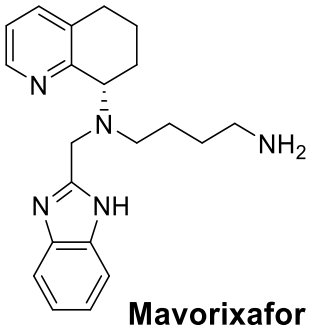
stem cells; in vitro experiments and murine models have demonstrated that CXCL12 is chemotactic for such cells.

[0004] Furthermore, there is now evidence implicating the CXCL12/CXCR4 axis in contributing to the loss or lack of tumor responsiveness to angiogenesis inhibitors (also referred to as "angiogenic escape"). In animal cancer models, interference with CXCR4 function has been demonstrated to alter the TME and sensitize the tumor to immune attack by multiple mechanisms such as elimination of tumor re-vascularization and increasing the ratio of CD8+ T cells to Treg cells. These effects result in significantly decreased tumor burden and increased overall survival in xenograft, syngeneic, and transgenic cancer models. See Vanharanta et al. (2013) Nat Med 19: 50-56; Gale and McColl (1999) BioEssays 21: 17-28; Highfill et al. (2014) Sci Transl Med 6: ra67; Facciabene et al. (2011) Nature 475: 226-230.

[0005] These data underscore the significant unmet need for CXCR4 inhibitors to treat the many diseases and conditions mediated by aberrant or undesired expression of the receptor, for example in cellular proliferative disorders.

SUMMARY

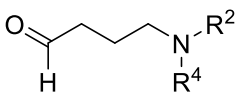
[0005a] In an aspect of the present disclosure, there is provided a method for preparing mavorixafor:



Mavorixafor

comprising the steps of:

(a) providing a compound of formula **B**:



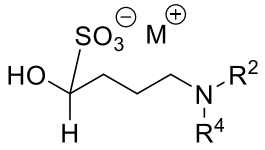
B

wherein:

R^2 is a suitable amino protecting group; and

R^4 is a suitable amino protecting group;

(b) sulfonating the compound of formula **B** to form a compound of formula **F-2a**:

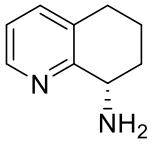


F-2a

wherein:

M is a metal selected from alkali metals;

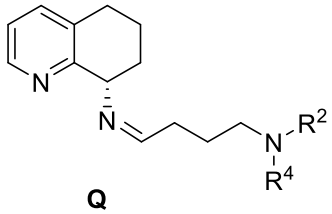
(c) condensing the compound of formula **F-2a** with compound **F-1**:



F-1

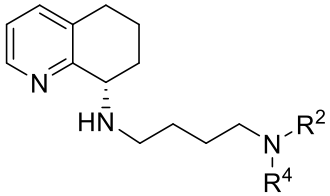
or a salt thereof,

to form a compound of formula **Q**:



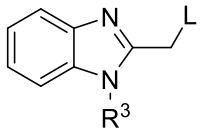
Q ;

(d) reducing the compound of formula **Q** to form a compound of formula **P**:



P ;

(e) reacting the compound of formula **P** with a compound of formula **F-3**:



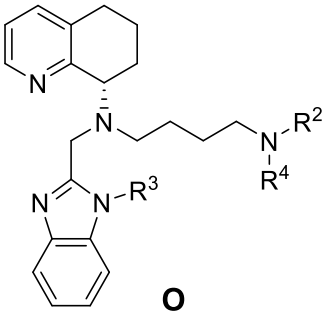
F-3

wherein:

R^3 is a suitable benzimidazole protecting group; and

L is a suitable leaving group;

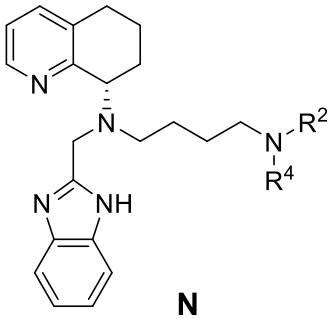
to form a compound of formula **O**:



O

;

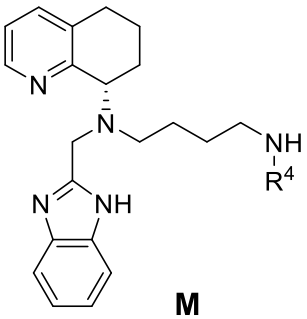
(f) deprotecting the compound of formula **O** to form a compound of formula **N**:



N

;

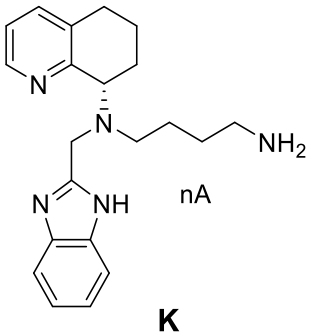
(g) deprotecting the compound of formula **N** to form a compound of formula **M**:



M

;

(h) deprotecting the compound of formula **M** to form a compound of formula **K**:



K

wherein:

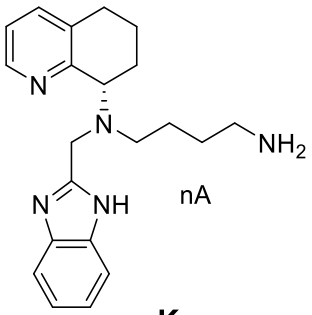
A is an acid; and

n is 1, 2 or 3;

and

(i) converting the compound of formula **K** to form mavorixafor.

[0005b] In another aspect of the present disclosure, there is provided a method for preparing a compound of formula **K**:



K

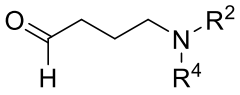
wherein:

A is an acid; and

n is 1, 2 or 3;

comprising the steps of:

(a) providing a compound of formula **B**:



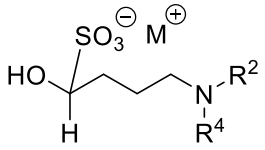
B

wherein:

R^2 is a suitable amino protecting group; and

R^4 is a suitable amino protecting group;

(b) sulfonating the compound of formula **B** to form a compound of formula **F-2a**:

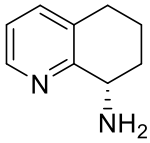


F-2a

wherein:

M is a metal selected from alkali metals;

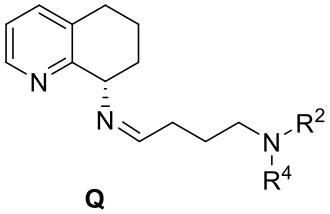
(c) condensing the compound of formula **F-2a** with compound **F-1**:



F-1

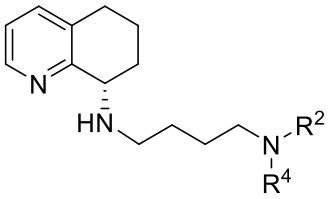
or a salt thereof,

to form a compound of formula **Q**:



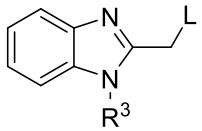
Q ;

(d) reducing the compound of formula **Q** to form a compound of formula **P**:



P ;

(e) reacting the compound of formula **P** with a compound of formula **F-3**:



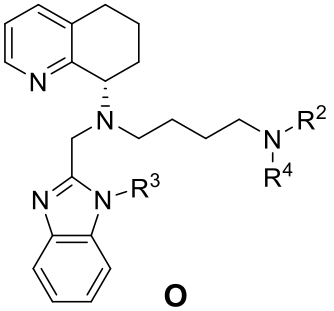
F-3

wherein:

R^3 is a suitable benzimidazole protecting group; and

L is a suitable leaving group;

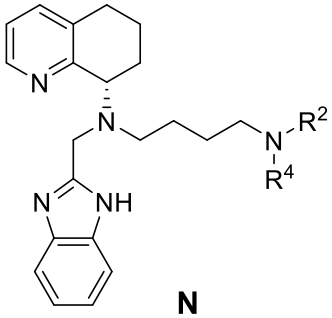
to form a compound of formula **O**:



O

;

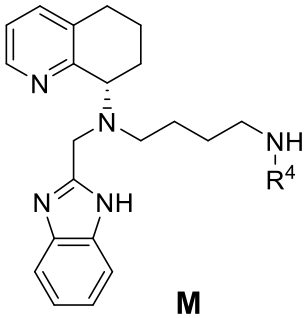
(f) deprotecting the compound of formula **O** to form a compound of formula **N**:



N

;

(g) deprotecting the compound of formula **N** to form a compound of formula **M**:

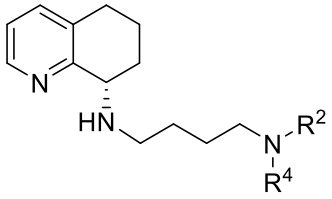


M

; and

(h) deprotecting the compound of formula **M** to form the compound of formula **K**.

[0005c] In a further aspect of the present disclosure, there is provided a method for preparing a compound of formula **P**:



P

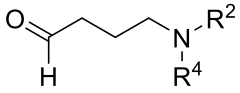
wherein:

R^2 is a suitable amino protecting group; and

R^4 is a suitable amino protecting group;

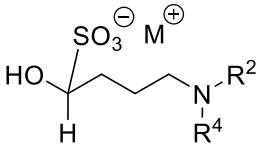
comprising the steps of:

(a) providing a compound of formula **B**:



B ;

(b) sulfonating the compound of formula **B** to form a compound of formula **F-2a**:



F-2a

wherein:

M is a metal selected from alkali metals;

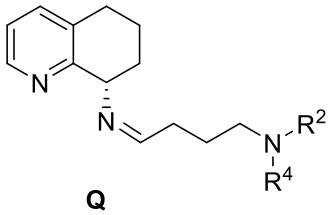
(c) condensing the compound of formula **F-2a** with compound **F-1**:



F-1

or a salt thereof;

to form a compound of formula **Q**:

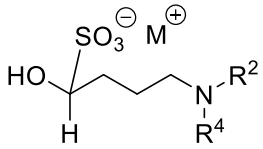


Q

; and

(d) reducing the compound of formula **Q** to form the compound of formula **P**.

[0005d] In another aspect of the present disclosure, there is provided a method for preparing a compound of formula **F-2a**:



F-2a

wherein:

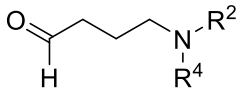
R^2 is a suitable amino protecting group;

R^4 is a suitable amino protecting group; and

M is a metal selected from alkali metals;

comprising the steps of:

(a) providing a compound of formula **B**:

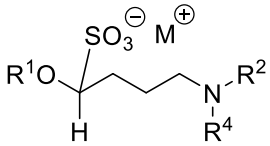


B

; and

(b) sulfonating the compound of formula **B** to form the compound of formula **F-2a**.

[0005e] In a further aspect of the present disclosure, there is provided a compound of formula **F-2**:



F-2

wherein:

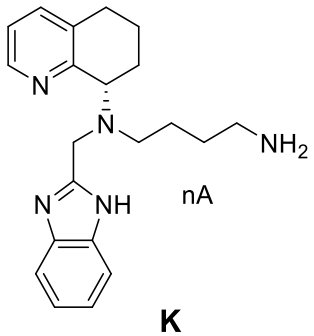
R^1 is hydrogen, -C(O)R', -C(O)OR', -C(O)NR'R", -$S(O)_m$R', -$Si(R')_3$ or an optionally substituted group selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, phenyl, aryl, or heteroaryl;

R^2 and R^4 independently are hydrogen, -C(O)R', -C(O)OR', -C(O)NR'R", -$S(O)_m$R', -$Si(R')_3$ or an optionally substituted group selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, phenyl, aryl, or heteroaryl;

R' and R" independently are hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

M is a metal selected from alkali metals.

[0005f] In another aspect of the present disclosure, there is provided a compound of formula **K**:



K

wherein:

A is H_2SO_4; and

n is 1, 2 or 3.

DETAILED DESCRIPTION OF THE INVENTION

[0006] Mavorixafor, and pharmaceutically acceptable compositions thereof, are effective as CXC receptor type 4 (CXCR4) inhibitors, and are useful for treating a variety of diseases, disorders, or conditions associated with CXCR4, such as hyperproliferative conditions including various cancers. The methods and intermediates of the present invention are useful for preparing mavorixafor, which is described in, e.g., US patent application serial number 16/215,963 (US 10,548,889), in the name of Brands, the entirety of which is incorporated herein by reference. The present invention relates to certain novel intermediates to the synthesis of mavorixafor that are easier to isolate, purify, and/or handle, and/or are more stable in comparison to corresponding intermediates in the existing methods. Furthermore, such intermediates enable methods of synthesis of mavorixafor that feature improved efficiency, reproducibility, purity, scalability, and manufacturability. In certain embodiments, the present compounds are generally prepared by assembly of three fragments **F-1**, **F-2**, and **F-3**, according to **Scheme I** set forth below: