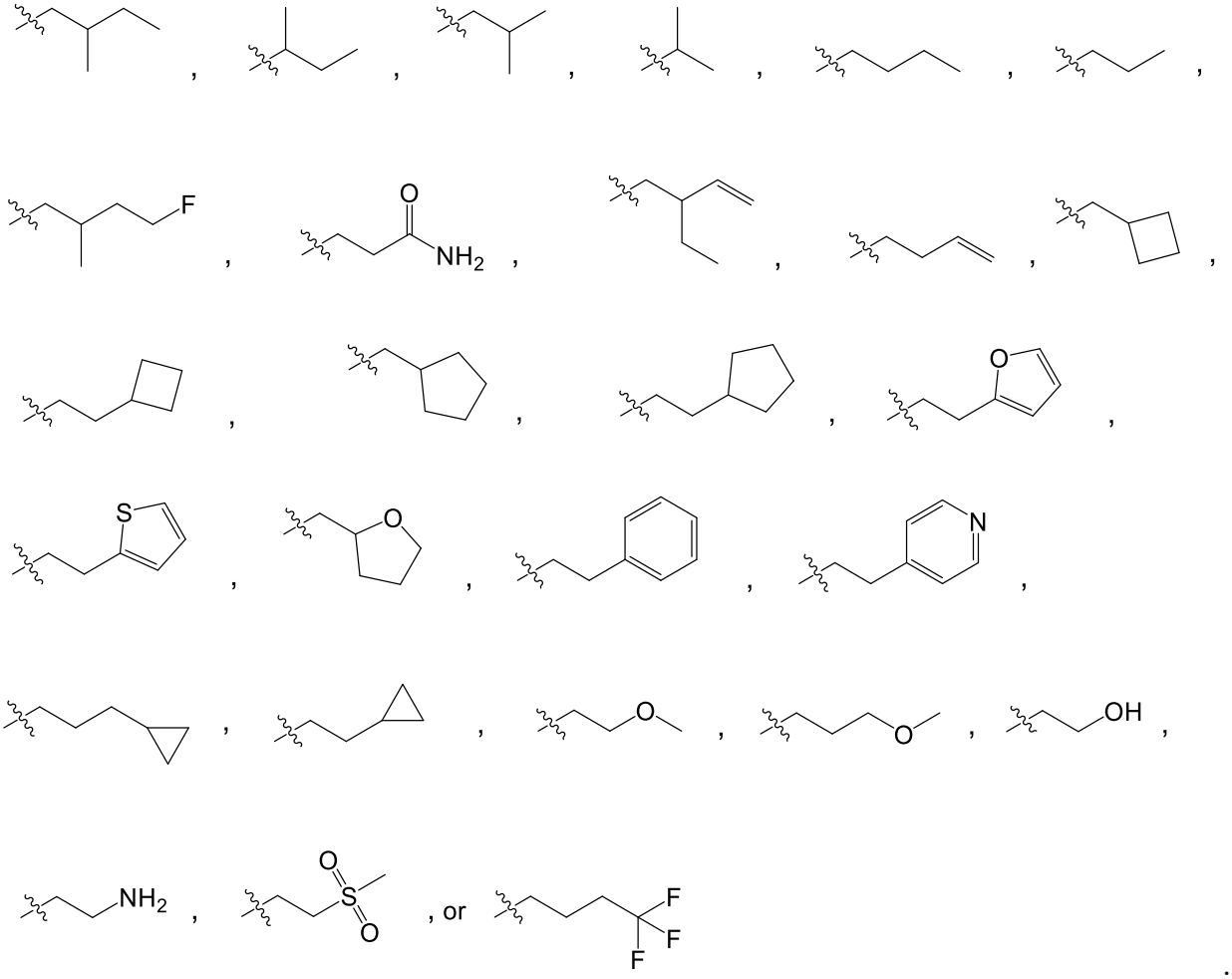
[0019] Example 14. The method of any one of examples 1-13, wherein R^3 is C_3-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_{12} cycloalkyl, C_3-C_6 cycloalkylalkyl, C_6-C_{10} arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocyclylalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C_1-C_6

haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, -(C=O)NH_2, nitro, -SO_2(C_1-C_6 alkyl), and -CO_2H.

[0020] Example 15. The method of any one of examples 1-13, wherein R^3 is C_2-C_6 alkyl optionally substituted by 1-3 substituents selected from halo, C_1-C_3 alkoxy, hydroxy, -NH_2, -SO_2(C_1-C_3 alkyl), and
-C(=O)NH_2; C_2-C_6 alkenyl; C_3-C_6 cycloalkylalkyl; 5- to 6-membered heteroarylalkyl; 5- to 6-membered heterocyclylalkyl; or C_6 arylalkyl.

[0021] Example 16. The method of example 15, wherein R^3 is C_2 alkyl substituted by 1-3 substituents selected from C_1-C_3 alkoxy, hydroxy, -NH_2, and -SO_2(C_1-C_3 alkyl).

[0022] Example 17. The method of any one of examples 14-16, wherein R^3 is:



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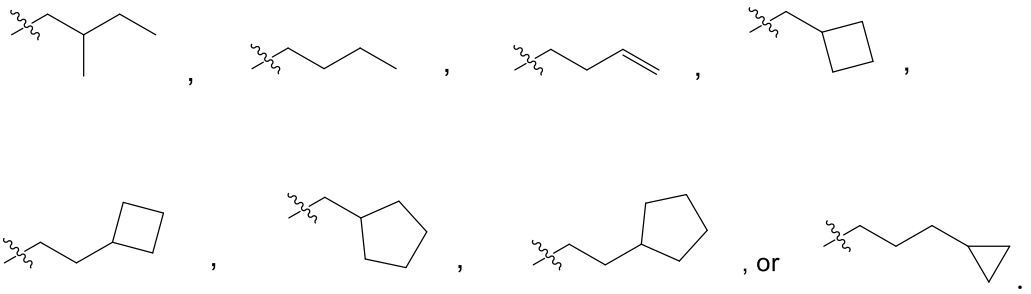
[0023] Example 18. The method of example 17, wherein R^3 is:



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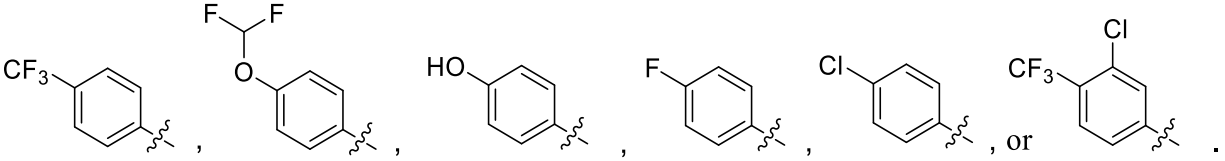
[0024] Example 19. The method of any one of examples 1-18, wherein R^4 is C_6-C_{10} aryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy.

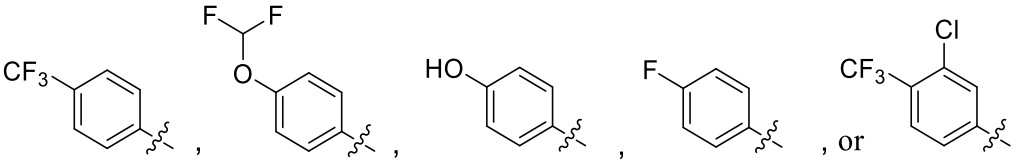
[0025] Example 20. The method of example 19, wherein R^4 is phenyl substituted with 1-3 substituents selected from $-CF_3$, $-OCHF_2$, -OH, fluoro, and chloro.

[0026] Example 21. The method of example 20, wherein R^4 is:



, , , , , or .

[0027] Example 22. The method of example 21, wherein R^4 is:

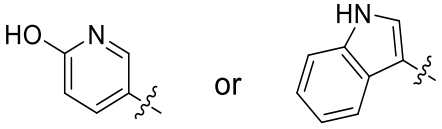


, , , , or .

[0028] Example 23. The method of any one of examples 1-18, wherein R^4 is 5- to 10-membered heteroaryl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy.

[0029] Example 24. The method of example 23, wherein R^4 is pyridyl or indolyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy.

[0030] Example 25. The method of example 24, wherein

R^4 is 

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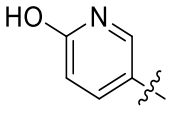
[0031] Example 26. The method of example 25, wherein

R^4 is 

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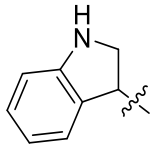
[0032] Example 27. The method of any one of examples 1-18, wherein R^4 is 5- to 10-membered heterocyclyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy.

[0033] Example 28. The method of example 27, wherein R^4 is indolinyl.

[0034] Example 29. The method of example 28, wherein R^4 is 

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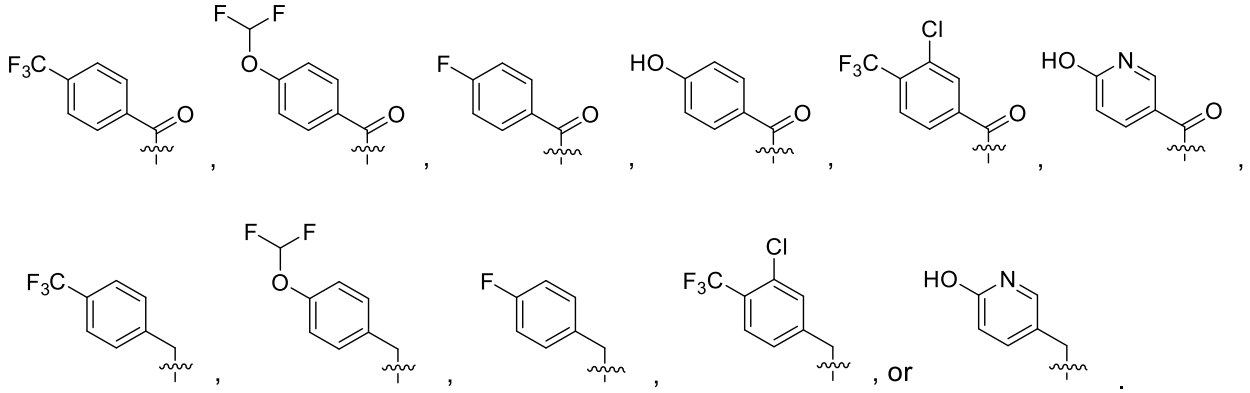
[0035] Example 30. The method of any one of examples 1-26, wherein -L-R^4 is:



[0036] Example 31. The method of any one of examples 1-30, wherein n is 0.

