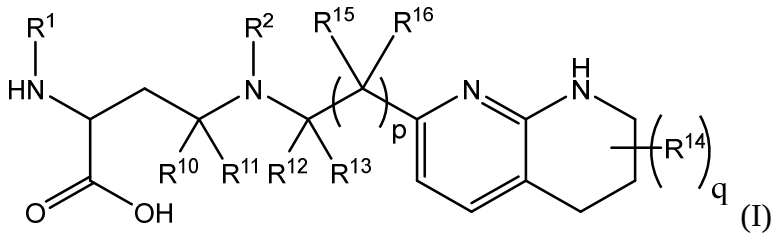
[0004] Fibrosis, a pathologic feature of many diseases, is caused by a dysfunction in the body's natural ability to repair damaged tissues. If left untreated, fibrosis can result in scarring of vital organs causing irreparable damage and eventual organ failure. Over-expression of integrins such as $\alpha_V\beta_6$ may lead to or be associated with pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis, or PFIC.

[0005] The $\alpha_V\beta_6$ integrin is expressed in epithelial cells, and binds to the latency-associated peptide of transforming growth factor-β1 (TGFβ1) and mediates TGFβ1 activation. Its expression level is significantly increased after injury to lung and cholangiocytes, and plays a critical *in vivo* role in tissue fibrosis. Increased levels related to disease or injury are also associated with increased mortality.

[0006] The present disclosure appreciates that treating diseases modulated by integrins may be a challenging endeavor.

SUMMARY

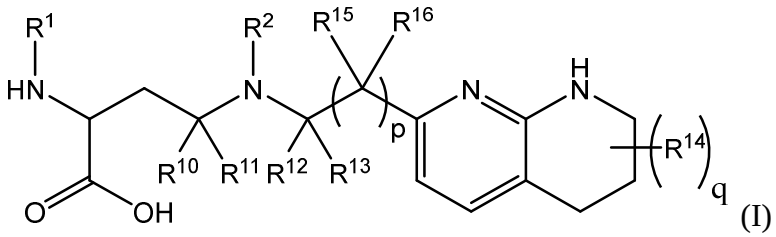
[0007] In one example, provided is a method of therapy for a condition in an individual in need thereof. The method can include providing the individual in need of treatment for the condition. The method can include administering to the individual a compound of formula (I):



(I)

[0008] or a salt thereof, wherein the variables in formula (I) are described herein. The condition can include one or more of: causation by or association with an infectious agent, shock, pancreatitis, or trauma. The condition can include one or more of pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis (PFIC). Also provided is a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutical composition thereof, for use in the treatment of a condition. The condition can include one or more of: causation by or association with an infectious agent, shock, pancreatitis, or trauma.

[0008a] In one aspect, the present disclosure refers to use of a compound of formula (I):



(I)

or a salt thereof, wherein:

R^1 is C_6-C_{14} aryl or 5- to 10-membered heteroaryl wherein the C_6-C_{14} aryl and 5- to 10-membered heteroaryl are optionally substituted by R^{1a};

R^2 is hydrogen; deuterium; C_1-C_6 alkyl optionally substituted by R^{2a}; -O-C_1-C_6 alkyl optionally substituted by R^{2a}; C_3-C_6 cycloalkyl optionally substituted by R^{2b}; -O-C_3-C_6 cycloalkyl optionally substituted by R^{2b}; 3- to 12-membered heterocyclyl optionally substituted by R^{2c}; or -$S(O)_2R^{2d}$; with the proviso that any carbon atom bonded directly to a nitrogen atom is either unsubstituted or substituted with deuterium;

each R^{1a} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_4-C_8 cycloalkenyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, deuterium, halogen, -CN, -OR^3, -SR^3, -NR^4R^5, -NO_2, -C=NH(OR^3), -$C(O)R^3$, -$OC(O)R^3$, -$C(O)OR^3$, -$C(O)NR^4R^5$, -$NR^3C(O)R^4$, -$NR^3C(O)OR^4$, -$NR^3C(O)NR^4R^5$, -$S(O)R^3$, -$S(O)_2R^3$, -$NR^3S(O)R^4$, -$NR^3S(O)_2R^4$, -$S(O)NR^4R^5$, -$S(O)_2NR^4R^5$, or -$P(O)(OR^4)(OR^5)$, wherein each R^{1a} is, where possible, independently optionally substituted by deuterium, halogen, oxo, -OR^6, -NR^6R^7, -$C(O)R^6$, -CN, -$S(O)R^6$, -$S(O)_2R^6$, -$P(O)(OR^6)(OR^7)$, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or C_1-C_6 alkyl optionally substituted by deuterium, oxo, -OH or halogen;

each R^{2a}, R^{2b}, R^{2c}, R^{2e}, and R^{2f} is independently oxo or R^{1a};

R^{2d} is C_1-C_6 alkyl optionally substituted by R^{2e} or C_3-C_5 cycloalkyl optionally substituted by R^{2f};

R^3 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl of R^3 are independently optionally substituted by halogen, deuterium, oxo, -CN, -OR^8, -NR^8R^9, -$P(O)(OR^8)(OR^9)$, or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

R^4 and R^5 are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl of R^4 and R^5 are independently optionally substituted by deuterium, halogen, oxo, -CN, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

or R^4 and R^5 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, oxo or -OH;

R^6 and R^7 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo;

R^8 and R^9 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^8 and R^9 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, oxo, or halogen;

each R^{10}, R^{11}, R^{12} and R^{13} are independently hydrogen or deuterium;

R^{14} is deuterium;

q is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{15} is independently selected from hydrogen, deuterium, or halogen;

each R^{16} is independently selected from hydrogen, deuterium, or halogen; and

p is 3, 4, 5, 6, 7, 8, or 9;

in the manufacture of a medicament for treating a condition in an individual in need thereof, wherein the medicament comprises an amount of the compound effective to treat the condition,

the condition comprising one or more of: causation by or association with an infectious agent, shock, pancreatitis, or trauma; or

the condition comprising one or more of pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis (PFIC).

[0009] Also provided is a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutical composition thereof, for use in the treatment of a condition. The condition can include one or more of pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis (PFIC).

[0010] Also provided is use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition including any of the foregoing, in the manufacture of a medicament for the treatment of a condition. The condition can include one or more of: causation by or association with an infectious agent, shock, pancreatitis, or trauma.

[0011] Also provided is use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition including any of the foregoing, in the manufacture of a medicament for the treatment of a condition. The condition can include one or more of pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis (PFIC).

[0012] Further provided is a kit including a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the kit includes instructions for use according to a method described herein, such as a method of therapy for a condition in an individual in need thereof. In various examples, the condition can include one or more of: causation by or association with an infectious agent, shock, pancreatitis, or trauma. In several examples, the condition can include one or more of pulmonary fibrosis associated with rheumatoid arthritis or progressive familial intrahepatic cholestasis (PFIC).

BRIEF DESCRIPTION OF THE FIGURES

[0013] FIG. 1 shows compounds 1-780 as disclosed herein.

[0014] FIG. 2 shows Table B-3, with biological data for various compounds disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present disclosure provides, *inter alia*, compounds of formula (I), and variations thereof, or a salt thereof, pharmaceutical compositions including compounds of formula (I) or