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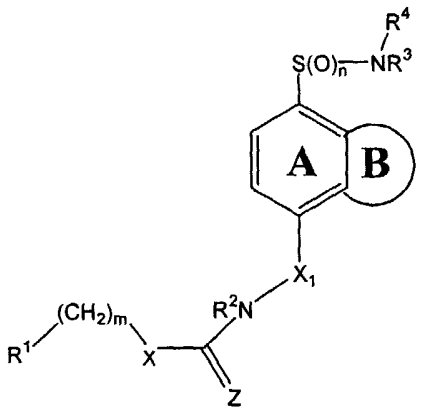
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(54) Title: CCR8 INHIBITORS



(I)

(57) Abstract: Disclosed is an inhibitor of CCR8 that is represented by Structural Formula (I). Also disclosed are pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent and a CCR8 inhibitor represented by Structural Formula (I). Also disclosed is a method of treating inflammatory disorders in a subject by administering a CCR8 inhibitor to the subject.

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CCR8 INHIBITORS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/436,508, filed on December 23, 2002. The entire teachings of the above application(s) are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation (Baggiolini, *et. al., Nature 15*:365 (1994)). Indeed, chemokines have been implicated in a wide range of human acute and chronic inflammatory diseases including, but not limited to, respiratory diseases such as asthma, inflammatory bowel disease, allergic disorders and certain autoimmune diseases such as rheumatoid arthritis.

Chemokines exert their biological activity by binding to specific G-protein receptors, which then transduce signals important for the development and trafficking of specific leukocyte subsets (Baggiolini, *et. al., Nature 15*:365 (1994)). A number of chemokine receptors have been characterized and each are differentially expressed among leukocyte populations. Significantly, each chemokine binds specifically to a single receptor or to a small group of receptors. Thus, the recruitment and activation of specific classes of leukocytes or lymphocytes can be modulated by agents which selectively act at one chemokine receptor and/or block the activity of a specific chemokine. Agents which selectively block the activity of a specific chemokine or chemokine receptor are therefore useful in treating inflammatory diseases caused by aberrant activation of leukocytes or lymphocytes which express those chemokine receptors (or are activated by the chemokine) and minimally affect immune system cells which express other chemokine receptors.

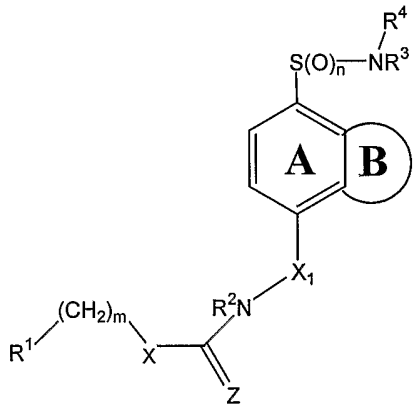
CCR8 is a chemokine receptor (see WO 99/065561) whose expression is primarily restricted to Th2 cells (Zingoni *et al., J. Immunol. 161*:547 (1998) and

D'Ambrosio *et al., J. Immunol. 161:*5111 (1998)). I-309 is a ligand for CCR8 and has shown to be chemotactic for the cells *in vitro* (D'Ambrosio *et al., J. Immunol. 161:*5111 (1998). CCR8 is also involved in eosinophil recruitment (see WO 99/065561). Thus, antagonists for CCR8 are expected to be useful in treating disorders mediated by Th2 and eosinophil cells, e.g., asthma.

SUMMARY OF THE INVENTION

Disclosed herein are 1,4-naphthylsulfonamides, also referred to herein as "1,4-naphthylene sulfonamides", which are effective inhibitors of CCR8 activity. For example, most of the naphthylsulfonamides shown in the Tables at the end of the Experimental Section inhibit CCR8 activity with a K_i less than 1 μM. Based on this discovery, novel CCR8 inhibitors, pharmaceutical compositions comprising these inhibitors and methods of treating inflammatory disorders with these inhibitors are disclosed herein.

One embodiment of the present invention is a compound (a CCR8 inhibitor) represented by Structural Formula (I):



(I).

X is a covalent bond, O or NR^5.

X_1 is a covalent bond, C=O or CR^aR^b. In one preferred embodiment, X_1 is a covalent bond; in another preferred embodiment, X_1 is CH_2.

C=Z is C=O, CH_2, C=NH, C=S or absent, provided that when X_1 is a covalent bond then C=Z is not CH_2. Preferably, when C=Z is absent then X is a covalent bond, and when X is NR^5 and C=Z is C=O then R^4 is not an aliphatic or substituted aliphatic group. More preferably, C=Z is C=O, CH_2, C=NH or C=S, provided that when X_1 is a covalent

bond then C=Z is not CH_2. Even more preferably C=Z is C=O or C=S.

R^a and R^b are independently –H or a C1-C3 alkyl.

R^1 is a substituted or unsubstituted aromatic group or a substituted or unsubstituted non-aromatic ring. Alternatively, when X is NR^5, then $-NR^5(CH_2)_mR^1$, taken together, is optionally a substituted or unsubstituted non-aromatic heterocyclic group.

R^2 is –H or a C1-C3 alkyl group.

R^3 is –H and R^4 is a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted non-aromatic ring or a substituted or substituted non-aromatic bridged bicyclic group (preferably, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted non-aromatic ring, more preferably, a substituted or unsubstituted aromatic group, or a substituted or unsubstituted non-aromatic ring) or, R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group.

R^5 is –H, or a C1-C3 alkyl group.

Rings **A** and **B** are independently substituted or unsubstituted.

Ring B is a phenyl ring or a five or six membered carbocyclic carbocyclic non-aromatic ring fused to Ring **A**. Preferably, Ring B is an optionally substituted phenyl or optionally substituted six membered non-aromatic carbocyclic ring (e.g., cyclohexyl or cyclohexenyl) fused to Ring **A**.

m is 0, 1, 2 or 3.

n is 1 or 2.

Another embodiment of the present invention method is a method of treating a subject with a CCR8 mediated condition or disease, e.g., a subject with asthma. The method comprises the step of administering to the subject an effective amount of a CCR8 inhibitor disclosed herein.

Yet another embodiment of the present invention is a pharmaceutical composition. The pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a CCR8 inhibitor disclosed herein. The pharmaceutical compositions can be used in therapy, for example, to treat a subject with a CCR8

mediated condition or disease, for example, a subject with asthma.

Yet another embodiment of the present invention is the use of one of the disclosed CCR8 inhibitors for the manufacture of a medicament for treating a subject with a CCR8 mediated condition or disease. The medicament comprises an effective amount of the CCR8 inhibitor.

The disclosed compounds are effective inhibitors of CCR8 and, as such, are expected to be useful in the treatment and prevention of diseases mediated by CCR8, particularly asthma. Other diseases for which the disclosed CCR8 inhibitors are expected to be effective include, but not limited to, inflammatory diseases such as atopic dermatitis, allergic rhinitis, systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies and inflammatory dermatoses such as dermatitis, eczema, allergic contact dermatitis, urticaria, atherosclerosis, restenosis and myositis (including polymyositis, dermatomyositis).

DETAILED DESCRIPTION OF THE INVENTION

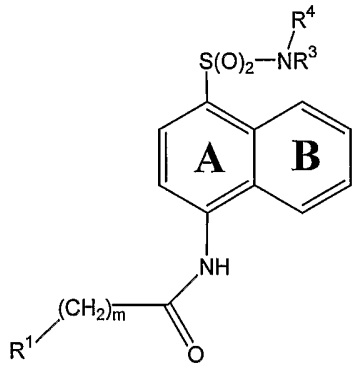
The present invention is directed to inhibitors of the chemokine receptor commonly referred to as "CCR8". CCR8 is expressed on monocytes and Th2 lymphocytes and in the brain, spleen and thymus. It is the receptor for the chemokine I-309, which is chemotactic for Th2 cells. I-309 has also shown to be involved in esinophil recruitment. Thus, the disclosed compounds can be used to inhibit CCR8 activity; to inhibit I-309 activity and to inhibit or treat (therapeutically or prophylactically) conditions mediated by CCR8 and/or I-309, including inflammatory disorders and allergic conditions. The disclosed compounds can also be advantageously used to inhibit conditions mediated by esinophils and by monocytes, T lymphocytes and other immune system cells which express CCR8, including inflammatory disorders and allergic conditions mediated by these cells.

The compound represented by Structural Formula (I) is preferably characterized by one, two, three or more of the following features: (1) C=Z is C=O and X_1 is a bond or C=Z is CH_2 and X_1 is CR^aR^b ; (2) X is a bond; (3) R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group optionally substituted with one or more substituent groups, e.g., the substituent groups represented by R^{10}; (4) R^2 is –H; (5) R^3 is –H or R^3

and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group; (6) R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl or benzyl group optionally substituted with one or more substituent groups, e.g., the substituent groups represented by R^{12}; (7) m is 0 or 1; and (8) n is 2. Exemplary values for R^{10} and R^{12} are provided below in the section describing suitable aromatic and aliphatic group substituents. Commonly, the compound is characterized by features (1); (2); (3); (4); (5); (6); (7); (8); (1) and (4); (1), (2) and (4); (1), (3) and (4); (1), (4) and (5); (1), (4), and (6); (1), (4) and (7); (1), (4) and (8); (1), (4), (7) and (8); (1), (2), (4), (7) and (8); (1), (3), (4), (7) and (8); (1), (4), (5), (7) and (8); (1), (4), (6), (7) and (8); (1), (2), (3), (4), (5), (7) and (8); (1), (2), (4), (5), (6), (7) and (8); and (1), (3), (4), (5), (6), (7) and (8). Preferably, the compound represented by Structural Formula (I) is characterized by all of Features (1)-(8).

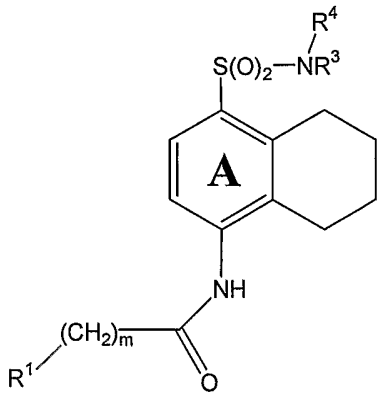
Alternatively, the compound represented by Structural Formula (I) is characterized as described in the previous paragraph, except that X_1 is C=O and C=Z is absent for feature (1).

In one preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (II):



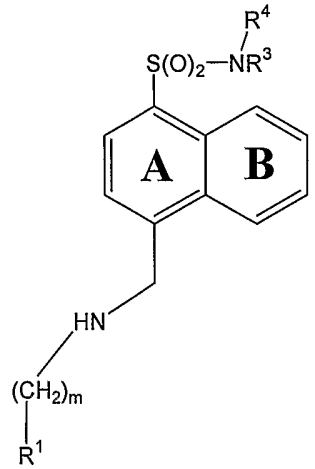
(II).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (III):



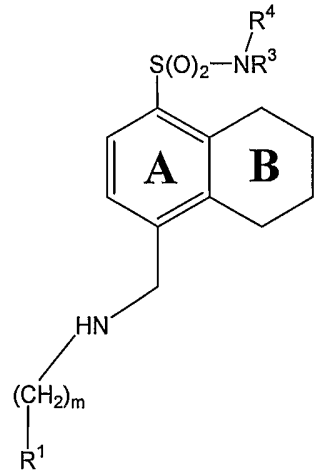
(III).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (IV):



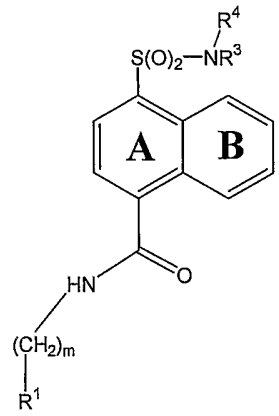
(IV).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (V):



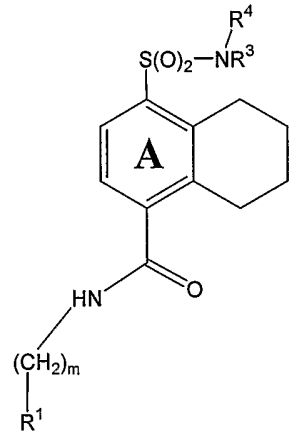
(V).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (VI):



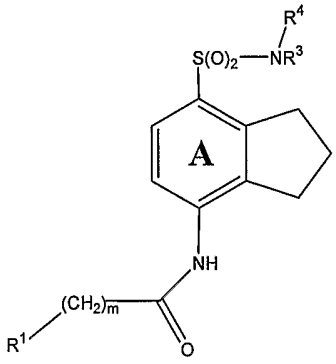
(VI).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (VII):



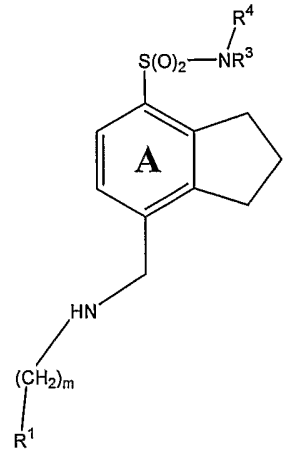
(VII).

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (VIII):



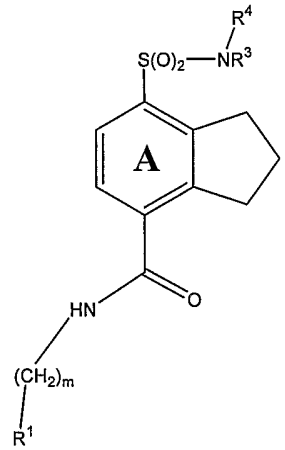
(VIII)

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (IX):



(IX)

In another preferred embodiment, the CCR8 inhibitor is represented by Structural Formula (X):



(X).

In Structural Formulas (II)-(X), R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group optionally substituted with one or more groups, for example, the substituent groups represented by R^{10}; R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups, for example the substituent groups represented by R^{12} or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group; m is 0 or 1; and Rings **A** and **B** are optionally and independently substituted at any one or more substitutable ring carbons. Exemplary values for R^{10} and R^{12} and exemplary substituents for Rings **A**

and **B** are provided hereinbelow in the section describing aromatic group and non-aromatic ring substituents. Preferred substituents for Rings **A** and **B** include alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, halogen, cyano and nitro. Preferably, Rings **A** and **B** are unsubstituted.

One preferred value for R^4 in Structural Formulas (I)-(X) is a substituted or unsubstituted non-aromatic ring. Suitable substituents for a non-aromatic ring represented by R^4 are provided hereinbelow in section describing substituents for a substitutable carbon on a non-aromatic ring and in the section describing substituents for the nitrogen atom of a non-aromatic heterocyclic group. When R^4 in Structural Formulas (I)-(X) is a non-aromatic ring, preferred values include a piperidinyl group, an *N*-substituted piperidinyl group, or a cyclohexyl group. Suitable substituents for the nitrogen atom in a piperidinyl group represented by R^4 are provided hereinbelow in the section describing substituents on the nitrogen atom of a non-aromatic heterocyclic group. Preferred substituents for the nitrogen atom in a piperidinyl group represented by R^4 include R^{15}, $-C(O)R^{15}$, $-C(O)OR^{15}$, and $-C(O)-NHR^{15}$. Other preferred substituents for the nitrogen atom in a piperidinyl group represented by R^4 include $-C(O)-N(R^{15})_2$ or $-C(O)CH[N(R^{16})_2]R^{17}$. R^{15} is –H, a non-aromatic ring, or a substituted or unsubstituted aliphatic group or a substituted or unsubstituted C7-C9 aralkyl group. Typically, however, $-C(O)OR^{15}$ is not -COOH. R^{15} can also be a substituted or unsubstituted non-aromatic ring. In addition, $N(R^{15})_2$ taken together can be a substituted or unsubstituted five or six membered non-aromatic nitrogen-containing heterocyclic group. Preferred substituents for a substitutable carbon of the non-aromatic ring represented by R^{15} or the non-aromatic heterocyclic group represented by $N(R^{15})_2$ included methyl, ethyl hydroxyethyl and iso-propyl; suitable substituents for a substitutable nitrogen of these groups include alkyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl and dialkylaminocarbonyl. R^{16} is –H or an alkyl group. R^{17} is –H; a C1-C6 alkyl group optionally substituted with –OH, $-NH_2$, phenyl or phenyl substituted with –OH; indolyl; imidazolyl; or phenyl optionally substituted with –OH.

Another preferred value for R^4 in Structural Formulas (I)-(X) is a phenyl group, a substituted phenyl group, a benzyl group or a substituted benzyl group. Suitable substituents for phenyl and benzyl groups represented by R^4 are provided hereinbelow in

the section describing suitable aromatic group substituents. Preferred substituents are electron donating groups such as methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_3$, $N(CH_2CH_3)_2$, $N(CH_3)(CH_2CH_3)$, $NH(CH_2CH_2CH_3)$, $N(CH_2CH_2CH_3)_2$, $N(CH_3)(CH_2CH_2CH_3)$ or $N(CH_2CH_3)(CH_2CH_2CH_3)$.

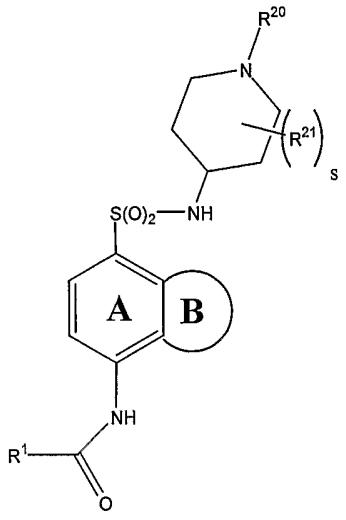
In another preferred embodiment, $-NR^3R^4$ in Structural Formulas (I)-(X), taken together, is a substituted or unsubstituted non-aromatic heterocyclic group. Suitable substituents for a non-aromatic heterocyclic group represented by $-NR^3R^4$ are provided hereinbelow in section describing suitable substituents for a substitutable carbon of a non-aromatic group and in the section describing suitable substituents for the nitrogen atom of a non-aromatic heterocyclic group.

In Structural Formulas (I)-(X), R^1 is preferably a substituted or unsubstituted cyclohexyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted pyridyl group, a substituted or a unsubstituted $-CH_2$-(pyridyl) group, a substituted or a unsubstituted thienyl group, a substituted or a unsubstituted $-CH_2$-(thienyl) group, a substituted or a unsubstituted benzothienyl group, a substituted or a unsubstituted $-CH_2$-(benzothienyl) group, a substituted or a unsubstituted furanyl group or a substituted or a unsubstituted $-CH_2$-(furanyl) group and more preferably is an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group. When R^1 has these values, then R^4 preferably is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group or $-NR^3R^4$ taken together is a nitrogen-containing non-aromatic heterocyclic ring, as described in the previous paragraph. Preferred substituents for the nitrogen atom in the piperidinyl group represented by R^4 and recited in this paragraph include R^{15}, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)-NHR^{15}$, $-C(O)-N(R^{15})_2$ and $-C(O)CH[N(R^{16})_2]R^{17}$.

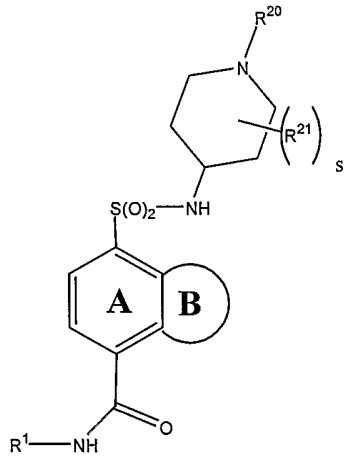
Also disclosed is a compound represented by Structural Formula (II) or (III) wherein the amide group connected to the napthyl ring is replaced with a carbamate (-O-

C(O)NH-), a thiocarbamate (-O-C(S)NH-), a urethane (NH-C(O)-NH-) or a thiourethane group (NH-C(S)-NH-).

Yet another preferred embodiment of the present invention is a compound represented by Structural Formulas (XI) or (XII):



(XI)



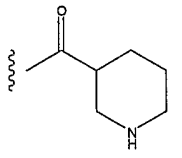
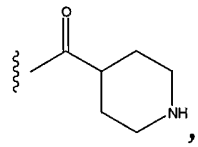
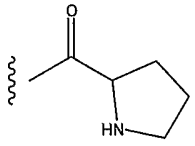
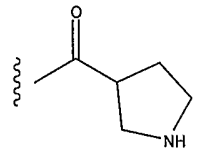
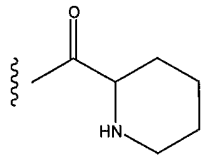
(XII)

The variables in Structural Formulas (XI) and (XII) are defined below.

Ring **A** is unsubstituted.

Ring **B** is an unsubstituted phenyl, cyclohexyl or cyclopentyl ring fused to Ring **A**.

R^1 is cyclohexyl or phenyl, furanyl, thienyl or pyridyl optionally substituted with C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, methylenedioxy, ethylenedioxy, halogen, cyano, or nitro.

R^{20} is $-C(O)R^{22}$, , , , , , $-C(O)OR^{22}$, $-C(O)-NHR^{22}$, $-C(O)-N(R^{22})_2$ or $-C(O)CH[N(R^{23})_2]R^{24}$.

R^{21} is methyl, ethyl 2-hydroxyethyl or iso-propyl. R^{21} indicates that the piperidinyl groups in Structural Formulas (XI) and (XII) are optionally substituted at up to four

substitutable carbon atoms with R^{21}. A substitutable methylene group in the piperidinyl rings can optionally be substituted with up to two independently selected R^{21}s.

R^{22} is –H or C1-C4 alkyl or -N(R^{22})$_2$ taken together is N-pyrollidinyl or N-piperidinyl, provided that R^{22} is not –H when R^{20} is –COOR^{22}.

R^{23} is –H, methyl or ethyl.

R^{24} is –H, methyl, ethyl, phenyl, benzyl, 4-hydroxyphenyl or 4-hydroxybenzyl.

s is 0, 1, 2, 3, or 4.

Also disclosed herein is a compound represented by Structural Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and methods of use thereof for treating a subject with a CCR8 mediated disease or condition and pharmaceutical compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in the Tables and Examples of the Exemplification Section and the remainder of the variables are as defined above.

Also disclosed herein is a compound represented by Structural Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and methods of use thereof for treating a subject with a CCR8 mediated disease or condition and pharmaceutical compositions comprising the same, wherein NR^3R^4 has the value corresponding to any one of the compounds in the Tables and Examples of the Exemplification Section and the remainder of the variables are as defined above.

Also disclosed is a compound represented by Structural Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and methods of use thereof for treating a subject with a CCR8 mediated disease or condition and pharmaceutical compositions comprising the same, wherein R^3 is –H and R^4 is a substituted or unsubstituted aromatic group or a substituted or unsubstituted non-aromatic ring, or -NR^3R^4 is a substituted or unsubstituted non-aromatic heterocyclic group, and the remainder of the variables are as described above.

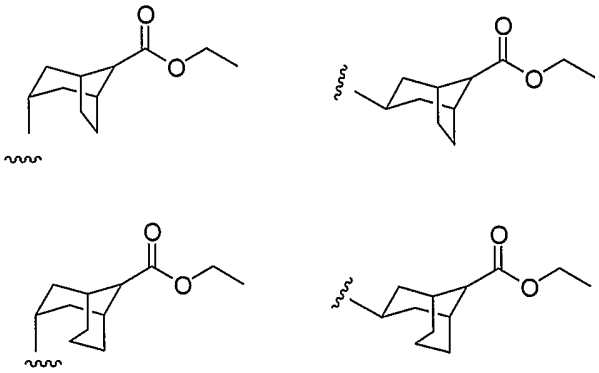
The term "aliphatic" as used herein means straight-chain or branched hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic. An aliphatic group is typically C_{1-8}, more typically C_{1-6}. For example, suitable aliphatic groups include substituted or unsubstituted linear or branched alkyl, alkenyl, alkynyl groups and hybrids thereof. The terms "alkyl",

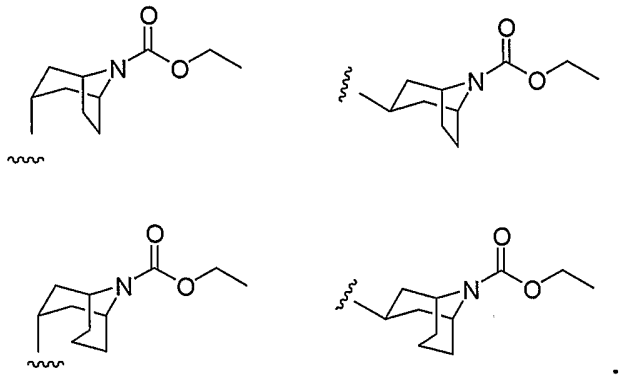
"alkoxy", "hydroxyalkyl", "alkoxyalkylene", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched saturated chains containing one to eight carbon atoms. The terms "alkenyl" and alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to eight carbon atoms and one or more double and/or triple bonds, respectively.

The term "non-aromatic ring", used alone or as part of a larger moiety, includes non-aromatic heterocyclic groups and cycloaliphatic groups.

The term "cycloaliphatic" used alone or as part of a larger moiety, shall include cyclic C_3-C_{10} hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic. Cycloaliphatic groups are typically C_{3-10}, more typically C_{3-7}. A "cycloalkyl" is a cyclic aliphatic group that is completely saturated.

The term "non-aromatic bridged bicyclic group", used alone or as part of a larger moiety, shall include bicyclic ring systems comprising from seven to fifteen ring atoms in which at least three adjacent ring atoms in the bicyclic ring system are shared by both rings. The ring systems can be carbocyclic, in which all ring atoms are carbon, or heterocyclic ("bridged bicyclic non-aromatic heterocyclic groups"), in which one or more ring carbons are replaced with nitrogen, oxygen, sulfur and the like. Examples are shown below:





Suitable substituents for substitutable carbon atoms of a non-aromatic bridged bicyclic group are as provided below for non-aromatic heterocyclic groups. Suitable substituents for substitutable nitrogen atoms of a non-aromatic bridged bicyclic group are as provided below for non-aromatic heterocyclic groups.

"Alkoxy" means (alkyl)-O-; "alkoxyalkylene" means (alkyl)-O-(alkylene) such as methoxymethylene (CH_3OCH_2); "hydroxyalkyl" means hydroxy substituted alkyl group; "alkoxy carbonyl means a carbonyl substituted with a carbonyl as in (alkyl)-O-C(O)-; and "aralkyl" means alkyl substituted with an aromatic group. A "C1-C4 aralkyl group", for example, has a C1-C4 alkyl group substituted with an aromatic group.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in *N*-substituted pyrrolidinyl).

The term "aromatic group" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", includes to carbocyclic aromatic ring groups and heteroaryl rings groups. The term "aromatic group" may be used interchangeably with the terms "aryl", "aryl ring" or "aromatic ring".