[0037] Example 32. The method of any one of examples 1-30, wherein n is 1.

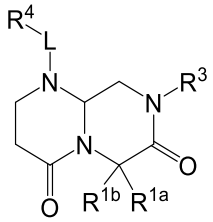
[0038] Example 33. The method of example 32, wherein R^5 is oxo or halo.

[0039] Example 34. The method of example 33, wherein R^5 is oxo or fluoro.

[0040] Example 35. The method of any one of examples 1-34, wherein R^6 is H.

[0041] Example 36. The method of any one of examples 1-35, wherein R^7 is oxo.

[0042] Example 37. The method of any one of examples 1-10, 13-31, 35, and 36, wherein the compound is of Formula (V):



(V) .

[0043] Example 38. The method of example 37, wherein:

L is -C(=O)- or -CH_2-;

R^{1a} and R^{1b} are independently H or C_1-C_3 alkyl optionally substituted with -CO_2H;

R^3 is C_4-C_5 alkyl, C_4-C_5 alkenyl, or C_1-C_3 alkyl substituted with C_3-C_5 cycloalkyl; and

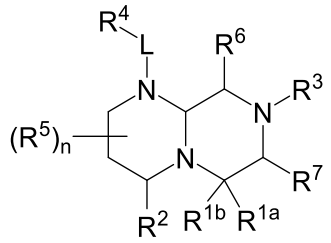
R^4 is phenyl or pyridyl substituted with 1-3 substituents selected from -CF_3, -$OCHF_2$, -OH, fluoro, and chloro.

[0044] Example 39. A method of treating mild cognitive impairment in a subject in need thereof, comprising administering an effective amount of a compound selected from the compounds of Table 1A and pharmaceutically acceptable salts thereof.

[0045] Example 40. The method of any one of the preceding claims, wherein the method slows progression of dementia in the subject.

[0046] Example 41. The method of any one of the preceding claims, wherein the method improves cognitive function and/or slows progression of cognitive dysfunction in the subject.

[0046a] In one aspect, the present disclosure provides a method of treating mild cognitive impairment in a subject in need thereof, comprising administering an effective amount of a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

L is a direct bond, -C(=O)-, -$(CR^aR^b)_m$-C(=O)-, -C(=O)-$(CR^aR^b)_m$-, or -$(CR^aR^b)_m$-;

each R^a and R^b is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R^{1a} and R^{1b} are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, or C_6-C_{10} arylalkyl;

R^2 is H, oxo, or thioxo;

R^3 is C_2-C_6 alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_{12} cycloalkyl, C_3-C_6 cycloalkylalkyl, C_6-C_{10} arylalkyl, 5- to 10-membered heteroarylalkyl, or 5- to 10-membered heterocyclylalkyl,

wherein the 5- to 10-membered heteroarylalkyl or 5- to 10-membered heterocyclylalkyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

R^4 is C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or 5- to 10-membered heterocyclyl,

wherein the 5- to 10-membered heteroaryl or 5- to 10-membered heterocyclyl contains 1-3 heteroatoms selected from nitrogen and oxygen;

each R^5 is independently C_1-C_6 alkyl, oxo, or halo;

R^6 is H, C_1-C_6 alkyl, or oxo;

R^7 is H or oxo;

m is 1 or 2; and

n is an integer from 0 to 3;

wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkylalkyl, C_6-C_{10} aryl, C_6-C_{10} arylalkyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroarylalkyl, 5- to 10-membered heterocyclyl, and 5- to 10-membered heterocyclylalkyl is optionally substituted with one to five substituents selected from hydroxyl, halo, amino, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, -(C=O)NH_2, nitro, -SO_2(C_1-C_6 alkyl), and -CO_2H.

[0046b] In another aspect, the present disclosure provides a method of treating mild cognitive impairment in a subject in need thereof, comprising administering an effective amount of a compound selected from the compounds of Table 1A and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION

Definitions

[0047] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. To the extent any material incorporated herein by reference is inconsistent with the express content of this disclosure, the express content controls. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended

claims, the singular forms “a,” “an”, and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

[0048] Unless the context requires otherwise, throughout the present specification and claims, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to”.

[0049] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size, or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. As used herein, the terms “about” and “approximately” mean ± 20%, ± 10%, ± 5%, or ± 1% of the indicated range, value, or structure, unless otherwise indicated.

[0050] Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment.