Abstract: Compounds, compositions and methods are provided for treating cancer and inflammatory diseases, and for releasing cells such as stem cells (e.g., bone marrow progenitor cells) into circulating blood and enhancing retention of the cells in the blood. More specifically, glycomimetic-peptidomimetic compounds that inhibit both E-selectins and CXCR4 chemokine receptors are described.
GLYCOMIMETIC-PEPTIDOMIMETIC INHIBITORS OF E-SELECTINS AND CXCR4 CHEMOKINE RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 61/409,883 filed November 03, 2010; where this provisional application is incorporated herein by reference in its entirety.

BACKGROUND

Technical Field

The present invention relates generally to compounds, compositions and methods for treating cancer and inflammatory diseases, and for enhancing retention of cells after releasing into circulating blood. More specifically, the present invention relates to glycomimetic-peptidomimetic compounds that inhibit E-selectins and CXCR4 chemokine receptors, and uses thereof.

Description of the Related Art

A number of cancers are highly treatable when treated before the cancer has moved beyond the primary site. However, often once the cancer has spread beyond the primary site, the treatment options are limited and the survival statistics decline dramatically. Bones are a common location for cancer to infiltrate once leaving the primary tumor location. Breast and prostate cancer are examples of cancers that migrate to bones. Even leukemic cells that arise in the bloodstream may home to the bone marrow. Once cancer resides in bone, it is frequently a cause of pain to the individual. Further, once in the bone marrow, the cancer cells may also become resistant to chemotherapy. In addition, if the particular bone affected is a source for production of blood cells in the bone marrow, the individual may develop a variety of blood cell related disorders. Thus, it is desirable to prevent cancer cells from leaving the primary site, or to prevent extravasation of cancer cells from the bloodstream and infiltration into other tissues. Retention of cancer cells in the bloodstream makes the cells more susceptible to treatment, such as chemotherapy.

Some cancers originate all or in part in bone. For such cancers, it is desirable to mobilize cancer cells from bone to the bloodstream and to prevent those cells (as well as any cancer cells already in the bloodstream) from homing to bone or otherwise leaving the bloodstream. Retention of cancer cells in the bloodstream (or
mobilization of cancer cells into the bloodstream and then retention therein) makes the cells more susceptible to treatment, such as chemotherapy.

Hematopoietic stem cells (HSCs) also reside in the bone marrow and are a source of material for cellular therapy. HSCs adhere to the stroma within the bone marrow and in order to be harvested must break these adhesions and mobilize out of the bone marrow. It is desirable to have improved agents to increase the HSCs available for harvesting. Such HSCs are useful for engraftment.

Accordingly, there is a need in the art for the treatment of cancers that may leave the primary site and cancers that originate all or in part in bone, and for improved methods to aid in the preparation of therapeutically grade stem cells. The present invention fulfills these needs and further provides other related advantages.

BRIEF SUMMARY

Briefly stated, compounds, compositions and methods for treating diseases and for improving methods in which an E-selectin and a CXCR4 chemokine receptor play a role, are provided. In the present invention, the compounds are glycomimetic-peptidomimetic compounds wherein an E-selectin inhibitor in the form of a glycomimetic is linked to a CXCR4 chemokine receptor inhibitor in the form of a peptidomimetic. Such compounds may be combined with a pharmaceutically acceptable carrier or diluent to form a pharmaceutical composition. The compounds may be used to treat cancer in which the cancer cells may leave the primary site, or to treat an inflammatory disease in which the adhesion or migration of cells occurs in the disease, or to release cells such as stem cells (e.g., bone marrow progenitor cells) into circulating blood and enhance retention of the cells in the blood (e.g., to mobilize cells out of bone marrow and maintain the cells in the peripheral bloodstream).

The present invention provides a glycomimetic-peptidomimetic compound for inhibition of E-selectin and the CXCR4 chemokine receptor, comprising a glycomimetic E-selectin inhibitor—Linker—a peptidomimetic CXCR4 chemokine receptor inhibitor, or a physiologically acceptable salt thereof.
In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein:

\[ Z = \text{end of bond to Linker;} \]

\[ R^1 = \text{H, Ci-Cs alkanyl, C}-\text{C}_8 \text{alkenyl, C}_1-\text{C}_8 \text{alkynyl, halogenated C}_1-\text{C}_8 \text{alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where } X = \text{H, d-C}_8 \text{alkanyl, C}_1-\text{C}_8 \text{alkenyl, C}_1-\text{C}_8 \text{alkynyl, halogenated C}_1-\text{C}_8 \text{alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH; C}(=\text{O})\text{OX, alkanyl substituted with C}(=\text{O})\text{OX, C}(=\text{O})\text{NHX, alkanyl substituted with C}(=\text{O})\text{NHX, where } X = \text{H, C}_1-\text{C}_8 \text{alkanyl, C}_1-\text{C}_8 \text{alkenyl, C}_1-\text{C}_8 \text{alkynyl, halogenated C}_1-\text{C}_8 \text{alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH; C}(=\text{O})\text{X, OX, NHX, NHC}(=\text{O})\text{X, where } X = \text{H, C}_1-\text{C}_8 \text{alkanyl, C}_1-\text{C}_8 \text{alkenyl, C}_1-\text{C}_8 \text{alkynyl, halogenated Cr-C}_8 \text{alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;}} \]

\[ R^2 = \text{-OH, -O-C}(=\text{O})\text{-X, -NH}_2\text{-NH-C}(=\text{O})\text{-NHX, or -NH-C}(=\text{O})\text{-X where } n = 0-2 \text{ and } X \text{ is independently selected from Ci-C}_8 \text{alkanyl, C}_1-\text{C}_8 \text{alkenyl, Ci-C}_8 \text{alkynyl,}} \]

\[ \ldots \]
where Q is H or a physiologically acceptable salt, Ci-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, aryl, (CH$_2$)$_m$-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF$_3$, d-C$_8$ alkoxy, NO$_2$, Ci-C$_8$ alkanyl, C$_1$-C$_8$ alkenyl, d-C$_8$ alkynyl, d-C$_{14}$ aryl, or OY, C(=0)OY, NY$_2$ or C(=0)NHY where Y is H, d-C$_8$ alkanyl, d-C$_8$ alkenyl, d-C$_8$ alkynyl, or C$_{14}$ aryl;

R$^3$ = H, Ci-Cg alkanyl, d-Cg alkenyl, d-C$_8$ alkynyl, CN, CH$_2$CN, C(=0)X where X is H, Ci-C$_8$ alkanyl, Ci-Cg alkenyl, d-Cg alkynyl, NHOH, NHOCH$_3$, NHCN, or NX$_2$, or C(=0)OY where Y is H, d-C$_g$ alkanyl, Ci-C$_g$ alkenyl or Ci-C$_8$ alkynyl; and

R$^4$ =
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, Q-C₈ alkanyl, Q-C₉ alkenyl, Q-C₉ alkynyl or OY where Y is H, Q-C₉ alkanyl, Q-C₉ alkenyl, Q-C₉ alkynyl or Q-C₁₄ aryl.

In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein Z = end of bond to Linker.
In one embodiment of the compound, the E-selectin inhibitor consists of:

\[
\begin{align*}
\text{O} & \text{C} \quad \text{OH} \\
\text{HN} & \\
\text{OH} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{OH} & \text{OH}
\end{align*}
\]

wherein \( Z = \text{end of bond to Linker.} \)

In one embodiment of the compound, the E-selectin inhibitor consists of:

\[
\begin{align*}
\text{O} & \text{C} \quad \text{NHOH} \\
\text{HN} & \\
\text{OH} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{OH} & \text{OH}
\end{align*}
\]

wherein \( Z = \text{end of bond to Linker.} \)

In one embodiment of the compound, the E-selectin inhibitor consists of:
wherein $Z =$ end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein $Z =$ end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:
wherein \( Z = \text{end of bond to Linker.} \)

In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:

\[
\text{Z} \quad \begin{array}{c} \text{KGVSLSYR} \quad \text{X} \quad \text{RYSLSVGK} \end{array}
\]

wherein \( Z = \text{end of bond to Linker.} \)

In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:

\[
\begin{array}{c}
\text{Arg} \\
\text{HN} \\
\text{O} \\
\text{O} \\
\text{Nal} \\
\text{HN} \\
\text{O} \\
\text{O} \\
\text{Arg} \\
\text{Tyr} \\
\text{O} \\
\text{Z}
\end{array}
\]

wherein \( Z = \text{end of bond to Linker.} \)

In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:
wherein \( Z = \text{end of bond to Linker} \).

In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:

wherein \( Z = \text{end of bond to Linker} \); and \( X = \text{H or halide} \).

In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:

wherein \( Z = \text{end of bond to Linker} \); and \( X = \text{H or halide} \).
In one embodiment of the compound, the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure]

wherein one of $R_1$, $R_2$ and $R_3$ is the end of bond to Linker and the other two are $H$; and wherein $X$ is $C(R_4)(R_5)$, NR4, O or S, where $R_4$ is $H$ or an electron withdrawing group and $R_5$ is $H$ or an electron withdrawing group.

In one embodiment, the compound has the formula:

![Peptide Sequence]

wherein:

$R^1 = H$, Ci-Cs alkanyl, C$_1$-C$_g$ alkenyl, C$_1$-C$_g$ alkynyl, halogenated C$_1$-C$_g$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where $X = H$, Q-C$_g$ alkanyl, Ci-C$_8$ alkenyl, Q-C$_g$ alkynyl, halogenated C$_1$-C$_g$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where $X = H$, Ci-C$_g$ alkanyl, C$_1$-C$_g$ alkenyl, C$_1$-C$_g$ alkynyl, halogenated C$_1$-C$_g$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where $X = H$, Q-C$_g$
alkanyl, d-C₈ alkenyl, Ci-C₈ alkynyl, halogenated C₁-C₈ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = -\text{OH}, \]

-0-C(=0)-X, -NH₂, -NH-C(=0)-NHX, or -NH-C(=0)-X where \( n = 0-2 \) and \( X \) is independently selected from d-C₈ alkanyl, Ci-C₈ alkenyl, d-C₈ alkynyl,

physiologically acceptable salt, d-C₈ alkanyl, d-C₈ alkenyl, C₁-C₈ alkynyl, aryl, (CH₂)m-aryl where \( m \) is 1-10, and where \( n = 0-10 \), and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF₃, d-C₈ alkoxy, N0₂, d-C₈ alkanyl, C₁-C₈ alkynyl, d-C₈ alkynyl, d-C₈ aryl, or OY, C(=0)OY, NY₂ or C(=0)NHY where \( Y \) is H, d-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl, or d-C₈ aryl;

\[ R^3 = \text{H, d-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl, CN, CH₂CN, C(=0)X where } X = \text{H, d-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl, NHOH, NHOCH₃, NHCN, or NX₂, or C(=0)OY where } Y = \text{H, d-C₈ alkanyl, d-C₈ alkenyl or d-C₈ alkynyl;} \]
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, d-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkylnyl or OY where Y is H, d-C₈ alkanyl, d-C₈ alkenyl, Ci-C₈ alkynyl or Ci-C₁₄ aryl; and

X = an amino acid.

In one embodiment, the compound has the formula:

wherein X is an amino acid.
In one embodiment, the compound has the formula:

![Chemical structure](image)

wherein X is an amino acid.

In one embodiment, the compound has the formula:

![Chemical structure](image)

wherein X is an amino acid.
wherein \( X \) is an amino acid.

In one embodiment, the compound has the formula:

![Chemical Structure 1](image1)

wherein \( X \) is an amino acid.

In one embodiment, the compound has the formula:

![Chemical Structure 2](image2)

wherein:

\[ R^1 = H, \text{Ci-Cg alkanyl, C}_1^\text{a} \text{Cg alkynyl, Ci-Cg alkynyl, halogenated C}_1^\text{a} \text{Cg alkynyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, C}_1^\text{a} \text{C}_8^\text{a} \text{alkanyl, C}_1^\text{a} \text{Cg alkynyl, C}_1^\text{a} \text{Cg alkynyl, halogenated C}_1^\text{a} \text{Cg alkynyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted} } \]
with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where X = H, d-Cg alkanyl, C]-C8 alkenyl, d-Cg alkynyl, halogenated d-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where X = H, d-C8 alkanyl, d-C8 alkenyl, d-C8 alkynyl, halogenated d-C8 alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = \text{-OH}, \]

-0-C(=0)-X, -NH, -NH-C(=0)-NHX, or -NH-C(=0)-X where n = 0-2 and X is independently selected from d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl,

physiologically acceptable salt, d-Cg alkanyl, d-Cg alkenyl, C1-Cg alkynyl, aryl, (CH2)m-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, C8F3, d-C8 alkoxy, NO2, d-C8 alkanyl, C1-Cg alkenyl, C1-Cg alkynyl, C1-C14 aryl, or OY, C(=0)OY, NY2, or C(=0)NHY where Y is H, C1-Cg aryl, d-C8 alkenyl, Ci-Cg alkynyl, or d-C14 aryl;
R³ = H, Ci-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl, CN, CH₂CN, C(=0)X
where X is H, Ci-C₈ alkanyl, d-C₁₄ alkenyl, Ci-C₈ alkynyl, NH₂OH,
NHOCH₃, NH₂CN, or N₂ or C(=0)OY where Y is H, d-C₈ alkanyl, C₁-C₈ alkynyl or d-C₈ alkynyl; and

\[
R^4 =
\begin{align*}
&\text{HO} &\text{OH}\\
&\text{HO} &\text{OH} &\text{HO} &\text{HN} &\text{Me} &\text{O} &\text{Me} &\text{HN} &\text{HO} &\text{HO}\\
&\text{HN} &\text{Me} &\text{O} &\text{Me} &\text{HN} &\text{HO} &\text{HO} &\text{HN} &\text{Me} &\text{O} &\text{Me} &\text{HN} &\text{HO} &\text{HO}
\end{align*}
\]

where the cyclopropane ring may be substituted with one to two, and the
cyclohexane ring may be substituted with one to three, independently
selected of Cl, F, d-C₁₄ alkanyl, C₁-C₈ alkenyl, d-C₈ alkynyl or OY
where Y is H, d-C₈ alkanyl, d-C₈ alkenyl, d-C₁₄ alkynyl or d-C₁₄
aryl.

In one embodiment, the compound has the formula:
In one embodiment, the compound has the formula:

\[ \text{Structure Image} \]

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\[ \text{Structure Image} \]

In one embodiment, the compound has the formula:
In one embodiment, the compound has the formula:

![Chemical Structure 1]

In one embodiment, the compound has the formula:

![Chemical Structure 2]
wherein:

\[ R^1 = H, \text{d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated d-Cg alkanyl, aryl which may be substituted with} \]

\[ \text{one or more of Me, OMe, halide, OH, or NHX where } X = H, \text{C-Cg alkanyl, C-8 alkenyl, d-Cg alkynyl, halogenated C-Cg alkanyl, aryl which may be substituted with} \]

\[ \text{one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with} \]

\[ \text{C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where } X = H, \text{d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated d-Cg alkanyl, aryl which may be substituted with} \]

\[ \text{one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where } X = H, \text{d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated d-Cg alkanyl, aryl which may be substituted with} \]

\[ \text{one or more of Me, OMe, halide, or OH; } \]

\[ R^2 = -\text{OH,} \quad -\text{N} \equiv \text{N}, \quad -\text{N} \equiv \text{N}(X)_n, \quad -\text{N} \equiv \text{N}, \quad -\text{N} \equiv \text{N}, \quad -\text{N} \equiv \text{N}, \quad -\text{N} \equiv \text{N}(X) \]

\[ -\text{O-C(=0)-X, -NH}_2, -\text{NH-C(=0)-NHX, or -NH-C(=0)-X where } n = 0-2 \text{ and } X \text{ is independently selected from C-Cg alkanyl, C-Cg alkenyl, C-Cg alkynyl,} \]
physiologically acceptable salt, C\textsubscript{1}-C\textsubscript{8} alkanyl, d-C\textsubscript{8} alkynyl, aryl, (CH\textsubscript{2})\textsubscript{m}-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF\textsubscript{3}, Ci-C\textsubscript{8} alkoxy, N0\textsubscript{2}, d-C\textsubscript{8} alkanyl, C\textsubscript{1}-C\textsubscript{8} alkenyl, d-C\textsubscript{8} alkynyl, d-C\textsubscript{8} alkynyl, or OY, C(=0)OY, NY\textsubscript{2} or C(=0)NHY where Y is H, d-C\textsubscript{8} alkanyl, Ci-Cs alkenyl, d-C\textsubscript{8} alkynyl, or d-C\textsubscript{14} aryl;

R\textsuperscript{3} = H, d-C\textsubscript{8} alkanyl, Ci-C\textsubscript{8} alkenyl, d-C\textsubscript{8} alkynyl, CN, CH\textsubscript{2}CN, C(=0)X where X is H, d-C\textsubscript{8} alkanyl, d-C\textsubscript{8} alkenyl, d-C\textsubscript{8} alkynyl, NHOH, NHOCH\textsubscript{3}, NHCN, or NX\textsubscript{2}, or C(=0)OY where Y is H, d-C\textsubscript{8} alkanyl, Ci-C\textsubscript{8} alkenyl or d-C\textsubscript{8} alkynyl; and

R\textsuperscript{4} =
where the cyclopropane ring may be substituted with one to two, and the
cyclohexane ring may be substituted with one to three, independently
selected of Cl, F, d-C$_8$ alkanyl, C$_7$-C$_8$ alkenyl, d-C$_8$ alkynyl or OY
where Y is H, d-C$_8$ alkanyl, d-C$_8$ alkenyl, d-C$_8$ alkynyl or d-C$_{14}$
aryl.

In one embodiment, the compound has the formula:
In one embodiment, the compound has the formula:
In one embodiment, the compound has the formula:

[Chemical Structure Image]

In one embodiment, the compound has the formula:

[Chemical Structure Image]
wherein:

\[ R^1 = \text{H}, \text{Ci}-\text{C}_8 \text{ alkanyl, Q}-\text{C}_g \text{ alkenyl, C}_1-\text{C}_g \text{ alkynyl, halogenated Q}-\text{C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where } X = \text{H, Q}-\text{C}_g \text{ alkanyl, C}_1-\text{C}_8 \text{ alkenyl, Q}-\text{C}_g \text{ alkynyl, halogenated Q}-\text{C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{OX, alkanyl substituted with C}(=0)\text{OX, C}(=0)\text{NHX, alkanyl substituted with C}(=0)\text{NHX, where } X = \text{H, C}_1-\text{C}_8 \text{ alkanyl, Q}-\text{C}_g \text{ alkenyl, Q}-\text{C}_g \text{ alkynyl, halogenated Q}-\text{C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{X, OX, NHX, NHC}(=0)\text{X, where } X = \text{H, C}_1-\text{C}_8 \text{ alkanyl, Q}-\text{C}_g \text{ alkenyl, Q}-\text{C}_g \text{ alkynyl, halogenated C}_1-\text{C}_8 \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;}} \]

\[ R^2 = \text{OH, } -\text{OH, } -\text{NH}_2, -\text{NH}-\text{C}(=0)-\text{NHX, or } -\text{NH}-\text{C}(=0)-\text{X where } n = 0-2 \text{ and } X \text{ is independently selected from C}_1-\text{C}_g \text{ alkanyl, Q}-\text{C}_g \text{ alkenyl, Ci-C}_8 \text{ alkynyl,}} \]
physiologically acceptable salt, d-C alkanyl, d-C alkenyl, C1-Cg alkynyl, aryl, (CH₂)ₘ·aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF₃, d-C alkoxy, N0₂, d-C alkanyl, Ci-Cs alkenyl, d-C alkynyl, Ci-Ci ary1, or OY, C(=0)OY, NY₂ or C(=0)NHY where Y is H, C1-Cg alkanyl, Cₐ-Cg alkynyl, d-C alkynyl, or C1-C1₄ aryl;

R³ = H, C₁-C₈ alkanyl, d-C alkynyl, d-C alkynyl, CN, CH₂CN, C(=0)X where X is H, d-C alkanyl, Ci-C₈ alkenyl, d-C alkynyl, NHOH, NHOCH₃, NHCN, or NX₂, or C(=0)OY where Y is H, d-C alkanyl, Ci-C₈ alkynyl or d-C alkynyl;

R⁴ =
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of CI, F, C1- Cg alkanyl, Q-Cg alkenyl, Q-Cg alkynyl or OY where Y is H, C1- Cg alkanyl, C1- Cg alkenyl, Q-Cg alkynyl or C1- C14 aryl; and

X = H or halide.

In one embodiment, the compound has the formula:

wherein X is H or halide.

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wherein X is H or halide.

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wherein $X$ is H or halide.

In one embodiment, the compound has the formula:
wherein:

$$R^1 = H, \text{-C}^8\text{-alkanyl, Q-Cg\alkenyl, Ci-Cg\alkynyl, halogenated Ci-C}^8\text{-alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where } X = H, \text{-C}^1\text{-C}^8\text{alkanyl, d-C}^8\text{-alkenyl, d-Cg\alkynyl, halogenated d-Cg\alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with } C(=0)OX, \text{ C(=0)NHX, alkanyl substituted with } C(=0)NHX, \text{ where } X = H, \text{-C}^1\text{-C}^8\text{alkanyl, C_1-Cgalkenyl, Ci-Cg\alkynyl, halogenated d-Cg\alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(-0)X, OX, NHX, NHC(=0)X, where } X = H, \text{-Q-Cg\alkenyl, Ci-Cg\alkenyl, d-C}^8\text{alkynyl, halogenated Ci-Cg\alkenyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; }$$

$$R^2 = \text{-OH, } \text{-NH}_2, \text{-NH-C(=0)-NHX, or } \text{-NH-C(=0)-X where } n = 0-2\text{ and } X\text{ is independently selected from d-Cg\alkenyl, C_1-Cg\alkenyl, Ci-Cg\alkynyl,}$$
physiologically acceptable salt, C_1-C_8 alkanyl, C_1-C_8 alkenyl, d-C_g alkynyl, aryl, (CH_2)_m-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF_3, d-C_g alkoxy, NO_2, Q-C_g alkanyl, d-C_g alkenyl, d-C_8 alkynyl, d-C_14 aryl, or OY, C(=0)OY, NY_2 or C(=0)NHY where Y is H, C_1-C_g alkanyl, d-C_g alkenyl, d-C_8 alkynyl, or C=C_14 aryl;

R^3 = H, d-C_g alkanyl, d-C_g alkenyl, d-C_g alkynyl, CN, CH_2CN, C(=0)X where X is H, d-C_8 alkanyl, d-C_g alkenyl, d-C_g alkynyl, NHOH, NHOCH_3, NHCN, or NX_2, or C(=0)OY where Y is H, d-C_g alkanyl, d-C_g alkynyl or d-C_g alkynyl;

R^4 =

\[
\text{HO} \quad \text{OH} \quad \text{O} \quad \text{HN} \quad \text{HO} \\
\text{HN} \quad \text{HO} \\
\text{O} \quad \text{Me} \\
\text{O} \quad \text{Me}
\]
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of CI, F, C_{1-8} alkanyl, d-C_{8} alkenyl, C_{1-8} alkynyl or OY where Y is H, C_{1-8} alkanyl, C_{1-8} alkenyl, C_{1-8} alkynyl or Cr-C_{4} aryl; and

\[ X = H \text{ or halide.} \]

In one embodiment, the compound has the formula:

\[ \text{wherein } X \text{ is } H \text{ or halide.} \]

In one embodiment, the compound has the formula:
wherein $X$ is H or halide.

In one embodiment, the compound has the formula:

wherein $X$ is H or halide.

In one embodiment, the compound has the formula:
wherein $X$ is H or halide.

In one embodiment, the compound has the formula:

wherein $X$ is H or halide.
In one embodiment, the compound has the formula:

$$\text{R}^1 = \text{H, Ci-Cg alkanyl, C}_1\text{-Cg alkenyl, C}_1\text{-C}_8\text{ alkynyl, halogenated C}_1\text{-C}_g\text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, C}_1\text{-Cg alkenyl, C}_1\text{-C}_g\text{ alkynyl, halogenated Q-Cg alkanyl, alkanyl substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{OX, alkanyl substituted with C}(=0)\text{OX, C}(=0)\text{NHX, alkanyl substituted with C}(=0)\text{NHX, where X = H, C}_1\text{-Cg alkenyl, C}_1\text{-C}_8\text{ alkenyl, C}_1\text{-Cg alkenyl, halogenated C}_1\text{-C}_g\text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{X, OX, NHX, NHXC}(=0)\text{X, where X = H, C}_1\text{-Cg alkanyl, C}_1\text{-C}_g\text{ alkenyl, C}_1\text{-C}_g\text{ alkynyl, halogenated C}_1\text{-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;}}$$

$$\text{R}^2 = \text{-OH, } \text{N} = \text{N} \text{, } \text{N} \text{=N}(\text{X})_n \text{, } \text{N} \text{=N} \text{, } \text{N} \text{=N} \text{, } \text{N} \text{=N} \text{, } \text{N} \text{=X} \text{, } \text{N} \text{=N} \text{, } \text{N} \text{=N} \text{, } \text{N} \text{=N} \text{, }$$

$$-\text{O-C}(=0)\text{-X, -NH}_2, -\text{NH-C}(=0)\text{-NHX, or -NH-C}(=0)\text{-X where } n = 0\text{-2 and X is independently selected from C}_1\text{-Cg alkenyl, Ci-Cg alkenyl, C}_1\text{-C}_g\text{ alkynyl,}$$
physiologically acceptable salt, d-Cg alkanyl, Ci-C8 alkenyl, C1-C8 alkynyl, aryl, (CH$_2$)$_m$-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF$_3$, d-Cg alkoxy, NO$_2$, d-Cg alkanyl, Ci-Cg alkenyl, Q-Cg alkynyl, d-C$_{14}$ aryl, or OY, C(=0)OY, NY$_2$ or C(=0)NHY where Y is H, d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, or d-C$_{14}$ aryl;

R$^3$ = H, d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, CN, CH$_2$CN, C(=0)X where X is H, d-Cg alkanyl, d-C$_8$ alkenyl, d-C$_8$ alkynyl, NHOH, NHOCH$_3$, NHCN, or NX$_2$, or C(=0)OY where Y is H, d-Cg alkanyl, d-Cg alkynyl or d-C$_g$ alkynyl;

R$^4$ =
where the cyclopropane ring may be substituted with one to two, and the
cyclohexane ring may be substituted with one to three, independently
selected of Cl, F, C₁- C₈ alkanyl, d-C₈ alkynyl or OY
where Y is H, d-C₈ alkanyl, C₁- C₈ alkenyl, Ci-C₈ alkynyl or d-C₈ ary1; and

\[ X = S, O, C(R₄)(R₅) \text{ or } NR₄, \]

where \( R₄ \) is H or an electron withdrawing group
and \( R₅ \) is H or an electron withdrawing group.

In one embodiment, the electron withdrawing group is a halogenated d -
C₈ alkanyl, a halogenated d-C₈ alkenyl, a halogenated d-C₈ alkynyl, -C-NÖ₂,
-\( \text{C} (=\text{O}) \)-Y or -\( \text{C} (=\text{O}) \)-OY, where Y is H, d-C₈ alkanyl, Ci-C₈ alkenyl, d-C₈ alkynyl,
halogenated d-C₈ alkanyl, halogenated d-C₈ alkenyl, or halogenated Ci-C₈ alkynyl.

In one embodiment, the compound has the formula:

wherein \( X = S, O, C(R₄)(R₅) \text{ or } NR₄, \) where \( R₄ \) is H or an electron withdrawing group
and \( R₅ \) is H or an electron withdrawing group.

In one embodiment, the compound has the formula:
wherein \( X = S, O, C(R_4)(R_5) \) or \( NR_4 \), where \( R_4 \) is H or an electron withdrawing group and \( R_5 \) is H or an electron withdrawing group.

In one embodiment, the compound has the formula:

wherein \( X = S, O, C(R_4)(R_5) \) or \( NR_4 \), where \( R_4 \) is H or an electron withdrawing group and \( R_5 \) is H or an electron withdrawing group.

In one embodiment, the compound has the formula:
wherein $X = S, O, C(R_4)(Rs)$ or $NR_4$, where $R_4$ is $H$ or an electron withdrawing group and $R_5$ is $H$ or an electron withdrawing group.

In one embodiment, the compound has the formula:

wherein $X = S, O, C(R_4)(R_5)$ or $NR_4$, where $R_4$ is $H$ or an electron withdrawing group and $R_5$ is $H$ or an electron withdrawing group.

In any of the above embodiments, $X$ may be $S, O, C(R_4)(Rs)$ or $N^+$. In one embodiment, the Linker of the compound is $-C(=0)-NH-(CH_2)_2-NH-$.

In one embodiment, the Linker of the compound is $-CH_2-NH-CH_2^-$. In one embodiment, the Linker of the compound is $-C(=0)-NH-CH_2^-$. 

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These linkers, as well as the others disclosed herein and those otherwise known in the art, are for use in a compound of the present invention such as the embodiments depicted above containing a Linker.

The present invention provides a method for the treatment of a cancer in which the cancer cells may leave the primary site in an individual who is in need of such treatment, comprising administering to the individual a compound of the present invention in an amount effective for treatment, wherein the compound is with or without a pharmaceutically acceptable carrier or diluent.

The present invention provides a method for the treatment of a cancer in which it is desired to mobilize cancer cells from a site into the bloodstream and retain the cancer cells in the bloodstream in an individual who is in need of such treatment, comprising administering to the individual a compound of the present invention in an amount effective for treatment, wherein the compound is with or without a pharmaceutically acceptable carrier or diluent. In an embodiment, the method further includes the step of collecting the cells released. In an embodiment, the step of collecting utilizes apheresis. In an embodiment, the cells are stem cells (e.g., bone marrow progenitor cells). In an embodiment, G-CSF is administered to the individual.

The present invention provides a method for the treatment of an inflammatory disease in which the adhesion or migration of cells occurs in the disease in an individual in need of such treatment, comprising administering to the individual a compound of the present invention in an amount effective for treatment, wherein the compound is with or without a pharmaceutically acceptable carrier or diluent.

The present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier or diluent.

In other embodiments, the above compounds thereof may be used in the manufacture of a medicament, and for any of the uses recited herein.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a diagram illustrating the synthesis of a first glycomimetic compound (compound 19).

Figure 2 is a diagram illustrating the synthesis of a peptidomimetic (compound 21).

Figure 3 is a diagram illustrating the synthesis of glycomimetic-peptidomimetic #1 (compound 23).

Figure 4 is a diagram illustrating the synthesis of a second glycomimetic (compound XX).

Figure 5 is a diagram illustrating the synthesis of glycomimetic-peptidomimetic #2 (compound 25).

Figure 6 is a diagram illustrating the synthesis of a third glycomimetic (compound XXIII).

Figure 7 is a diagram illustrating the synthesis of glycomimetic-peptidomimetic #3 (compound 27).

Figures 8A-8B are a diagram illustrating the synthesis of glycomimetic-peptidomimetic #4 (compound 36).

Figure 9 is a diagram illustrating the synthesis of glycomimetic-peptidomimetic #5 (compound 37).

Figures 10A-10B are a diagram illustrating the synthesis of glycomimetic-peptidomimetic #6 (compound 54).

Figure 11 is a diagram illustrating the synthesis of glycomimetic-peptidomimetic #7 (compound 65).

DETAILED DESCRIPTION

As noted above, the present invention provides compounds, compositions and methods for treating diseases in which an E-selectin and a CXCR4 chemokine receptor play a role, and for enhancing retention of cells after releasing into circulating blood. The compounds have a variety of uses in vitro and in vivo.

As used herein, the term "E-selectin inhibitor" refers to an inhibitor of E-selectin only, as well as to an inhibitor of E-selectin and either P-selectin or L-selectin, or E-selectin and both P-selectin and L-selectin. Thus, there is E-selectin inhibition regardless of whether there is also inhibition of either P-selectin or L-selectin or both P-selectin and L-selectin.
All compounds of the present invention or useful thereto (e.g., for pharmaceutical compositions or methods of treating) include physiologically acceptable salts thereof. Examples of such salts are Na, K, Li, Mg, Ca, and Cl.

A compound of the present invention is a glycomimetic-peptidomimetic compound wherein an E-selectin inhibitor is linked (i.e., covalently bonded) to a CXCR4 chemokine receptor inhibitor. Such a compound comprises, or consists of, the formula:

Glycomimetic E-selectin inhibitor—Linker—Peptidomimetic CXCR4 chemokine receptor inhibitor. Accordingly, the compound functions to inhibit E-selectin and to inhibit the CXCR4 chemokine receptor.

E-selectin inhibitors are well known in the art. Some E-selectin inhibitors are specific for E-selectin only. Other E-selectin inhibitors have the ability to inhibit not only E-selectin but additionally P-selectin or L-selectin or both P-selectin and L-selectin. Examples of E-selectin inhibitors (specific for E-selectin or otherwise) are disclosed in U.S. Patent No. 7,060,685; U.S. Application Publication No. US-2007-0054870; U.S. Application Publication No. US-2008-0161546; and references cited in any of these patent or published application documents.

In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein Z = end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:
wherein $Z$ = end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein $Z$ = end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:
wherein $Z =$ end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:

wherein $Z =$ end of bond to Linker.

In one embodiment of the compound, the E-selectin inhibitor consists of:
wherein $Z = \text{end of bond to Linker}$.

Peptidomimetic CXCR4 chemokine receptor inhibitors are well known in the art. Such inhibitors will typically prevent the binding of stromal derived factor-1 (SDF-1) to a CXCR4 receptor. An example of peptidomimetic CXCR4 chemokine receptor inhibitors is CTCE-9 (Faber et al., *J Biomed. Biotech*, Volume 2007, Article ID 26065, 10 pages). In one embodiment of a compound of the present invention, the CXCR4 chemokine receptor inhibitor is KGVLSYR—K—RYSLSVGK. In other words, the X between the two peptides is K. As used herein, the term "peptidomimetic" refers to peptides composed of naturally occurring amino acids, non-naturally occurring amino acids or non-amino acid mimics of either, and peptides composed of any combination of the above. As used herein, the term "amino acid" refers to a naturally occurring amino acid (protein or non-protein amino acid), a non-naturally occurring amino acid, or a non-amino acid mimic of either, and all isomers, tautomers, enantiomers, hydrates, esters, racemates, polymorphs, metabolites and prodrugs of any. For example, an orothylamido group exists as a tautomer of enol and keto forms. Where an orothylamido group is depicted herein, only the enol form is shown and, as is well known in the art, encompasses the keto form as well. Such an amino acid includes a post-translationally modified amino acid, an enzymatically synthesized amino acid and a derivatized amino acid. Examples of a derivatized or unusual amino acid include homo arginine, homo lysine, and naphthylalanine ("Nal"), *e.g.*, 3-(1-naphthyl)alanine and 3-(2-naphthyl)alanine. Additional examples of an "amino acid" as used herein, include those described in *Synthetic Peptides: A User's Guide*, G.A. Grant, editor, W.H.
In a compound of the present invention, a glycomimetic E-selectin inhibitor and a peptidomimetic CXCR4 chemokine receptor inhibitor are covalently joined via a linker (i.e., interposed between the two inhibitors is a "Linker"). A linker may be (or may include) a spacer group, such as -(CH₂)ᵩ or -0(CH₂)ᵩ where p is generally about 1-20 (including any whole integer range therein). Other examples of spacer groups include a carbonyl or carbonyl containing group such as an amide. An embodiment of such spacer groups is

Embodiments of linkers include the following:

- **Squaric acid**
- **Thiourea**
- **Dithiadiazoleoxide**
- **Acetylation via Thiofuran**
- **N-Pentenoylation and Reductive amination**
- **Coupling Via Bifunctional amination NHS reagent**
Other linkers, e.g., polyethylene glycols (PEG) or \(-\text{C}(=\text{O})-\text{NH-(CH}_2\text{)}_p-\text{C}(=\text{O})-\text{NH}_2\)
where \(p\) is as defined above, will be familiar to those in the art or in possession of the present disclosure.

In another embodiment, the linker is

\[
\begin{align*}
\text{N} & \text{H} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{N} & \text{H} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{N} & \text{H} \\
\text{C}(=\text{O}) & \\
\end{align*}
\]

In another embodiment, the linker is

\[
\begin{align*}
\text{N} & \text{H} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{N} & \text{H} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{N} & \text{H} \\
\text{C}(=\text{O}) & \\
\end{align*}
\]

In another embodiment, the linker is \(-\text{C}(=\text{O})-\text{NH-(CH}_2\text{)}_2-\text{NH}-\).

In another embodiment, the linker is \(-\text{CH}_2\text{-NH-CH}_2\text{-}.

In another embodiment, the linker is \(-\text{C}(=\text{O})-\text{NH-CH}_2\text{-}.

In one embodiment of a compound of the present invention, the E-selectin inhibitor consists of:

\[
\begin{align*}
\text{R}^1 & \text{R}^2 \text{R}^3 \\
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{OH} & \text{OH} \\
\text{OH} & \text{OH} \\
\text{Me} & \text{OH} \\
\text{OH} & \text{OH} \\
\end{align*}
\]

wherein \(Z\) is the end of the bond to Linker.

In the present disclosure, there are several chemical abbreviations. "Me" is methyl. "Et" is ethyl. "Ar" is aryl. "Bz" is benzoyl. For peptides, either the single letter abbreviations for amino acids (e.g., K is lysine, R is arginine, etc.) or the three letter abbreviations (e.g., Arg is arginine, Tyr is tyrosine, etc.) are used herein.

Selection of a substituent at \(R^1\) includes H, \(\text{C}_1\text{-C}_8\) alkanyl, \(\text{C}_1\text{-C}_8\) alkenyl, \(\text{C}_j\text{-Cs}\) alkynyl, halogenated \(\text{C}_1\text{-C}_8\) alkanyl, aryl which may be substituted with
one or more of Me, OMe, halide, OH, or NHX where X = H, d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated d-C8 alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where X = H, d-Cg alkenyl, d-C8 alkynyl, Ci-Cg alkynyl, halogenated C1-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where X = H, d-C8 alkanyl, Ci-Cg alkenyl, d-Cg alkynyl, halogenated d-C8 alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH.

Selection of a substituent at R2 includes –OH, –C(=O)X, –NH2, –NH–C(=O)–NHX, or –NH–C(=O)–X where n = 0–2 and X is independently selected from C1–C8 alkanyl, C1–C8 alkenyl, C1–C8 alkynyl, C1–C8 alkynyl, and or a physiologically acceptable salt, Q-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, aryl, (CH2)m-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF3, d-Cg alkoxy, N02, d-Cg alkenyl, Ci-Cg alkenyl, Ci-Cg alkynyl, C1–C14 aryl, or OY, C(=0)OY, NY2 or C(=0)NHY where Y is H, d-Cg alkenyl, Ci-Cg alkenyl, d-Cg alkynyl, or d-C14 aryl.

Selection of a substituent at R3 includes H, d-Cg alkenyl, Ci-Cg alkenyl, d-Cg alkynyl, CN, CH2CN, C(=0)X where X is H, Ci-Cg alkanyl, d-Cg
alkenyl, d-C₈ alkynyl, NHOH, NHOCH₃, NHCN, or NX₂, or C(=0)OY where Y is H, d-C₈ alkanyl, C₁-C₈ alkenyl or d-C₈ alkynyl; and

Selection of a substituent at R⁴ includes

where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, Cl-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl or OY where Y is H, Cl-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl or d-Ci₄ aryl.

As used herein, a "d-C₈ alkanyl" refers to an alkane substituent with one to eight carbon atoms and may be straight chain, branched or cyclic (cycloalkanyl). Examples are methyl, ethyl, propyl, isopropyl, butyl and t-butyl. A "halogenated d-C₈ alkanyl" refers to a "d-C₈ alkanyl" possessing at least one halogen. Where there is more than one halogen present, the halogens present may be the same or different or both (if at least three present). A "d-C₈ alkenyl" refers to an alkene substituent with one to eight carbon atoms, at least one carbon-carbon double bond, and may be straight chain, branched or cyclic (cycloalkenyl). Examples are similar to "d-C₈ alkanyl" examples except possessing at least one carbon-carbon double bond. A "d-C₈ alkynyl" refers to an alkyne substituent with one to eight carbon atoms, at least one carbon-carbon triple bond, and may be straight chain, branched or cyclic (cycloalkynyl). Examples are similar to "Ci-C₈ alkanyl" examples except possessing at least one carbon-carbon triple bond. An "alkoxy" refers to an oxygen substituent possessing a "d-C₈ alkanyl," "d-C₈ alkenyl" or "d-C₈ alkynyl." This is -O-alkyl; for example methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and the like; and alkenyl or alkynyl variations thereof (except for methoxy). It further refers to the group
O-alkyl-W-alkyl where W is O or N; for example -O-(CH₂)ₙ-W-(CH₂)ₘ where n and m are independently 1-10. An "aryl" refers to an aromatic substituent with one to fourteen carbon atoms as ring atoms in one or multiple rings which may be separated by a bond or fused. As used herein, "aryl" includes "heteroaryl." A "heteroaryl" is similar to an "aryl" except the aromatic substituent possesses at least one heteroatom (such as N, O or S) in place of a ring carbon. Where an aromatic substituent is an aryl in which all the ring atoms are carbon (i.e., not a heteroaryl), there are typically six to fourteen ring atoms. Where an aryl is a heteroaryl, there may be less than six carbon ring atoms. Examples of aryls include phenyl, naphthyl, pyridinyl, pyrimidinyl, triazolo, furanyl, oxazolyl, thiophenyl, quinolinyl and diphenyl.

In one embodiment of a compound of the present invention, the CXCR4 chemokine receptor inhibitor consists of:

\[
\text{ZKGVSLSYR-X-RYSLSVGK}
\]

wherein Z is the end of the bond to Linker. X is an amino acid, e.g., K.

In one embodiment, the compound has the formula:

\[
\text{KGVSLSYR-X-RYSLSVGK}
\]

wherein R¹, R², R³, R⁴ and X are as defined above.

In one embodiment in which the linker is \(-\text{C(=0)}-\text{NH-(CH}_2)_2-\text{NH}-\), the compound has the formula:
wherein $R_1, R_2, R_3, R_4$ and $X$ are as defined above.

In one embodiment in which the linker is $-\text{CH}_2-\text{NH-CH}_2-$, the compound has the formula:

wherein $R_1, R_2, R_3, R_4$ and $X$ are as defined above.

In one embodiment in which the linker is $-\text{C(=0)-NH-CH}_2-$, the compound has the formula:

wherein $R_1, R_2, R_3, R_4$ and $X$ are as defined above.

In one embodiment in which the linker is $-\text{C(=0)-NH-(CH}_2)_2-\text{NH-}$, the compound has the formula:
wherein \( X \) is an amino acid.

In one embodiment in which the linker is \(-\text{CH}_2\text{-NH-CH}_2\)-, the compound has the formula:

\[
\text{KGVSLSYR} - X \rightarrow \text{RYSLSVGK}
\]

wherein \( X \) is an amino acid.

In one embodiment in which the linker is \(-\text{C}(=\text{O})\text{-NH-CH}_2\)-, the compound has the formula:

\[
\text{KGVSLSYR} - X \rightarrow \text{RYSLSVGK}
\]

wherein \( X \) is an amino acid.

In one embodiment in which the linker is \(-\text{C}(=\text{O})\text{-NH-(CH}_2)_2\text{-NH-}\), the compound has the formula:

\[
\text{KGVSLSYR} - X \rightarrow \text{RYSLSVGK}
\]
wherein X is an amino acid.

In one embodiment in which the linker is -C(=0)-NH-(CH₂)₂-NH-, the compound has the formula:

wherein X is an amino acid.

Other examples of peptidomimetic CXCR4 chemokine receptor inhibitors include:

wherein Z = end of bond to Linker.
wherein $Z$ = end of bond to Linker.

wherein $Z$ = end of bond to Linker; and $X$ is H or halide.

wherein $Z$ = end of bond to Linker; and $X$ = H or halide.
wherein one of $R_1$, $R_2$, and $R_3$ is the end of bond to Linker and the other two are H; and wherein $X$ is $C(R_4)(R_5)$, $NR_4$, O or S, where $R_4$ is H or an electron withdrawing group or electron donating group and $R_5$ is H or an electron withdrawing group or electron donating group.

In such an embodiment containing "X" (as depicted immediately above), $R_4$ or $R_5$ or both may be H or an electron withdrawing group or electron donating group. Examples of electron withdrawing groups include a halogenated $C_1$-$C_8$ alkanyl, a halogenated $C_1$-$C_8$ alkenyl, a halogenated $C_1$-$C_8$ alkynyl, -C-N0$_2$, -C(=0)-Y or -C(=0)-OY, where $Y$ is H, $Ci$-$C_8$ alkanyl, $Q$-Cgalkenyl, d-$C_8$alkynyl, halogenated $C_1$-$C_8$alkanyl, halogenated $C_1$-$C_8$alkenyl, or halogenated $C_1$-$C_8$alkynyl. Examples of electron donating groups include $Ci$-$C_8$alkanyl.

All compounds of the present invention or useful thereto (e.g., for pharmaceutical compositions or methods of treating), include physiologically acceptable salts thereof. Examples of such salts are Na, K, Li, Mg, Ca and Cl.

Compounds as described herein may be present within a pharmaceutical composition. A pharmaceutical composition comprises one or more compounds in combination with (i.e., not covalently bonded to) one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextran), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) or preservatives. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate. Compositions of the present invention may be formulated for any
appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous, or intramuscular administration.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of compound release. The amount of compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

The above-described compounds including equivalents thereof are useful in methods of the present invention. In one embodiment, the compounds may be used in a method for the treatment of a cancer in which the cancer cells may leave the primary site. A primary site may be, for example, solid tissue (e.g., breast or prostate) or the bloodstream. An individual who is in need of such treatment is administered at least one (i.e., one or more) of the above-described compounds in an amount effective for the treatment. In addition to breast cancer and prostate cancer, other examples of infiltrating diseases include lung cancer and melanoma, as well as the hematological malignancies (e.g., leukemias and myelomas). As used herein, the term "treatment" (including variations such as "treating") includes for the disease or a complication associated with the disease, and includes prevention. For example, a complication associated with the cancer may not have presented itself in an individual with the disease, and a compound may be administered to prevent presentation of the complication in the individual. Complications associated with a cancer in which the cancer cells may leave the primary site include, for example, metastasis and infiltration of cancer cells to other tissues. For example, acute myelogenous leukemia (AML) and multiple myeloma (MM) cells migrate to the endosteal region of the bone marrow where the cells become quiescent and are protected from chemotherapy-induced apoptosis. Administration of a compound described herein may prevent adhesion or migration of cancer cells. Such prevention can result in making the cancer cells more susceptible to treatment with chemotherapy. Administration of a compound described herein in the context of prevention may be to an individual who is at risk of occurrence of a cancer for the first time, or for recurrence of a cancer. For example, while a brain cancer such as glioblastoma multiforme is typically treated with another type of therapy
(such as radiation or chemotherapy) for the first occurrence, such therapy is usually not effective to prevent recurrence.

The term "treatment" as used herein refers to any of a variety of positive effects from the treatment including, for example, eradicating a complication associated with the disease, relieving to some extent a complication, slowing or stopping progression of the disease, enhancing the effectiveness of one or more therapies for the disease, and prolonging the survival time of the recipient. The treatment may be used in conjunction with one or more other therapies for a cancer or a complication associated therewith.

In another embodiment, the above-described compounds including equivalents may be used in a method for the treatment of a cancer in which it is desired to mobilize cancer cells from a site into the bloodstream and retain the cancer cells in the bloodstream. An individual who is in need of such treatment is administered at least one (i.e., one or more) of the compounds in an amount effective for the treatment. Examples of cancers for such treatment include leukemias and myelomas (e.g., AML and MM). Mobilizing cancer cells into the bloodstream from a site and retaining the cells therein can result in making the cancer cells more susceptible to treatment with chemotherapy. An example of a site from which to mobilize cancer cells is bone. Cancer cells may, for example, be in circulation and then home to bone. Once in bone, the cancer cells are protected from chemotherapy. A compound described herein may be used, for example, to mobilize cancer cells from bone into the bloodstream and prevent cancer cells from homing to bone, thereby retaining the cancer cells in the bloodstream. Administration of a compound described herein in the context of prevention may be to an individual who is at risk of occurrence of a cancer for the first time, or for recurrence of a cancer. For example, while a brain cancer such as glioblastoma multiforme is typically treated with another type of therapy (such as radiation or chemotherapy) for the first occurrence, such therapy is usually not effective to prevent recurrence.

In another embodiment, the above-described compounds including equivalents may be used in a method for releasing cells (such as hematopoietic stem cells) into circulating blood and enhancing retention of the cells in the blood. An individual who is in need of such treatment is administered at least one (i.e., one or more) of the compounds in an amount effective for the treatment. One use of the method is, for example, for stem cell harvesting. Stem cells may be needed, for example, after high-dose chemotherapy treatment. Many chemotherapies suppress bone marrow which disrupts the production of certain components of blood in an
individual. As a result, the individual may develop a variety of blood cell related disorders and continuation of chemotherapy may be compromised. A compound described herein may be used, for example, to release stem cells into circulating blood and enhance retention of the stem cells in the blood. The method may include a further step of collecting cells that are released. For example, released stem cells may be collected. A variety of techniques are known in the art for collecting cells. For example, apheresis may be utilized. An example of a stem cells is a bone marrow progenitor cell. The release of such cells from bone marrow into circulating blood and retention therein has a variety of uses. For example, the mobilized bone marrow progenitor cells may be collected from the blood. A use of such collected cells is to obtain healthy bone marrow progenitor cells from an individual prior to treatment of the individual in a manner such that bone marrow is suppressed. Following treatment, the individual can receive a bone marrow transplantation utilizing the bone marrow progenitor cells collected prior to treatment. This is useful, for example, where an individual needs to be subjected to a chemotherapy protocol that will suppress bone marrow.

It can be desirable to additionally treat an individual with at least one \textit{i.e.,} one or more) colony stimulating factor. Such a factor may be administered, for example, before or simultaneous with administration of at least one of the above-described compounds. Where administration is simultaneous, the combination may be administered from a single container or two (or more) separate containers. An example of a suitable colony stimulating factor is granulocyte-colony stimulating factor (G-CSF). G-CSF induces the bone marrow to grow and produce more stem cells. A compound described herein aids in releasing stem cells into circulating blood. Stem cells produced in bone marrow and released into circulating blood, as a result of the combination of the administration (separately or together) of a compound described herein and G-CSF, may be collected as described above. Such collected stem cells may be, for example, administered to the individual after chemotherapy. The stem cells return to the bone marrow and produce blood cells. Application of a compound described herein to mobilization and harvesting of healthy bone marrow progenitor cells from bone marrow treated with G-CSF provides cells useful, for example, for bone marrow transplantation.

In another embodiment, the above-described compounds including equivalents may be used in a method for the treatment of an inflammatory disease in which the adhesion or migration of cells occurs in the disease. An individual who is in need of such treatment is administered at least one \textit{i.e.,} one or more) of the compounds
in an amount effective for the treatment. Example of inflammatory diseases include inflammatory skin disorders such as atopic dermatitis and psoriasis. The treatment may reduce (partially or totally) the disease or a complication associated therewith, such as pain. The treatment may be used in conjunction with one or more other therapies for such an inflammatory disease or a complication associated therewith.

The above-described compounds may be administered in a manner appropriate to the disease to be treated. Appropriate dosages and a suitable duration and frequency of administration may be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment regimen provides the compound(s) in an amount sufficient to provide therapeutic or prophylactic benefit. Within particularly preferred embodiments of the invention, a compound may be administered at a dosage ranging from 0.001 to 1000 mg/kg body weight (more typically 0.01 to 1000 mg/kg), on a regimen of single or multiple daily doses. Appropriate dosages may generally be determined using experimental models or clinical trials. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated, which will be familiar to those of ordinary skill in the art.

At least one (i.e., one or more) of the above-described compounds may be administered in combination with at least one (i.e., one or more) agent, e.g., chemotherapeutic agent or anti-inflammatory agent. In addition, the administration may be in conjunction with one or more other therapies for reducing toxicities of chemotherapy. For example, at least one (i.e., one or more) agent to counteract (at least in part) a side effect of chemotherapy may be administered. At least one compound described herein may be administered before, after or simultaneous with administration of at least one chemotherapeutic agent or anti-inflammatory agent. Where administration is simultaneous, the combination may be administered from a single container or two (or more) separate containers.

The following Examples are offered by way of illustration and not by way of limitation.
EXAMPLES

EXAMPLE 1
SYNTHESIS OF FIRST GLYCOMIMETIC (COMPOUND 19 OF FIG. 1)

Synthesis of Compound 2: Commercially available (Aldrich Chemical Co., Milwaukee, WI) cis-1,2,3,6-tetrahydrophthalic anhydride (compound 1, 50 g) is added to a suspension of amberlyst 15 (50 g, dried under vacuum) in methanol (1L) with stirring. Triethylorthoformate (100 ml) is added immediately while stirring. The reaction mixture is then vigorously stirred for 5 days at room temperature (RT) and additional triethylorthoformate is added. Stirring is continued for an additional 4 days, then the reaction mixture is filtered over celite and washed with methanol. The solvent is removed in vacuum and the residue is dissolved in CH2Cl2 (200 ml). The solution is washed with a cold saturated solution of NaHCO3 (200 ml) and cold brine (200 ml). The organic layer is dried (Na2SO4), filtered and concentrated to dryness to afford compound 2 (55 g).

Synthesis of compound 3: To a suspension of compound 2 (10 g) in phosphate buffer (400 ml, pH 7) is added PLE (40 mg, 1080 unit). The pH of the mixture is maintained at 7 by continuous dropwise addition of IM NaOH solution via syringe pump. The reaction is stirred at 20°C until 1 equivalent of NaOH (50 ml) is used. The reaction mixture is transferred to a separatory funnel and EtOAc (400 ml) is added. The layers are separated and the organic layer is extracted with phosphate buffer (2x250 ml, pH7). The combined aqueous layers are acidified (pH 2) with aqueous HCl (IM) and extracted with EtOAc (3x400 ml). The combined organic layers are dried (Na2SO4), filtered and concentrated to dryness to afford compound 3 (7.8 g).

Synthesis of compound 4: To a solution of compound 3 (2 g) in dry CH2Cl2 (35 ml) is added (COCl)2 (1.4 ml) and DMF (0.025 ml) and stirred for 3h at RT. The solution is evaporated to dryness (rotavapor was purged with argon). The residue is dissolved in dry THF (40 ml) and added dropwise over a period of 20 min to a boiling suspension of 2-mercaptopyridine-1-oxide sodium salt (2 g), t-BuSH (6 ml), and DMAP (52 mg) in dry THF (100 ml). The solution is stirred under reflux for 3 h. The reaction mixture is cooled down to RT and transferred into a separatory funnel with EtOAc (100 ml) and washed with H2O (100 ml). The aqueous layer is extracted with EtOAc (2x200 ml). The combined organic layers are dried (Na2SO4), filtered and concentrated to dryness. The crude product is purified by column chromatography (silica) to afford compound 4 as yellowish oil (1.1 g).
Synthesis of compound 5: To a suspension of compound 4 (4 g) in phosphate buffer (400 ml, pH 7) is added PLE (42 mg) with stirring. The pH is kept at 7 by adding NaOH solution (1M) via syringe pump. The reaction mixture is stirred at RT until 1 equivalent of NaOH is used. The reaction mixture is transferred to a separatory funnel and washed with EtOAc (2x250 ml). The layers are separated and the organic layers are extracted with phosphate buffer (2x250 ml, pH 7). The combined aqueous layers are acidified to pH 2 with aqueous HCl solution and extracted with EtOAc (3x300 ml). The combined organic layers are dried (Na2SO4), filtered and evaporated to dryness. The crude product is filtered through a short plug of silica to afford compound 5 (3 g).

Synthesis of compound 6: Compound 5 (4 g) is suspended in water (90 ml) and cooled down to 0°C. NaHC03 (8 g) is added followed by a solution of KI (32 g) and I2 (8 g) in water (75 ml). The reaction mixture is stirred at RT for 24 h and then extracted with CH2Cl2 (3x30 ml). The combined organic layers are washed with a saturated solution of Na2S203 in water (125 ml). The aqueous layer is extracted with CH2Cl2 (2x30 ml). The combined organic layers are protected from light, dried (Na2SO4), filtered, and concentrated quickly under high vacuum to dryness to afford iodolactone 6 as an off-white solid (7.5 g).

Synthesis of compound 7: Compound 6 (7 g) is dissolved in dry THF (170 25 ml) and DBU (7 ml) is added. The reaction mixture is refluxed for 20 h and then cooled down to RT. Diethyl ether (100 ml) is added and transferred into a separatory funnel and extracted with an aqueous solution of HCl (200 ml, 0.5M). The aqueous layers are extracted with Et2O (3x100 ml). The combined organic layers are washed with brine (200 ml), dried (Na2SO4), filtered, and concentrated to dryness. The crude product is purified by column chromatography (silica gel) to afford compound 7 (3.7 g).

Synthesis of compound 8: NaHC03 (2.2 g) is dried under vacuum and then dry MeOH (132 ml) added with stirring followed by compound 7 (3 g). The reaction mixture is then stirred at RT under argon for 12 h. The solvent is evaporated off and the residue is transferred into a separatory funnel with CH2Cl2 (35 ml), extracted with water (40 ml), and with brine (40 ml). The aqueous layer is extracted with CH2Cl2 (2x35 ml). The combined organic layers are dried (Na2SO4), filtered, and concentrated to dryness to give compound 8 (5 g).

Synthesis of compound 9: To a solution of compound 8 (4 g) in dry CH2Cl2 (80 ml) is added tert-butyldimethylsilyl chloride (7.2 ml) in small portions, followed by DBU (9.5 ml). The reaction mixture is stirred for 12 h and then quenched
with MeOH (12 ml). The reaction mixture is transferred into a separatory funnel with CH2Cl2 (60 ml), washed with cold saturated solution of NaHC03 (50 ml) and cold brine (50 ml). The aqueous layers are extracted with CH2Cl2 (2x50 ml). The combined organic layers are dried (Na2SO4), filtered and concentrated to dryness. The residue is purified by column chromatography (silica) to give compound 9 (6 g).

Synthesis of compound 10: To a cold (10°C) solution of compound 9 (5 g) in CH2Cl2 (125 ml) is added m-CPBA (8 g) with stirring, and stirring is continued for 15 h at 10°C. The temperature is raised to RT over a period of 2h and the mixture diluted with CH2Cl2 (400 ml). The mixture is transferred into a separatory funnel, and washed with cold saturated solution of Na2S203 solution in water (2 x 400 ml). The organic layer is successively washed with cold saturated solution NaHCO3 (400 ml) and cold brine (100 ml). The aqueous layers are extracted with CH2Cl2 (2 x 400 ml). The combined organic layers are dried (Na2SO4), filtered, and concentrated to dryness. The crude product is purified by column chromatography (silica) to give compound 10 (4 g).

Synthesis of compound 11: CuCN (1.5 g) is dried in high vacuum at 150°C for 30 min, suspended in dry THF (25 ml) and cooled down to -78°C. MeLi (1.6 M in Et20, 22.5 ml) is added slowly via syringe and the temperature raised to -10°C over a period of 30 min. The mixture is again cooled down to -78°C, followed by the addition of BF3 etherate (1.4 ml) in THF (5 ml). After stirring for 20 min, compound 10 (1 g) in THF (25 ml) is added and stirring is continued for 5 h at -78°C. The excess of MeLi is quenched with a mixture of MeOH (10 ml) and Et3N (10 ml). The mixture is diluted with Et20 (250 5 ml) and transferred into a separatory funnel and extracted with aqueous 25% NH3/satd. NH4Cl (1:9) solution. The organic layer is successively washed with brine (150 ml), 5% AcOH (150 ml), saturated solution of NaHC03 (150 ml), and brine (150 ml). The aqueous layers are extracted with Et20 (2 x 250 ml). The combined organic layers are dried (Na2SO4), filtered, and concentrated to dryness. The crude product is purified by column chromatography (silica) to give compound 11 (800 mg).

Synthesis of compound 13: A solution of Br2 (0.08 ml) in CH2Cl2 (1 ml) is added dropwise at 0°C to a solution of commercially available (Carbosynth Ltd., Compton, Berkshire, UK) compound 12 (640 mg) in CH2Cl2 (10 ml) and stirred at 0°C for 1h. Cyclohexene (0.02 ml) is added and the reaction mixture stirred for another 30 min. The mixture is added dropwise to a solution of 11 (310 mg) and Et4NBr (280 mg, oven dried at 200°C) in DMF/CH2Cl2 (20 ml, 1:1) containing molecular sieve (1 g, 3A) with stirring at RT. The stirring is continued for 60 h. The reaction is quenched with pyridine (2 ml), filtered over celite, and washed with CH2Cl2 (20 ml). The solution is
washed with brine (50 ml) and the aqueous layer is extracted 3 times with CH2Cl2 (3x50 ml). The combined organic layers are dried (Na2SO4), filtered, and concentrated to dryness. The crude product is purified by column chromatography (silica) to give compound 13 (144 mg).

**Synthesis of compound 14:** To a solution of compound 13 (140 mg) in THF (5 ml), TBAF (0.39 ml) is added. After 24 h additional TBAF (0.2 ml) is added and the stirring is continued for 50 h. The reaction mixture is concentrated to dryness and the crude product purified by column chromatography (silica) to afford compound 14 (95 mg).

**Synthesis of compound 16:** A mixture of compound 14 (0.16 g) and compound 15 (0.35 g, synthesized as described by Banteli et al., Helvetica Chimica Acta 53:2893-2907, 2000) is co-evaporated with toluene twice and then dried under vacuum. The mixture is dissolved in dry CH2Cl2 (10 ml) and stirred with flame dried molecular sieve (4A) and 2,6-di-tert-Bu-pyridine (0.59 ml) for 30 min at RT. The reaction mixture is cooled to 0°C and MeOTf (0.25 ml) added with stirring. The reaction mixture is stirred for 4 h at RT, filtered through a bed of Celite, washed with CH2Cl2 (2x10 ml) and then transferred to a separatory funnel. The organic layer is washed with a cold saturated solution of NaHCCb (25 ml) and brine (25 ml), dried (Na2SO4), filtered, and concentrated to dryness. The residue is purified by column chromatography (silica) to give compound (0.23 g).

**Synthesis of compound 17:** Compound 16 (0.96 mg) is dissolved in dioxane-water (10:2, 12 ml) and AcOH (0.2 ml) added. 10% Pd/C (0.8 g) is added and stirred vigorously under hydrogen (40 psi) for 16 h at RT. The reaction mixture is filtered through a bed of Celite and washed with MeOH. Solvent is evaporated off to give compound 17 (700 mg).

**Synthesis of compound 18:** Compound 17 (500 mg) is treated at RT with 0.01N NaOMe in MeOH (20 ml) for 1 h. The reaction is neutralized with AcOH and the solvent evaporated off to give compound 18 (300 mg).

**Synthesis of compound 19:** Compound 18 (200 mg) is dissolved in ethylenediamine (3 ml) and the solution stirred for 3 h at 70°C. Solvent is evaporated off and the residue is purified by Sep-Pak CI8 column to give compound 19 (160 mg).
EXAMPLE 2
SYNTHESIS OF PEPTIDOMIMETIC (COMPOUND 21 OF FIG. 2)

Synthesis of compound 20: Fmoc protected Octapeptide (KGVSLSYR) is synthesized using corresponding amino acid building block by solid phase peptide synthesis method (well known in the field) and purified by HPLC.

Synthesis of compound 21: To a solution of Lysine (K) in DMF is added DIPEA and TBTU with stirring. To this solution is added a solution of compound 20 in DMF and the reaction mixture is stirred at room temperature for 2h. Solvent is evaporated off and the residue is purified by HPLC to give compound 21.

EXAMPLE 3
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #1 (COMPOUND 23 OF FIG. 3)

Synthesis of compound 22: To a solution of compound 21 (Example 2) in DMF is added DIPEA and TBTU and stirred for 5 min. To this solution is added compound 19 (Example 1) and the reaction mixture is stirred for 1h at room temperature. The solvent is evaporated off and the residue is purified by HPLC to give compound 22.

Synthesis of compound 23: To solution of compound 22 in DMF is added piperidine (20% v/v) and stirred at room temperature for 5h. The reaction mixture is concentrated to dryness and purified by HPLC to give compound 23.

EXAMPLE 4
SYNTHESIS OF SECOND GLYCOMIMETIC (COMPOUND XX OF FIG. 4)

Synthesis of intermediate II: (-)-Shikimic acid (20 g) in MeOH (200 ml) and concentrated hydrochloric acid (2 ml) are stirred at RT for 50 h. The reaction mixture is neutralized with 2N aqueous NaOH in the cold. After evaporation to dryness, the residue is purified by silica gel chromatography to afford II (19.2 g).

Synthesis of intermediate (III): Methyl shikimate (II, 10 g), 2,2 dimethoxypropane (10 ml) and p-TsOH (0.8 g) are dissolved in acetonitrile (125 ml) and stirred at RT for 1 h. The reaction mixture is then neutralized with triethylamine (2 ml) and evaporated to dryness. The residue is chromatographed on silica gel to yield III (11 g).

Synthesis of intermediate IV: The shikimic acid derivative III (10 g) and Pt02/C (10%, 250 mg) in MeOH (40 ml) are hydrogenated at RT under vigorous
stirring. After 16 h the reaction mixture is filtered over celite and evaporated to dryness. The residue is chromatographed on silica gel to yield IV.

**Synthesis of intermediate V:** To a solution of IV (8 g) in DCM (100 ml) at 0°C is added pyridine (12 ml), acetic anhydride (7 ml) and a DMAP (25 mg). The reaction mixture is stirred at RT for 1 h, and diluted with EtOAc (250 ml). After washing with 0.5 M aqueous HCl (3 x 50 ml), saturated solution of KHCO3 (3 x 50 ml) and brine (3 x 50 ml), the combined organic layers are dried (Na2SO4) and evaporated to dryness. The residue is purified by chromatography on silica gel (toluene/EtOAc 9:1) to yield X (700 mg).

**Synthesis of intermediate VI:** A solution of V (6.0 g) in acetic acid (30 ml, 80%) is stirred at 80°C for 1 h. Solvent is evaporated off and the residue is purified by chromatography on silica gel (DCM/MeOH 14:1) to yield VI (3.6 g).

**Synthesis of intermediate (VIP):** A solution of VI (3 g) and p-TsCl (3.5 g) in pyridine (30 ml) is stirred at RT for 6 h. MeOH (5 ml) is added and the solvent evaporated at reduced pressure, the residue dissolved in EtOAc (3 x 150 ml) and the organic layers are washed with 0.5 M aqueous HCl (0°C), water (cold) and brine (cold). The combined organic layers are dried (Na2SO4), filtered on Celite and evaporated to dryness. The residue is purified by chromatography on silica gel (toluene/EtOAc 4:1) to yield VII (3.7 g).

**Synthesis of compound VIII:** A solution of VII (3 g) and NaN3 (2.5 g) in DMF (20 ml) is stirred at 80°C. The reaction mixture is cooled to RT and diluted with EtOAc (200 ml) and water (50 ml). The organic layer is additionally washed twice with water (2 x 50 ml) and once with brine (50 ml). All aqueous layers are extracted twice with EtOAc (2 x 50 ml). The combined organic layers are dried with Na2SO4, filtered and the solvent evaporated off. The residue is purified by chromatography on silica gel (petroleum ether/EtOAc 5:2) to give VIII (2.2 g).

**Synthesis of compound X:** To a solution of ethyl 2,3,4-tri-O-benzyl-a-L-fucothiopyanoside IX (1.5 g) in DCM (3 ml), bromine (150 µl) is added at 0°C under argon. After 5 min the cooling bath is removed and the reaction mixture stirred for an additional 25 min at RT. Cyclohexene (200 µl) is added and the reaction mixture added to a solution of VIII (400 mg), (Et)2NBr (750 mg) and powdered 4A molecular sieves in DCM (10 ml) and DMF (5 ml). After 16 h, triethylamine (1.5 ml) is added and stirred for an additional for 10 min, diluted with EtOAc (50 ml) and washed with sat. aqueous NaHCO3, water and brine. The aqueous layers are extracted twice with EtOAc (2 x 50 ml). The combined organic layers are dried (Na2SO4), filtered and evaporated to dryness. The residue is purified by chromatography on silica gel (toluene/EtOAc 9:1) to yield X (700 mg).
Synthesis of compound XI: To a solution of X (1.5 g) in MeOH (20 ml) is added freshly prepared NaOMe (80 mg) and the reaction mixture stirred in a pressure tube at 80°C for 20 h. The reaction mixture is cooled to RT and neutralized with acetic acid. Solvent is evaporated to dryness and the residue is dissolved in ether. Freshly prepared diazomethane is added and the excess diazomethane neutralized with acetic acid. Solvent is evaporated off to give XI (1.25 g).

Synthesis of building block XV: This synthesis is done exactly in the same way as described previously /Helvetica Chemica Acta#5:2893-2907 (2000)).

Synthesis of compound XVI: A mixture of XI (1.6 g), XV (3 g) and activated powdered molecular sieves 4Å (1 g) in DCM (17 ml) is stirred at RT under argon for 2 h. DMTST (2 g) is then added in 4 equal portions over a period of 1.5 h. After 24 h the reaction mixture is filtered over Celite and the filtrate diluted with DCM (100 ml). The organic layer is washed with sat. aqueous NaHCO3 and brine and the aqueous layers extracted twice with DCM. The combined organic layers are dried (Na2SO4), filtered and evaporated to dryness. The residue is purified by chromatography on silica gel (toluene/EtOAc 8:1) to yield XVI (1.5 g).

Synthesis of compound XVII: To a solution of XVI (500 mg) and orotic acid chloride (500 mg) in dichloromethane (10 ml) is added a solution of triphenylphosphine (500 mg in 5 ml dichloromethane) dropwise during 10 min. The reaction mixture is stirred at RT for 25 h and the solvent evaporated off. The residue is purified (chromatography on silica gel DCM/MeOH 19:1) to give XVII (250 mg).

Synthesis of compound XVIII: To a solution of XVII (200 mg) in dioxane water (5:1, 12 ml) is added 10% Pd-C (100 mg) and the reaction mixture stirred vigorously under hydrogen (55psi) for 24 h. Catalyst is filtered through a bed of celite and the solvent evaporated off. The residue is purified by silica gel chromatography to give compound XVIII (150 mg).

Synthesis of XIX: To a solution of compound XVIII (145 mg) in MeOH (5 ml) is added a solution of NaOMe in MeOH (25%, 0.025 ml) and the reaction mixture stirred at RT for 4 h, neutralized with acetic acid and the solvent evaporated off. The residue is dissolved in water and passed through a bed of Dowex 50wX-8 (Na-form) resin. Water wash is evaporated off to afford compound XIX (100 mg).

Synthesis of XX: XIX (80 mg) is heated at 70°C with ethylenediamine (EDA) (1 ml) with stirring for 5 h. Solvent is evaporated off and purified by sephadex G-25 column to give EDA-XX (82 mg).
EXAMPLE 5
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #2 (COMPOUND 25 OF FIG. 5)

Synthesis of compound 24: Compound XX (Example 4) is reacted with compound 21 (Example 2) in DMF in the presence of TBTU and DIPEA in the same way as described above and purified by HPLC to give compound 24.

Synthesis of compound 25: Compound 24 is treated with piperidine in the same way as described above to give compound 25 after purification by HPLC.

EXAMPLE 6
SYNTHESIS OF THIRD GLYCOMIMETIC (COMPOUND XXIII OF FIG. 6)

Synthesis of compound XXI: To a solution of compound XVIII (Example 4; 0.250g) in THF (5 ml) is added DMF (1.2 ml) and Et₂N (0.16ml) with stirring. The solution is cooled down to 0°C and ethylchloroformate (0.108ml) added dropwise. The stirring is continued for 15 min at 0°C and then a solution of NH₂OH·HCl (0.093g) in DMF (0.25 ml) is added dropwise. The reaction mixture is stirred at 0°C to room temperature for 2.5h. Solvent is evaporated off and the residue purified by column chromatography (silica gel) to give compound XXI (0.18g).

Synthesis of compound XXII: To a solution of compound XXI (0.17g) in MeOH (3ml) is added a solution of 25% NaOMe (0.35 ml) in MeOH with stirring. Stirring is continued for 3h at RT and then water (1.4 ml) is added. The reaction mixture is stirred overnight at RT, neutralized with AcOH and concentrated to dryness. The residue is dissolved in water and purified by Sep-Pak C18 column to give compound XXII.

Synthesis of compound XXIII: Compound XXII (0.025g) is treated with ethylenediamine (1ml) as described above. The solvent is evaporated off and the residue purified by HPLC to give compound XXIII.

EXAMPLE 7
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #3 (COMPOUND 27 OF FIG. 7)

Synthesis of compound 26: Compound XXIII (Example 6) in DMF is reacted with compound 21 (Example 2) in presence of TBTU and DIPEA for 2h and the solvent evaporated off. The residue is purified by HPLC to give compound 26.
Synthesis of compound 27: Compound 26 is treated with piperidine in DMF exactly same way as described above solvent is evaporated off. The residue is purified by HPLC to give compound 27.

EXAMPLE 8
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #4 (COMPOUND 36 OF FIGURE 8)

Synthesis of compound 29: To a solution of commercially available compound 28 (0.61g0 in DMF (5ml) is added Cs₂CO₃ (0.84g) and C₆H₅CH₂Br (0.3ml) and the mixture is stirred overnight at room temperature. Solid was filtered off and the filtrate is concentrated to dryness. The residue was purified by column chromatography (silica gel) to give compound 29 (0.71g).

Synthesis of compound 30: Compound 29 (0.7g) was dissolved in CH₂C₁₂ (8ml) and the solution is cooled to 0 °C. To this solution is added trifluoroacetic acid (4ml) slowly with stirring at 0 °C and stirring is continued for 1.5h. The temperature of the solution is raised to room temperature during this time. The solution is concentrated to dryness and the residue is dissolved in MeOH (12ml). Dowex Monosphere (OH-) (550 A) is added in portion at 0 °C until the pH of the solution raised to 7.5. The resin is filtered off and the filtrate is concentrated to dryness to give compound 30 (0.6g).

Synthesis of compound 32: A solution of compound 30 (0.27g) in C₃H₂Cl₂ (1ml) is cooled to -30 °C and a solution of commercially available compound 31 (0.4ml) in CH₂C₁₂ (1ml) is added dropwise over 5 min. period with stirring. The resulting reaction mixture is stirred overnight from -30 °C to room temperature. The solution is concentrated and purified by column chromatography (silica gel) to give compound 32 (0.17g).

Synthesis of compound 33: To a solution of compound 32 (0.16g) in MeOH (5ml) is added a solution of NaOH (0.05g) in H₂O (5ml). The white heterogeneous mixture is stirred for 2h at 40 °C. During this the solution became clear. The solution is concentrated to dryness and the solid is dissolved in EtOAc/MeOH (5:1) and purified by column chromatography (silica gel) to give compound 33 (0.06g).

Synthesis of compound 35: Compound 33 (0.05g) and commercially available compound 34 (0.1g) is dissolved in CH₃CN (5ml) and the reaction mixture is refluxed for 5h at 80 °C. The solution is concentrated to dryness and purified column chromatography (silica gel) to give compound (0.055g).

Synthesis of compound 36: Compound 35 (0.025g) is dissolved in DMF (1ml) and cooled to 0 °C. To this solution is added DMAP (0.004g) and HATU (0.04g)
and the solution is stirred for 5 min. at 0 °C. To this solution is added a solution of compound XX (0.1g) in DMF (2ml). The reaction mixture is stirred for 20 min. at 0 °C and at room temperature for 15 min., concentrated to dryness and purified by reverse phase in C18 column to give compound 36 (0.035g).

EXAMPLE 9
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #5 (COMPOUND 37 OF FIGURE 9)

Synthesis of compound 37: Compound 35(0.02g) and compound 35 (0.08g) is reacted exactly in the same way as described for the synthesis of compound 36 to give compound 37 (0.02g).

EXAMPLE 10
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #6 (COMPOUND 54 OF FIGURE 10)

Synthesis of compound 38: All operations of this step are done in argon atmosphere. CuCN (9.42g) is dried at 160 °C under vacuum for 40 min, cooled down to room temperature and suspended in THF (80ml). The mixture was cooled down to -78 °C. During this time, tetravinyltin (12ml) and n-BuLi in hexane (2.5M, 100ml) are reacted for 30 min at 0 °C in THF (30ml). This solution is added to the mixture of CuCN in THF, and the resulting mixture is stirred for 30 min. at -20 °C. The mixture is then cooled to -78 °C and is added a solution of freshly distilled BF₃.Et₂O (6ml) in THF (20ml). The mixture is stirred for 20 min. at -78 °C. Compound 10 (5g) in THF (40ml) is added and the reaction mixture is stirred at -78 °C for 5h. MeOH (7ml) and Et₃N (3ml) is added and the mixture is concentrated to dryness. The residue is dissolved in EtOAc (200ml) and washed with saturated solution of NaHCO₃ (2X100ml), brine (100ml), dried (Na₂SO₄), filtered, and concentrated to dryness. The residue is purified by Combiflash system (Si02) using solvent EtOAc-Hexanes (0→5%) to give compound 38 (2.5g).

Synthesis of compound 39: Compound 38 (2.4g) is reacted with compound 12 (8g) exactly in the same way as described for the synthesis of compound X, and the crude reaction mixture is dissolved in THF (20ml). To this solution is added a solution of TBAF (3ml, 1M in THF) and the reaction mixture is stirred at room temperature for 5h. Solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 39 (2.5g).

Synthesis of compound 41: Commercially available compound 40 (10g) dried overnight under vacuum overnight and added to a solution of NaOMe (5M, 10ml)

68
in MeOH (200ml) with stirring at room temperature under argon. Stirring is continued for overnight at room temperature argon and is added Et₂N (7ml) followed by allylchloroformate (3.5ml) dropwise. Stirring is continued for 6h at room temperature under argon. Reaction mixture is concentrated to dryness and dissolved in pyridine (100ml). Ac₂O (50ml) is added at room temperature under argon and stirred at room temperature for overnight. The reaction mixture is concentrated to dryness and purified by column chromatography on CombiFlash system using EtOAc-Hexanes (0-100%). The desired fractions are collected and concentrated to dryness to give compound 41 (10.2g).

**Synthesis of compound 42:** Compound 41 (7.5g) is dissolved in DMF (140 ml) and is added NH₄OAC (4.05g) with stirring. Stirring is continued for overnight at room temperature under argon. Next day the reaction mixture is stirred at 50°C under argon for 8h. The reaction mixture is concentrated to dryness and the residue was dissolved in EtOAc (150ml), washed with brine (100ml), dried (Na₂SO₄), filtered, and concentrated to dryness. The residue is purified by column chromatography (Si0₂, Hexanes-EtOAc 2:1 → 1:2) to give compound 42 (6g).

**Synthesis of compound 43:** Compound 42 (6g) is dissolved in CH₂Cl₂ (50ml) and is added CCl₃CN (6ml) and DBU (0.5ml). The reaction mixture is stirred at room temperature for 0.5h, solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 43 (4.5g).

**Synthesis of compound 44:** Compound 39 (2g) and compound 43 (2.1g) is dissolved in CH₂Cl₂ (40ml). To this solution added molecular sieves (4A, 0.8g) and stirred at room temperature for 30 min. The solution is then cooled to 0°C and BF₃·Et₂O (0.25ml dissolved in 5ml) is added with stirring at 0°C. The reaction mixture is stirred at 0°C for 2h. Et₂N (0.5ml) is added and the solvent is evaporated off. The residue is purified by column chromatography (silica gel) to give compound 44 (1.8g).

**Synthesis of compound 45:** Compound 44(1.7g) is treated with 0.01N NaOMe in MeOH (10ml) for 2h and neutralized with IR-120 (H⁺) resin, filtered, and concentrated to dryness to give compound 45 (1.25g).

**Synthesis of compound 46:** To a solution of compound 45 (1.2g) in CH₃CN (30ml) is added Et₃N (0.28ml) and cooled to 0°C. To this solution is added BzCN (0.35mg in 10 ml CH₃CN) dropwise during 20 min at 0°C. The reaction mixture is stirred for 1h at 0°C and concentrated to dryness. The residue is purified by column chromatography (silica gel) to give compound 46 (0.95g).

**Synthesis of compound 48:** Compound 46 (0.9g) is dissolved in MeOH (12ml). To this solution is added Bu₂SnO (0.4g) and the mixture is refluxed for 2h.
Solvent is evaporated off and the residual solvent is co-evaporated off with toluene 3 times. The residue is dissolved in dimethoxy ethane (15ml). To this solution is added CsF (0.8g) and compound 47 (2.1g, synthesized as described previously, J. Med. Chem. 1999, 42, 4909). The reaction mixture is stirred overnight at room temperature, and the solvent is evaporated off. The residue is purified by column chromatography to give compound 48 (0.8g).

**Synthesis of compound 49:** Compound 48 (0.7g) is dissolve in C4C12 (20ml). To this solution is added Pd(Ph)4 (0.14g), Bu3SnH (0.15ml), andAc2O (0.3ml) and the reaction mixture is stirred at room temperature for 1h. Solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 49 (0.5g).

**Synthesis of compound 50:** To a solution of compound 49 (0.45g) in dioxane-H2O-AcOH (10:2:1, 2.6ml) is 10%Pd-C (0.15g) and the reaction mixture is shaken at room temperature under positive pressure (20psi) of hydrogen for 5h. The solid is filtered off and the filtrate is concentrated to dryness. The residue is purified by column chromatography (silica gel) to give compound 50 (0.3g).

**Synthesis of compound 51:** Compound 50 (0.28g) is treated with 0.025N NaOMe in MeOH (5ml) for 4h, neutralized with IR-120 (H+) resin, filtered, and the filtrate is concentrated to dryness to give compound 51 (0.21g).

**Synthesis of compound 52:** Compound 51 (0.18g) is dissolved in ethylenediamine (2ml) and stirred at 80 °C for 8h. Solvent is evaporated off and the residue is purified Sep-pak C18 cartridges to give compound 52 (0.15g).

**Synthesis of compound 53:** Compound 35 (0.025g) is dissolved in DMF (1ml) and cooled to 0 °C. To this solution is added DMAP (0.004g) and HATU (0.04g) and the solution is stirred for 5 min. at 0 °C. To this solution is added a solution of compound 52 (0.1g) in DMF (2ml). The reaction mixture is stirred for 20 min. at 0 °C and at room temperature for 15 min., concentrated to dryness and purified by reverse phase in C18 column to give compound 53 (0.030g).

**Synthesis of compound 54:** To a solution of compound 53 (0.02g) in THF (0.5ml) added Et3N (0.01ml) and the solution is cooled to 0 °C. To this solution is added ethylchloroformate (0.012ml). The stirring is continued for 15 min at 0 °C and then a solution of NH2OH.HCl (O.Olg) in DMF (0.025ml) is added dropwise. The reaction mixture is stirred at 0 °C to room temperature for 2.5h. Solvent is evaporated off and the residue is purified by C18 reverse phase column to give compound 54 (O.Olg).
EXAMPLE 11
SYNTHESIS OF GLYCOMIMETIC-PEPTIDOMIMETIC #7 (COMPOUND 65 OF FIGURE 11)

Synthesis of compound 57: Commercially available compound 55 (5g) is treated with commercially available compound 56 (5g) in CH₂Cl₂ (50ml) under anhydrous condition to give compound 57 (2g) after purification by column chromatography (silica gel).

Synthesis of compound 59: A suspension of commercially available compound 58 (2g) and phthalamide (3g) in DMF (50ml) is heated to 60 °C overnight with stirring. Solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 59 (1g).

Synthesis of compound 60: Compound 59 (1g) is treated with NH₂N³/₄ (1ml) in DMF (20ml) overnight, solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 60 (0.4g).

Synthesis of compound 61: Compound 57 (0.6g) and compound 60 (0.3g) is dissolved in CH₃CN (5ml) and the reaction mixture is refluxed for 5h at 80 °C. The solution is concentrated to dryness and purified column chromatography (silica gel) to give compound 61 (0.3g).

Synthesis of compound 62: Compound 61 (0.25g) is treated with 20% CF₂COOH in CH₂Cl₂ (5ml) for 1h. The solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 62 (0.15g).

Synthesis of compound 63: Succinic acid (0.4g) is suspended in DMF (5ml) cooled to 0 °C. To this suspension is added DIPEA (0.05ml) followed by HATU (0.1g) and the reaction mixture is stirred for 5 min at 0 °C. To this mixture is added compound 62 (0.1g) and stirred for another 15 min. at 0 °C and then at room temperature for 15 min. Solvent is evaporated off and the residue is purified by column chromatography (silica gel) to give compound 63 (0.08g).

Synthesis of compound 64: Compound 63 (0.07g) is reacted with compound 52 (0.05g) exactly in the same way as described for compound 53 to give compound 64 (0.035g) after purification by reverse phase hplc purification.

Synthesis of compound 65: Compound 64 (0.025g) is treated with Ethyl chloroformate and NH₂H₂O.HCl exactly in the same way as described for compound 54 to give compound 65 (0.01g) after purification by reverse phase hplc.
EXAMPLE 12
ASSAY TO ASSESS BINDING OF COMPOUNDS TO CXCR4

Methods

The assay assesses the ability of glycomimetic-peptidomimetic compounds to inhibit binding of an anti-CXCR4 antibody conjugated to phycoerythrin ("PE"), to CXCR4 on the surface of SupT1 cells. SupT1 cells are a T lymphoblast derived from a lymphoblastic leukemia and constitutively express CXCR4 on the cell surface. The cells are purchased from ATCC (ATCC number CRL-1942). Anti-human CXCR4-phycoerythrin monoclonal antibody (anti-CXCR4-PE) is purchased from R&D Systems (catalog number FAB170P, clone 12G5). The cells are grown in RPMI 1640 medium supplemented with 10% FBS. Approximately 2 x 10^6 cells are washed three times by centrifuging the cells at 400 x g for 10 minutes and the cell pellet is resuspended in PBS plus 0.05% BSA. After the third centrifugation, the cell pellet is resuspended in PBS plus BSA to a concentration of 5 x 10^5 cells per ml. To block nonspecific binding, human Ig is added to the cells to a concentration of 1 µg per 10^5 cells. Next, 200 µl (1 x 10^5 cells) are added to 5 ml polypropylene round-bottom tubes (Falcon 2053 tubes). A glycomimetic-peptidomimetic compound is added to the cells at final concentrations of 0.5, 5, 10, and 50 µM. To achieve a final concentration of 0.5 µM, 2.2 µl of 50 µM compound plus 19.8 µl of PBS/BSA are added to 200 µl of cells. To achieve a final concentration of 5 µM, 22 µl of 50 µM compound is added to 200 µl of cells. To achieve a final concentration of 10 µM, 4.4 µl of 500 µM compound plus 17.6 µl of PBS/BSA are added to 200 µl of cells. To achieve a final concentration of 50 µM, 22 µl of 500 µM compound is added to 200 µl of cells. Other aliquots of cells are treated with either 1 or 5 µM of the bicyclam CXCR4 antagonist AMD-3 100 (Sigma Aldrich, catalog # A5602). To achieve a final concentration of 1 µM AMD-3 100, 4.4 µl of 50 µM AMD-3 100 plus 17.6 µl of PBS/BSA are added to 200 µl of cells and to achieve a final concentration of 5 µM, 22 µl of 50 µM AMD-3 100 are added to 200 µl of cells. In addition, one tube of cells is treated with 1 µg/ml of SDF-1α (R&D Systems catalog #350-NS), the natural ligand of CXCR4. The tubes are placed at 4°C for 15 minutes. Subsequently, each tube receives 10 µl of anti-CXCR4-PE, except one tube of cells receives 10 µl of mouse IgG 2A isotype control antibody. The tubes are incubated at 4°C for 45 minutes. The cells are washed twice with PBS plus 0.05% BSA and the final cell pellet is resuspended in 100 µl of PBS/BSA. To fix the samples, 100 µl of 2% formaldehyde (Polysciences, Inc. ultrapure EM grade, catalog number 04018)
are added to each tube. Flow cytometry is performed using a Cytomation MoFlo instrument.

EXAMPLE 13
E-SELECTIN ACTIVITY - BINDING ASSAY

Methods

The inhibition assay to screen glycomimetic antagonists of E-selectin is a competitive binding assay, which allows the determination of IC50 values. Briefly, E-selectin/Ig chimera is immobilized by incubation at 37 °C in 96 well microtiter plates for 2 hours. To reduce nonspecific binding, bovine serum albumin is added to each well and incubated at room temperature for 2 hours. The plate is washed and serial dilutions of the test compounds are added to the wells in the presence of conjugates of biotinylated, sLeα polyacrylamide with streptavidin/horseradishperoxidase and incubated for 2 hours at room temperature. To determine the amount of sLeα bound to immobilized E-selectin after washing, the peroxidase substrate, 3,3',5,5' tetramethylbenzidin (TMB) is added. After 3 minutes, the enzyme reaction is stopped by the addition of H3PO4 and the absorbance of light at a wavelength of 450 nm is determined. The concentration of test compound required to inhibit binding by 50% is determined and reported as the IC50 value for each glycomimetic-peptidomimetic compound. In addition to reporting the absolute IC50 value as measured above, relative IC50 values are determined by a ratio of the IC50 measured for the test compound to that of an internal control (reference) stated for each assay.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.
CLAIMS

1. A glycomimetic-peptidomimetic compound for inhibition of E-selectin and the CXCR4 chemokine receptor, comprising a glycomimetic E-selectin inhibitor—Linker—a peptidomimetic CXCR4 chemokine receptor inhibitor, or a physiologically acceptable salt thereof.