Carbocyclic aromatic ring groups have only carbon ring atoms and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "carbocyclic aromatic ring", as it is used herein, is a group in which an

aromatic ring is fused to one or more non-aromatic rings (aliphatic or heterocyclic), such as in an indanyl, phthalimidyl, naphthimidyl, phenantriidinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

The term "heteroaryl", "heteroaromatic" or "heteroaryl ring", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to heteroaromatic ring groups having five to fourteen members, including monocyclic heteraromatic rings and polycyclic aromatic rings in which a monocyclic aromatic ring is fused to one or more other carbocyclic or heteroaromatic aromatic rings . Examples of heteroaryl rings include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisazolyl. Other than R°, pyrazolyl is also a suitable value for variables which represent heteroaryl rings. Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroaryl ring is fused to one or more cycloaliphatic or non-aromatic heterocyclic groups where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido [3, 4-d] pyrimidinyl.

The term "non-aromatic heterocyclic ring", used alone or as part of a larger moiety as in "hetercyclylalkyl", refers to non-aromatic ring systems typically having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Examples of non-aromatic heterocyclic rings include 3-1H-benzimidazol-2-one, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrorolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl,

diazolonyl, N-substituted diazolonyl, 1-pthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl.

As noted above, the CCR8 inhibitors of the present invention comprise aromatic groups, aliphatic groups and non-aromatic rings, including cycloaliphatic groups and non-aromatic heterocyclic groups, which are optionally substituted, i.e., which comprise one or more substituents. Substituents can be found at one or more substitutable carbon atoms in aromatic groups, aliphatic groups and non-aromatic rings and substitutable nitrogen atoms in heteroaromatic groups and non-aromatic heterocyclic rings. For ease of reference, exemplary substituents at the carbon atoms of an aromatic group represented by R^1 are represented by R^{10}; exemplary substituents at the carbon atoms of an aliphatic group represented by R^4 are represented by R^{11}; and exemplary substituents at the carbon atoms of an aromatic group represented by R^4 are represented by R^{12}.

Suitable values for the substituents represented by R^{10}-R^{12} and suitable substituents for the substitutable carbon atoms of Rings **A** and **B** and for other aromatic groups, aliphatic groups and non-aromatic rings (including cycloaliphatic rings and non-aromatic heterocyclic rings) that form part(s) of the disclosed CCR8 inhibitors are those which do not significantly reduce the compounds ability to antagonize the activity of CCR8 and/or which do not significantly increase toxicity to the subject. Examples include -R°, -OH, -OR°, -O(haloalkyl), -SH, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH_2(Ph), substituted –CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -CN, -NR'CO_2R°, -NR'NR'C(O)R°, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO_2R°, -C(O)C(O)R°, -C(O)CH_2C(O)R°, -CO_2R°, -C(O)R°, -OC(O)R°, -OC(O)N(R°)$_2$, -S(O)$_2R^\circ$, -SO_2N(R')$_2$, -S(O)R°, -NR'SO_2N(R')$_2$, -NR'SO_2R°, -C(=S)N(R')$_2$, -$(CH_2)_y$N(R')$_2$, -C(=NH)-N(R')$_2$, haloalkyl, -V-R°, -V-OH, -V-OR°, -V-SH, -V-SR°, -NR'C(O)R°, -V-CN, -V-NR'CO_2R°, -V-NR'NR'C(O)R°, -V-N(R')C(O)N(R')$_2$, -V-NR'NR'C(O)N(R')$_2$, -V-NR'NR'CO_2R°, -V-C(O)C(O)R°, -V-C(O)CH_2C(O)R°, -V-CO_2R°, -V-C(O)R°, -V-OC(O)R°, -V-OC(O)N(R°)$_2$, -V-S(O)$_2R^\circ$, -V-SO_2N(R')$_2$, -V-S(O)R°, -V-NR'SO_2N(R')$_2$, -V-NR'SO_2R°, -V-C(=S)N(R')$_2$, -V-$(CH_2)_y$N(R')$_2$, or -V-C(=NH)-N(R')$_2$. Additionally, -NO_2, -N(R')$_2$, -C(O)N(R°)$_2$, -NR'C(O)R°, -C(O)N(R°)$_2$, -V-NO_2, -V-N(R')$_2$, -V-C(O)N(R°)$_2$, -V-NR'C(O)R° and -V-C(O)N(R°)$_2$

are permissibly values for R^{10} and R^{11} and $COOR^{o}$ is a permissible substituent for the substitutable carbon atoms of an aromatic group represented by R^1 and R^4 and Rings **A** and **B** and for other aromatic groups, aliphatic groups and non-aromatic rings that form part(s) of the disclosed CCR8 inhibitors. Other examples of suitable substituents on the saturated carbon of an aliphatic group (including aliphatic groups represented by R^4) and a non-aromatic heterocycle include: =O, =S, =NNHR*, $=NN(R^*)_2$, =NNHC(O)R*, $=NNHCO_2$(alkyl), $=NNHSO_2$ (alkyl), or =NR*. Except as otherwise provided, preferred substituents for aromatic groups, aliphatic groups and non-aromatic rings (including cycloaliphatic rings and non-aromatic heterocyclic rings) that form part(s) of the disclosed CCR8 inhibitors are haloalkyl, alkyl, halogen, cyano, nitro, hydroxy, haloalkoxy and alkoxy. Amine, alkylamine and dialkyamine are also a preferred substituents for substitutable carbon atoms of an aliphatic group or a non-aromatic ring of the disclosed CCR8 inhibitors. A substitutable methylene group in an aliphatic or non-aromatic ring permissably has up to two substituents. Most commonly, however, the carbon atoms of aliphatic groups and non-aromatic rings (e.g., a non-aromatic ring represented by R^1, a non-aromatic heterocyclic group formed from $NR^5(CH_m)R^1$, a non-aromatic ring formed from NR^3R^4 or a non-aromatic ring represented by R^4) of the disclosed CCR8 inhibitors are unsubstituted or substituted with an alkyl group, hydroxyalkyl group or halogen.

Each R* is independently selected from hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group, preferably from hydrogen or an alkyl group.

Each R^{o} is independently hydrogen or substituted or unsubstituted aliphatic group, a substituted or unsubstituted cycloaliphatic group, a substituted or unsubstituted non-aromatic heterocyclic group or a substituted or unsubstituted aromatic group, preferably phenyl group. Preferably, each R^{o} is independently hydrogen, an alkyl group, a cycloalkyl group, a non-aromatic heterocyclic group or an aromatic group (preferably phenyl).

Each R' is independently R^{o}, $-CO_2R^{o}$, $-SO_2R^{o}$ or $-C(O)R^{o}$.

V is a C1-C6 alkylene group.

Suitable substituents on the nitrogen of a non-aromatic heterocyclic group include $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, and $-NR^+SO_2R^+$. Other examples include

$-C(O)-NHR^+$, $-C(O)-N(R^+)_2$, $-C(O)-CH[N(R^+)_2]R^+$ and $-C(O)-CH[OR^+]R^+$.

Each R^+ is independently hydrogen, an aliphatic group, a substituted aliphatic group, phenyl, substituted phenyl, -benzyl, substituted benzyl or an unsubstituted heteroaryl or non-aromatic heterocyclic ring. R^+ can also be a substituted non-aromatic heterocyclic group and a substituted or unsubstituted cycloaliphatic group; or $N(R^+)_2$ is a non-aromatic heterocyclic group.

Examples of substituents on the aliphatic group represented by R^*, examples of substituents on the aliphatic, aromatic, cycloaliphatic or non-aromatic heterocyclic group represented by R^o and examples of substituents on the aliphatic group, phenyl group or benzyl group represented by R^+ include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

An "electron donating group" is a substituent which results in a phenyl ring that has more electron density when the group is present than when it is absent. Electron donating groups have a Hammet sigma value greater than one (see, for example , C. Hansch, A. Leo and D. Hoeckman, "Exploring QSAR Hydrophobic, Electronic and Steric Constants", American Chemical Society (1995), pages 217-32). Examples of electron donating groups include hydroxy, alkoxy, alkyl, alkylamine dialkylamine and amine.

Additionally, pharmaceutically acceptable salts of the compounds disclosed herein are also included in the present invention and can be used in the compositions and methods disclosed herein. For example, an acid salt of a compound containing an amine or other basic group can be obtained, by reacting the compound with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acid such as lysine and arginine.

Some of the disclosed CCR8 inhibitors contain one or more chiral centers. The presence of chiral centers in a molecule gives rise to stereoisomers. For example, a pair of optical isomers, referred to as "enantiomers", exist for every chiral center in a molecule; and a pair of diastereomers exist for every chiral center in a compound having two or more chiral centers.

It is to be understood that, when a disclosed CCR8 inhibitor has at least one chiral center, the present invention encompasses one enantiomer of inhibitor free from the corresponding optical isomer, racemic mixture of the inhibitor and mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a mixture is enriched in one enantiomer relative to its optical isomers, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a

further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a disclosed CCR8 inhibitor has at least two chiral centers, the present invention encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diasteromeric pairs, mixtures of diasteromers, mixtures of diasteromeric pairs, mixtures of diasteromers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diasteromeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). When a mixture is enriched in one diastereomer or diastereomeric pair(s) relative to the other diastereomers or diastereomeric pair(s), the mixture enriched with the depicted or referenced diastereomer or diastereomeric pair(s) relative to other diastereomers or diastereomeric pair(s), for example, by a molar excess of at least 50%, 75%, 90%, 95% 99% or 99.5%.

The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of compounds disclosed herein are provided in Example 1.

In certain instances compounds of the present invention may associated in isolated form with solvent or water, as in a "solvate" or "hydrate". References to the disclosed compounds or structural formulas depicting the disclosed compounds are meant to include such solvates and hydrates.

The disclosed compounds, pharmaceutical compositions and methods can be used to inhibit CCR8 activity, to inhibit I-309 activity and to inhibit or treat (therapeutically or prophylactically) conditions mediated by CCR8 and/or I-309, including inflammatory disorders and allergic conditions. The disclosed compounds can also be advantageously used to inhibit conditions mediated by esinophils and monocytes, T lymphocytes and other immune system cells which express CCR8, including inflammatory disorders and allergic mediated by these cells.

Examples of allergic conditions for which the disclosed compounds,

pharmaceutical compositions and methods are particularly effective include asthma. Other allergic conditions which are expected to be treatable by inhibiting CCR8 activity include, atopic dermatitis, allergic rhinitis, systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies and dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis and urticaria.

Examples of diseases with an inflammatory component for which the disclosed compounds, pharmaceutical composition and methods are effective include rheumatoid arthritis, osteoarthritis, inflammatory bowel disease [e.g., such as ulcerative colitis, Crohn's disease, ileitis, Celiac disease, nontropical Sprue, enteritis, enteropathy associated with seronegative arthropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy, and ileoanal anastomosis] and disorders of the skin [e.g., psoriasis, erythema, pruritis, and acne].

Many autoimmune diseases also have an inflammatory component. Examples include multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes, glomerulonephritis and other nephritides, autoimmune thyroiditis, Behcet's disease and graft rejection (including allograft rejection or graft-versus-host disease). The inflammatory component of these disorders is believed to be mediated, at least in part, by CCR8.

Diseases characterized by repurfusion have an inflammatory component that is believed to be mediated, at least in part by CCR8. Examples include stroke, cardiac ischemia, and the like. The disclosed compounds and compositions also can be used to treat these disorders.