2. The compound of claim 1 wherein the E-selectin inhibitor consists of:

\[
\begin{align*}
R^1 &= H, C_1-C_g alkanyl, d-C_8 alkenyl, d-C_g alkynyl, halogenated d-C_g alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, Ci-C_g alkanyl, Ci-C_g alkenyl, d-C_g alkynyl, halogenated d-C_g alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where X = H, Ci-C_g alkanyl, Ci-C_g alkenyl, d-C_g alkynyl, halogenated Ci-C_g alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, alkanyl substituted with C(=0)X, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where X = H, d-C_g alkanyl, d-C_g alkenyl, d-C_g alkynyl, halogenated C_1-C_g alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

R^2 &= -OH, \\
& \quad N, N, N, N, N, N, X, \quad N, N, N, N, N, X, \quad N, N, N, N, N, X, \quad N, N, N, N, N, X, \quad N, N, N, N, N, X, \\
& -O-C(=0)-X, -NH_2, -NH-C(=0)-NHX, or -NH-C(=0)-X where n = 0-2 and X is independently selected from Q-C_g alkanyl, Ci-C_g alkenyl, Ci-C_g alkynyl,
Here Q is a physiologically acceptable salt, d-Cg alkanyl, C1-Cg alkenyl, Ci-Cg alkynyl, aryl, (CH2)m-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF3, C1-Cg alkoxy, NO2, Q-Cg alkanyl, C1-Cg alkenyl, Ci-Cg alkynyl, Ci-C14 aryl, or OY, C(=0)OY, NY2 or C(=0)NHY where Y is H, Ci-C8 alkanyl, d-Cg alkenyl, Cl-Cg alkynyl, or C1-C14 aryl; and

\[ R^3 = H, C1-Cg alkanyl, C1-Cg alkenyl, C1-Cg alkynyl, CN, CH2CN, C(=0)X \text{ where } X \text{ is } H, d-Cg alkanyl, d-C8 alkenyl, Ci-Cg alkynyl, NHOH, NHOCH3, NHCN, or NX2, or C(=0)OY \text{ where } Y \text{ is } H, d-C8 alkanyl, d-Cg alkenyl or d-C8 alkynyl; and

\[ R^4 = \]
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, C₁₋₈ alkanyl, d-C₈₋₁₄ alkenyl, C₁₋₈ alkynyl or OY where Y is H, d-C₈₋₁₄ alkanyl, d-C₈₋₁₄ alkenyl, d-Cg alkynyl or Ci-C₁₄ aryl.

3. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

wherein Z = end of bond to Linker.
4. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

![Chemical Structure Image]

wherein Z = end of bond to Linker.

5. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

![Chemical Structure Image]

wherein Z = end of bond to Linker.
6. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

\[
\text{wherein } Z = \text{end of bond to Linker.}
\]

7. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

\[
\text{wherein } Z = \text{end of bond to Linker.}
\]
8. The compound of claim 1 or claim 2 wherein the E-selectin inhibitor consists of:

![Chemical structure](image)

wherein Z = end of bond to Linker.

9. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

```
KGVSLSYRXRYSLSVGK
```

wherein Z = end of bond to Linker; and X is an amino acid.

10. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical structure](image)

wherein Z = end of bond to Linker.
11. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure](image1)

wherein Z = end of bond to Linker.

12. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure](image2)

wherein Z = end of bond to Linker; and X = H or halide.

13. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure](image3)

wherein Z = end of bond to Linker; and X = H or halide.
14. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure]

wherein one of R₁, R₂ and R₃ is the end of bond to Linker and the other two are H; and

wherein X is C(R₄)(R₅), NR₄, O or S, where R₁ is H or an electron withdrawing group and R₅ is H or an electron withdrawing group.

15. The compound of claim 14 wherein the electron withdrawing group is a halogenated d-C₈ alkanyl, a halogenated d-C₈ alkenyl, a halogenated C₆-C₈ alkynyl, -C-N₂, -C(=O)-Y or -C(=O)-OY, where Y is H, d-C₈ alkanyl, d-C₈ alkenyl, d-C₈ alkynyl, halogenated d-C₈ alkanyl, halogenated d-C₈ alkenyl, or halogenated d-C₈ alkynyl.

16. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

![Chemical Structure]

wherein one of R₁, R₂ and R₃ is the end of bond to Linker and the other two are H.
17. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

wherein one of R₁, R₂, and R₃ is the end of bond to Linker and the other two are H.

18. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

wherein one of R₁, R₂, and R₃ is the end of bond to Linker and the other two are H; and where R₄ is H or an electron withdrawing group.
19. The compound of claim 1 wherein the CXCR4 chemokine receptor inhibitor consists of:

\[
\begin{align*}
\text{wherein one of } R_1, R_2 \text{ and } R_3 \text{ is the end of bond to Linker and the other two are } H; \text{ and where } R_4 \text{ is } H \text{ or an electron withdrawing group and } R_5 \text{ is } H \text{ or an electron withdrawing group.}
\end{align*}
\]

20. The compound of claim 1 having the formula:

\[
\begin{align*}
\text{wherein: } R^1 = H, \text{ Ci-Ce alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated d-Cg alkanyl,}
\text{ aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where } X = H, d-Cg alkanyl, d-C_8 alkenyl, d-Cg alkynyl, halogenated C_8 alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where } X = H, d-Cg alkanyl, C_8 Cg alkynyl, d-C_8 alkynyl, halogenated d-C_8 alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where } X = H, d-C_8 alkanyl, d-C_8 alkynyl, d-C_8 alkynyl,
\end{align*}
\]
halogenated d-C₈ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = \text{-,OH, } \]

-0-C(=0)-X, -NH₂, -NH-C(=0)-NHX, or -NH-C(=0)-X where \( n = 0-2 \) and \( X \) is independently selected from \( \text{C}_1-\text{C}_8 \) alkanyl, \( \text{C}_1-\text{C}_8 \) alkenyl, \( \text{C}_1-\text{C}_8 \) alkynyl,

\[
\begin{align*}
\text{Q} & \quad \text{is H or a physiologically acceptable salt, d-C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, aryl, (CH}_2)_m-\text{aryl where } m \text{ is 1-10, and where } n = 0-10, \text{ and any of the} \\
\text{above ring compounds may be substituted with one to three independently selected of CI, F, CF}_3, \text{C}_1-\text{C}_8 \text{ alkoxy, N0}_2, \text{C}_1-\text{C}_8 \text{ alkanyl, C}_1-\text{C}_8 \text{ alkenyl, C}_1-\text{C}_8 \text{ alkynyl, C}_1-\text{C}_{14} \text{ aryl, or OY, C(=0)OY, NY}_2 \text{ or C(=0)NHY where } Y \text{ is H, d-} \\
\text{C}_8 \text{ alkanyl, C}_{14} \text{ alkynyl, or C}_{14} \text{ aryl;}
\end{align*}
\]

\[ R^3 \quad = \text{H, C}_1-\text{C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, CN, CH}_2\text{CN, C(=0)X where } X \text{ is H, d-C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl, C}_1-\text{C}_8 \text{ alkynyl, NHOH, NHOCH}_3, \text{NHCN,} \\
\text{or NX}_2, \text{ or C(=0)OY where } Y \text{ is H, d-C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl or d-C}_8 \text{ alkynyl;}}
\]
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, C₁-C₈ alkanyl, Q-C₈ alkynyl, or OY where Y is H, d-C₈ alkanyl, C₁-C₈ alkenyl, C₈ alkynyl or C₁₋C₁₄ aryl; and

X = an amino acid.

21. The compound of claim 1 having the formula:

wherein X is an amino acid.
22. The compound of claim 1 having the formula:

wherein X is an amino acid.

23. The compound of claim 1 having the formula:

wherein X is an amino acid.
24. The compound of claim 1 having the formula:

wherein X is an amino acid.

25. The compound of claim 1 having the formula:

wherein X is an amino acid.
26. The compound of claim 1 having the formula:

wherein:

\[ R^1 = H, \text{C}_1^\text{C}_g \text{alkanyl}, \text{d-C}_8 \text{alkenyl}, \text{d-C}_8 \text{alkynyl}, \text{halogenated d-C}_8 \text{alkanyl}, \]

aryl which may be substituted with one or more of Me, OMe, halide, OH, or

NHX where X = H, Cj-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, halogenated

Cg alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where X = H, Cj-Cg alkanyl, d-Cg alkynyl, d-Cg alkynyl, halogenated d-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = \text{-OH, } \text{N} = \text{N}, \text{N} \text{-N}(X)_{n}, \text{N} \text{-N}(X), \text{N} \text{-N}(X), \text{N} \text{-N}(X) \]

-0-C(=0)-X, -NH,2, -NH-C(=0)-NHX, or -NH-C(=0)-X where n = 0-2 and

X is independently selected from Cj-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl,
here is Hor a physiologically acceptable salt, C\textsubscript{1}-C\textsubscript{8} alkanyl, d-C\textsubscript{g} alkenyl, Ci-Cg alkynyl, aryl, \((\text{CH}_2)_m\)-aryl where \(m\) is 1-10, and where \(n = 0-10\), and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF\textsubscript{3}, d-C\textsubscript{g} alkoxy, N\textsubscript{0}\textsubscript{2}, d-C\textsubscript{g} alkanyl, d-C\textsubscript{8} alkenyl, Cj-Cg alkynyl, Ci-C\textsubscript{14} aryl, or OY, C(=0)OY, NY\textsubscript{2} or C(=0)NY where Y is H, d-C\textsubscript{g} alkanyl, d-C\textsubscript{8} alkenyl, d-C\textsubscript{g} alkynyl, or d-C\textsubscript{14} aryl;

\[ R^3 = H, d-C\textsubscript{8} alkanyl, d-C\textsubscript{8} alkenyl, Ci-Cg alkynyl, CN, CH\textsubscript{2}CN, C(=0)X \text{ where } X \text{ is } H, d-C\textsubscript{g} alkanyl, d-C\textsubscript{8} alkenyl, d-C\textsubscript{8} alkynyl, NHOH, NHOCH\textsubscript{3}, NHCN, or NX\textsubscript{2}, or C(=0)OY \text{ where } Y \text{ is } H, d-C\textsubscript{8} alkanyl, d-C\textsubscript{8} alkenyl or d-C\textsubscript{g} alkynyl; \text{ and} \]

\[ R^4 = \]

\[ \text{O} \quad \text{Me} \]

\[ \text{O} \quad \text{Me} \]
where the cyclopropane ring may be substituted with one to two, and the
cyclohexane ring may be substituted with one to three, independently selected of
Cl, F, Ci-Cg alkanyl, d-Cg alkenyl, d-C8 alkynyl or OY where Y is H, C1-C8
alkanyl, Ci-Cg alkenyl, d-C8 alkynyl or d-C14 aryl.

27. The compound of claim 1 having the formula:

28. The compound of claim 1 having the formula:
29. The compound of claim 1 having the formula:

![Chemical Structure 1]

30. The compound of claim 1 having the formula:

![Chemical Structure 2]
31. The compound of claim 1 having the formula:

![Chemical structure 1]

wherein:

\( R^1 = H, \text{Cg-alkanyl, Cg-alkenyl, Cg-alkynyl, halogenated Cg-alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, Ci-Cg alkanyl, Ci-Cg-alkenyl, Ci-Cg-alkynyl, halogenated Ci-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe,} \)

32. The compound of claim 1 having the formula:

![Chemical structure 2]

wherein:

\( R^1 = H, \text{Cg-alkanyl, Cg-alkenyl, Cg-alkynyl, halogenated Cg-alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, Ci-Cg alkanyl, Ci-Cg-alkenyl, Ci-Cg-alkynyl, halogenated Ci-Cg alkanyl, aryl which may be substituted with one or more of Me, OMe,} \)
halide, or OH; C(=0)OX, alkanyl substituted with C(=0)OX, C(=0)NHX, alkanyl substituted with C(=0)NHX, where X = H, d-Cg alkanyl, C1-C8 alkenyl, Cj-Cg alkynyl, halogenated d-Cg alkanyl, aryI which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, Ox, NHX, NHC(=0)X, where X = H, d-C8 alkanyl, Q-Cg alkynyl, halogenated Ci-Cg alkynyl, aryI which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = \text{OH, } \]

\[ -0-C(=0)-X, \text{ -NH}_2, \text{-NH-C(=0)-NHX, or -NH-C(=0)-X where } n = 0-2 \text{ and } X \text{ is independently selected from C}_1-C_8 \text{ alkanyl, C}_1-C_8 \text{ alkenyl, C}_1-C_8 \text{ alkynyl,} \]

\[ \text{Q is H or a physiologically acceptable salt, d-Cg alkanyl, Cj-Cg alkynyl, Ci-Cg alkynyl, aryI, (CH}_2\text{)}_m\text{-aryI where } m \text{ is 1-10, and where } n = 0-10, \text{ and any of the above ring compounds may be substituted with one to three independently selected of CI, F, CF}_3, \text{ Ci-Cg alkoxy, N0}_2, \text{ d-Cg alkanyl, d-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, d-C}_14 \text{ aryI, or OY, C(=0)OY, NY}_2 \text{ or C(=0)NHY where Y is H, Cj-Cg alkynyl, Ci-Cg alkenyl, d-Cg alkynyl, or d-C}_14 \text{ aryI;} \]

\[ R^3 = \text{H, d-C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl, Cj-Cg alkenyl, CN, CH}_2\text{CN, C(=0)X where X is H, d-Cg alkanyl, d-Cg alkenyl, d-Cg alkynyl, NHOH, NHOCH}_3, \text{ NHCN, or NX}_2, \text{ or C(=0)OY where Y is H, d-Cg alkanyl, d-C}_8 \text{ alkenyl or d-Cg alkynyl; and} \]
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, C1–C8 alkanyl, Ci-Cg alkenyl, d-C8 alkynyl or OY where Y is H, Ci-C8 alkanyl, Ci-Cg alkenyl, Ci-C8 alkynyl or C1-C14 aryl.

33. The compound of claim 1 having the formula:
34. The compound of claim 1 having the formula:

35. The compound of claim 1 having the formula:
36. The compound of claim 1 having the formula:

```latex
\begin{center}
\begin{tikzpicture}
\end{center}
```

37. The compound of claim 1 having the formula:

```latex
\begin{center}
\begin{tikzpicture}
\end{center}
```
38. The compound of claim 1 having the formula:

\[ R^1 = H, \text{Ci-Cg alkanyl, C}_r^g \text{ alkynyl, halogenated C}_r^g \text{ alkanyl, ary}
\]

aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where \( X = H, \text{Ci-Cg alkanyl, C}_r^g \text{ alkynyl, halogenated C}_r^g \text{ alkanyl, ary}
\]

aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)O\( X \), alkanyl substituted with C(=0)O\( X \), C(=0)NH\( X \), alkanyl substituted with C(=0)NH\( X \), where \( X = H, \text{d-Cg alkanyl, d-C}_8 \text{ alkenyl, Ci- C}_8 \text{ alkynyl, halogenated C}_r^g \text{ alkynyl, ary}
\]

aryl which may be substituted with one or more of Me, OMe, halide, or OH; C(=0)X, OX, NHX, NHC(=0)X, where \( X = H, \text{Ci-Cg alkanyl, C}_r^g \text{ alkynyl, Q-Cg alkynyl, halogenated Ci-Cg alkynyl, ary}
\]

aryl which may be substituted with one or more of Me, OMe, halide, or OH;

\[ R^2 = -\text{OH}, -\text{NH}, -\text{NH}(=0)-\text{NHX}, \text{or -NH}(=0)-\text{X where n = 0-2 and X is independently selected from Ci-Cg alkanyl, C}_r^g \text{ alkynyl, C}_r^g \text{ alkynyl,}
\]
Q is H or a physiologically acceptable salt, d-C\textsubscript{g} alkanyl, d-C\textsubscript{g} alkenyl, C\textsubscript{j}-C\textsubscript{8} alkynyl, aryl, (CH\textsubscript{2})\textsubscript{m}-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF\textsubscript{3}, d-C\textsubscript{8} alkoxy, N0\textsubscript{2}, d-C\textsubscript{g} alkanyl, Ci-C\textsubscript{8} alkenyl, Ci-Cg alkynyl, d-C\textsubscript{14} aryl, or OY, C(=0)OY, N\textsubscript{X}\textsubscript{2} or C(=0)NH\textsubscript{Y} where Y is H, d-C\textsubscript{g} alkanyl, d-Cg alkenyl, Ci-Cg alkynyl, or Ci-C\textsubscript{14} aryl;

R\textsubscript{3} = H, d-C\textsubscript{g} alkanyl, d-C\textsubscript{8} alkenyl, Ci-C\textsubscript{8} alkynyl, CN, CH\textsubscript{2}CN, C(=0)X where X is H, d-C\textsubscript{g} alkanyl, d-C\textsubscript{g} alkenyl, d-Cg alkynyl, NHOH, NHOCH\textsubscript{3}, NHCN, or N\textsubscript{X}\textsubscript{2}, or C(=0)OY where Y is H, d-C\textsubscript{g} alkanyl, d-C\textsubscript{g} alkenyl or d-C\textsubscript{g} alkynyl;

R\textsubscript{4} =
where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, C₁₋₈ alkanyl, C₁₋₈ alkenyl, C₁₋₈ alkynyl or OY where Y is H, C₁₋₈ alkanyl, C₁₋₈ alkenyl, C₁₋₈ alkynyl or C₁₋₁₄ aryl; and

\[ X = \text{H or halide.} \]

39. The compound of claim 1 having the formula:

wherein \( X \) is H or halide.
40. The compound of claim 1 having the formula:

wherein X is H or halide.

41. The compound of claim 1 having the formula:

wherein X is H or halide.
42. The compound of claim 1 having the formula:

\[
\begin{align*}
&\text{Arg} \quad \text{Nal} \\
&\text{X} \quad \text{NH} \\
&\text{Tyr} \\
&\text{Linker}
\end{align*}
\]

wherein \( X \) is H or halide.

43. The compound of claim 1 having the formula:

\[
\begin{align*}
&\text{Arg} \quad \text{Nal} \\
&\text{X} \quad \text{NH} \\
&\text{Tyr} \\
&\text{Linker}
\end{align*}
\]
wherein X is H or halide.

44. The compound of claim 1 having the formula:

![Chemical Structure Image]

wherein:

\[ R^1 = H, \text{C}_1-\text{C}_8 \text{ alkanyl, Ci-C}_8 \text{ alkenyl, Ci-C}_g \text{ alkynyl, halogenated C}[\text{-C}_8 \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where X = H, Ci-C}_g \text{ alkanyl, Ci-C}_g \text{ alkenyl, Ci-C}_g \text{ alkynyl, halogenated Ci-C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{OX, alkanyl substituted with C}(=0)\text{OX, C}(=0)\text{NHX, alkanyl substituted with C}(=0)\text{NHX, where X = H, C}_1-\text{C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl, Ci-C}_g \text{ alkynyl, halogenated C}_1-\text{C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; C}(=0)\text{X, OX, NHX, NHC}(=0)\text{X, where X = H, C}_1-\text{C}_8 \text{ alkanyl, C}_1-\text{C}_8 \text{ alkenyl, Q-C}_g \text{ alkynyl, halogenated d-C}_g \text{ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;}}

\[ R^2 = \text{-OH, } \text{N}(=\text{O})\text{H}, \text{N}(=\text{O})\text{-R}, \text{N}(=\text{O})\text{-Me, N}(=\text{O})\text{-Me, -OH, -NH}_2, -\text{NH-C}(=0)-\text{NHX, or -NH-C}(=0)-\text{X where n = 0-2 and X is independently selected from Ci-C}_g \text{ alkanyl, Ci-C}_g \text{ alkenyl, d-C}_g \text{ alkynyl,}} \]

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Q is H or a physiologically acceptable salt, Ci-C\(_8\) alkanyl, d-C\(_8\) alkenyl, d-C\(_8\) alkynyl, aryl, (CH\(_2\)_m-aryl where m is 1-10, and where n = 0-10, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, CF\(_3\), Ci-C\(_8\) alkoxy, NO\(_2\), d-C\(_8\) alkanyl, C\(_1\)-C\(_8\) alkenyl, Ci-C\(_8\) alkynyl, C\(_1\)-C\(_14\) aryl, or OY, C(=0)OY, NY\(_2\) or C(=0)NHY where Y is H, d-C\(_8\) alkanyl, C\(_1\)-C\(_8\) alkenyl, d-C\(_8\) alkynyl, or Ci-C\(_14\) aryl;

R\(^3\) = H, C\(_1\)-Cs alkanyl, d-C\(_8\) alkenyl, Ci-C\(_8\) alkynyl, CN, CH\(_2\)CN, C(=0)X where X is H, d-C\(_8\) alkanyl, d-C\(_8\) alkenyl, d-C\(_8\) alkynyl, NHOH, NHOCH\(_3\), NHCN, or NX\(_2\), or C(=0)OY where Y is H, Ci-C\(_8\) alkanyl, d-C\(_8\) alkenyl or d-C\(_8\) alkynyl;

R\(^4\) =
where the cyclopropane ring may be substituted with one to two, and the
cyclohexane ring may be substituted with one to three, independently selected of
Cl, F, d-C\textsubscript{8} alkanyl, d-C\textsubscript{8} alkenyl, C\textsubscript{14}C\textsubscript{8} alkynyl or OY where Y is H, d-C\textsubscript{8}
alkanyl, d-C\textsubscript{8} alkenyl, d-C\textsubscript{8} alkynyl or d-C\textsubscript{14} aryl; and

\[ X = H \text{ or halide}. \]

45. The compound of claim 1 having the formula:

\[
\text{\includegraphics[width=\textwidth]{compound.png}}
\]

wherein X is H or halide.
46. The compound of claim 1 having the formula:

wherein X is H or halide.

47. The compound of claim 1 having the formula:

wherein X is H or halide.
48. The compound of claim 1 having the formula:

wherein X is H or halide.
49. The compound of claim 1 having the formula:

![Chemical Structure](image)

wherein X is H or halide.

50. The compound of claim 1 having the formula:

![Chemical Structure](image)

wherein:
$R^1 = H, Ci-Cg$ alkanyl, $d-Cg$ alkenyl, $d-Cg$ alkynyl, halogenated $d-Cg$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, OH, or NHX where $X = H, Ci-Cg$ alkanyl, $d-Cg$ alkenyl, $C_{1-Cg}$ alkynyl, halogenated $Ci-Cg$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; $C(=0)OX$, alkanyl substituted with $C(=0)OX$, $C(=0)NHX$, alkanyl substituted with $C(=0)NHX$, where $X = H, d-Cg$ alkanyl, $d-Cg$ alkenyl, $Ci-Cg$ alkynyl, halogenated $C_{1-Cg}$ alkynyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

$R^2 = -OH,\ -O-C(=0)-X,\ -NH_2,\ -NH-C(=0)-NHX,\ or\ -NH-C(=0)-X$ where $n = 0-2$ and $X$ is independently selected from $C_{1-Cg}$ alkanyl, $C_{1-Cg}$ alkenyl, $C_{1-Cg}$ alkynyl, $NH_{2}$, $d-C_{1-Cg}$ alkenyl, $C_{1-Cg}$ alkynyl, halogenated $d-Cg$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH; $C(=0)OX$, alkanyl substituted with $C(=0)OX$, $C(=0)NHX$, $NHC(=0)X$, where $X = H, d-Cg$ alkanyl, $d-C_{8}$ alkenyl, $Ci-Cg$ alkynyl, halogenated $d-Cg$ alkanyl, aryl which may be substituted with one or more of Me, OMe, halide, or OH;

$Q$ is H or a physiologically acceptable salt, $Ci-Cg$ alkanyl, $d-Cg$ alkenyl, $d-Cg$ alkynyl, aryl, $(CH_2)_m$ aryl where $m$ is 1-10, and where $n = 0-10$, and any of the above ring compounds may be substituted with one to three independently selected of Cl, F, $CF_3$, $d-Cg$ alkoxy, $N0_2$, $d-C_{8}$ alkanyl, $d-C_{8}$ alkenyl, $d-Cg$ alkynyl, $d-C_{14}$ aryl, or OY, $C(=0)OY$, $NY_2$ or $C(=0)NHY$ where $Y$ is H, $Ci-Cg$ alkanyl, $Ci-Cg$ alkenyl, $d-Cg$ alkynyl, or $d-C_{14}$ aryl;
R^3 = \text{H, d-C}_g \text{ alkanyl, d-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, CN, CH}_2\text{CN, C(=0)X where X is H, C}_1\text{C}_8 \text{ alkanyl, Ci-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, NHOH, NHOCH}_3, \text{NHCN, or NX}_2, or C(=0)\text{OY where Y is H, d-C}_8 \text{ alkanyl, d-C}_8 \text{ alkenyl or d-C}_8 \text{ alkynyl;}}

\[ R^4 = \]

where the cyclopropane ring may be substituted with one to two, and the cyclohexane ring may be substituted with one to three, independently selected of Cl, F, Ci-C_8 alkanyl, d-C_8 alkenyl, d-C_8 alkynyl or OY where Y is H, Ci-C_8 alkanyl, Ci-C_8 alkenyl, d-C_8 alkynyl or C_1-C_14 aryl; and

\[ X = S, O, C(r_4)(r_4) \text{ or NR}_4, \text{ where R}_4 \text{ is H or an electron withdrawing group and R}_5 \text{ is H or an electron withdrawing group.} \]

51. The compound of claim 50 wherein the electron withdrawing group is a halogenated d-C_8 alkanyl, a halogenated d-C_g alkanyl, a halogenated C_1-C_8 alkynyl, -C-\text{NO}_2, -C(=0)-\text{Y or -C(=0)-OY, where Y is H, C}_1\text{-C}_8 \text{ alkanyl, C}_1\text{-C}_8 \text{ alkenyl, d-C}_8 \text{ alkynyl, halogenated d-C}_8 \text{ alkanyl, halogenated d-C}_g \text{ alkenyl, or halogenated d-C}_g \text{ alkynyl.}
52. The compound of claim 1 having the formula:

wherein $X = S, O, C(R_4)(R_5)$ or $NR_4$, where $R_4$ is H or an electron withdrawing group and $R_5$ is H or an electron withdrawing group.

53. The compound of claim 1 having the formula:
wherein $X = S, O, C(R_4)(R_5)$ or NR4, where $R_4$ is H or an electron withdrawing group and $R_5$ is H or an electron withdrawing group.

54. The compound of claim 1 having the formula:

wherein $X = S, O, C(R_4)(R_5)$ or NR4, where $R_4$ is H or an electron withdrawing group and $R_5$ is H or an electron withdrawing group.
55. The compound of claim 1 having the formula:

wherein \( X = S, O, C(R_4)(R_5) \) or \( NR_4 \), where \( R_4 \) is H or an electron withdrawing group and \( R_5 \) is H or an electron withdrawing group.

56. The compound of claim 1 having the formula:

wherein \( X = S, O, C(R_4)(R_5) \) or \( NR_4 \), where \( R_4 \) is H or an electron withdrawing group and \( R_5 \) is H or an electron withdrawing group.

57. The compound of any one of claims 52-56 wherein \( X \) is S.

58. The compound of any one of claims 52-56 wherein \( X \) is O.
59. The compound of any one of claims 52-56 wherein \( X = C(R_\text{4})(R_5) \) where \( \frac{1}{2} \) is H or an electron withdrawing group and \( R_5 \) is H or an electron withdrawing group.

60. The compound of any one of claims 52-56 wherein \( X = N R_4 \) where \( R_4 \) is H or an electron withdrawing group.

61. The compound of claim 59 wherein \( R_4 \) or \( R_5 \), or both \( R_4 \) and \( R_5 \), are an electron withdrawing group.

62. The compounds of claim 60 wherein \( R_4 \) is an electron withdrawing group.

63. The compound of any one of claims 1-62 where Linker is \(-\text{C(=O)-NH-} (\text{CH}_2)_2 \text{-NH-}\).

64. The compound of any one of claims 1-62 where Linker is \(-\text{CH}_2 \text{-NH-} \text{CH}_2 \).

65. The compound of any one of claims 1-62 where Linker is \(-\text{C(=O)-NH-} \text{CH}_2 \).

66. A method for the treatment of a cancer in which the cancer cells may leave the primary site in an individual who is in need of such treatment, comprising administering to the individual a compound in an amount effective for treatment, wherein the compound is according to any one of claims 1 to 65 with or without a pharmaceutically acceptable carrier or diluent.

67. A method for the treatment of a cancer in which it is desired to mobilize cancer cells from a site into the bloodstream and retain the cancer cells in the bloodstream in an individual who is in need of such treatment, comprising administering to the individual a compound in an amount effective for treatment, wherein the compound is according to any one of claims 1 to 65 with or without a pharmaceutically acceptable carrier or diluent.
68. A method for releasing cells into circulating blood and enhancing retention of the cells in the blood of an individual who is in need of such treatment, comprising administering to the individual a compound in an amount effective for treatment, wherein the compound is according to any one of claims 1 to 65 with or without a pharmaceutically acceptable carrier or diluent.

69. The method of claim 68, further including the step of collecting the cells released.

70. The method of claim 68 wherein the step of collecting utilizes apheresis.

71. The method of claim 68 wherein the cells are bone marrow progenitor cells.

72. A method for the treatment of an inflammatory disease in which the adhesion or migration of cells occurs in the disease in an individual who is in need of such treatment, comprising administering to the individual a compound in an amount effective for treatment, wherein the compound is according to any one of claims 1 to 65 with or without a pharmaceutically acceptable carrier or diluent.
Fig. 1
Fig. 3
Fig. 4
Fig. 5
Fig. 6
Fig. 7
Fig. 8A
Fig. 8B
Fig. 9
Synthesis of Compound 39

1. CuCN, Tetraethyl tin, nBuLi, BF₃-etherate, THF
2. -78 to -20 degrees
3. Str, 4h

Synthesis of compound 43

1. Allylchloroformate, NaOMe, MeOH, TFA
2. Py/AgO

Synthesis of compound 53

1. BF₃-Etherate
2. NaOMe-MeOH

Fig. 10A
Fig. 10B
Fig. 11
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/059243

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/7034 C07H15/207 A61P35/00 A61K38/04 C07K7/00
ADD. C07K7/Q8 C07K7/64

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07H A61P C07K

Documented searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEI LSTEIN Data, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

X, P
4 November 2010 (2010-11-04)
the whole document

X
abstract
figures 4,5,6
paragraphs [0003], [0011] - [0018]
examples 8,9,10
claims 1-13

1-72
1,66,67,
72
1-72

X Further documents are listed in the continuation of Box C.
X See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"Z" document member of the same patent family

Date of the actual completion of the international search
1 February 2012

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Garabatos-Perera, J
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