Other diseases and conditions with an inflammatory component believed to be mediated by CCR8 include mastitis (mammary gland), vaginitis, cholecystitis, cholangitis or pericholangitis (bile duct and surrounding tissue of the liver), chronic bronchitis, chronic sinusitis, chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, or other autoimmune conditions), hypersensitivity pneumonitis, collagen diseases and sarcoidosis. Yet other diseases or conditions with inflammatory components which are amendable to treatment according to

methods disclosed herein include vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis), spondyloarthropathies, scleroderma, atherosclerosis, restenosis and myositis (including polymyositis, dermatomyositis), pancreatitis and insulin-dependent diabetes mellitus.

A subject with a condition having one or more symptoms mediated by CCR8, including one of the aforementioned diseases or conditions, is said "to be in need of CCR8 inhibition". The subject with a disease or condition of this type is "treated" when at least one of the symptoms associated with the disease or condition is alleviated (therapeutic treatment) or inhibited or prevented (prophylactic treatment), in whole or in part.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). As noted above, a "subject in need of CCR8 inhibition" is a subject in whom a beneficial therapeutic or prophylactic effect can be achieved by inhibiting CCR8 function or activity.

An "effective amount" of the disclosed CCR8 inhibitors is the quantity which inhibits CCR8 activity in a subject in need of such inhibition, or which, when administered to a subject with a CCR8 mediated condition or disease, ameliorates the symptoms of the disease, delays the onset of the symptoms and/or increases longevity. The precise amount of CCR8 inhibitor administered to the subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The dosage may also vary according to the route of administration, which includes oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal and intranasal.
The skilled artisan will be able to determine appropriate dosages depending on these and other factors. An "effective amount" typically ranges between about 0.01 mg/kg/day to about 100 mg/kg/day, preferably between about 0.5 mg/kg/day to about 50 mg/kg/day.

The CCR8 inhibitors described herein, and the pharmaceutically acceptable salts thereof can be used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable

carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The CCR8 inhibitor will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein. Techniques for formulation and administration of the compounds of the instant invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995).

For oral administration, the CCR8 inhibitor or salts thereof can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, pills, powders, syrups, solutions, suspensions and the like.

The tablets, pills, capsules, and the like contain from about 1 to about 99 weight percent of the active ingredient and a binder such as gum tragacanth, acacias, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, a lubricant such as magnesium stearate; and a sweetening agent such as sucrose lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

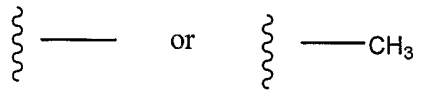
Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

For parental administration, the disclosed CCR8 inhibitor, or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

In addition, to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by

implantation, for example, subcutaneously or intramuscularly or by intramuscular injection. Thus, for example, as an emulsion in an acceptable oil, or ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

In accordance with conventional methods for showing structural formulas of compounds, a terminal methyl group in a compound described herein can be shown as a straight line with or without "CH3" on its terminus:



In certain aspects, the present invention is directed to a compound represented by Structural Formulas (I), (II) or (III) (and methods of use thereof), provided that when R^1 is pyridyl and R^4 is a phenyl group, then the phenyl group represented by R^4 is substituted with a group other than $-NO_2$, $-NR^xR^x$, $-CONR^xR^x$, $-NR^xCOR^X$, or an aliphatic group substituted with $-NO_2$, $-NR^xR^x$, $-CONR^xR^x$ or $-NR^xCOR^X$. Each R^x is independently H, an aliphatic group, a substituted aliphatic group, an aryl group a substituted aryl group, a non-aromatic ring or a substituted non-aromatic ring. Alternatively, or in addition, the subject matter encompassed by Structural Formlas (I)-(III) excludes N-[4-[[(4-methoxyphenyl)amino]sulfonyl]-1-naphthalenyl]-benzamide,
N-[4-[(2-propenylamino)sulfonyl]-1-naphthalenyl]-benzamide,
N-[4-(4-morpholinylsulfonyl)-1-naphthalenyl]-benzamide or
N-[4-(1-piperidinylsulfonyl)-1-naphthalenyl]-benzamide.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

EXPERIMENTAL PROCEDURE FOR NAPHTHALENE SULFONAMIDES

General

All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere. Reagents were used as received from commercial suppliers unless otherwise noted. Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and dioxane were obtained from Aldrich Chemical Company in Sure/Seal bottles. ^1H NMR data were recorded using the Bruker UltraShield 300 MHz/54mm instrument equipped with Bruker B-ACS60 Auto Sampler or the Varian 300 MHz instrument. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are reported in the following order: ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; quin, quintet), and number of protons. Intermediates and final compounds were purified by flash chromatography using one of the following instruments: 1. Biotage 4-channel Quad UV Flash Collector equipped with a Quad 1 Pump Module and the Quad 12/25 Cartridge module. 2. Biotage 12-channel Quad UV Flash Collector equipped with a Quad 3 Pump Module and a Quad 3 Cartridge module. 3. Flash column combi-flash chromatography instrument. LC/MS spectra were obtained using a MicroMass Platform LC (Phenomenx C18 column, 5 micron, 50 x 4.6 mm) equipped with a Gilson 215 Liquid Handler. Standard LC/MS conditions are as follows:

Formic acid-Standard conditions:

% C (Water)	95.0
% D (Acetonitrile)	5.0
% Formic Acid	0.1
Flow (mL/min)	3.500
Stop Time (mins)	4.4
Min Pressure (bar)	0
Max Pressure (bar)	400
Oven Temperature Left(°C)	25.0
Oven Temperature Right(°C)	25.0

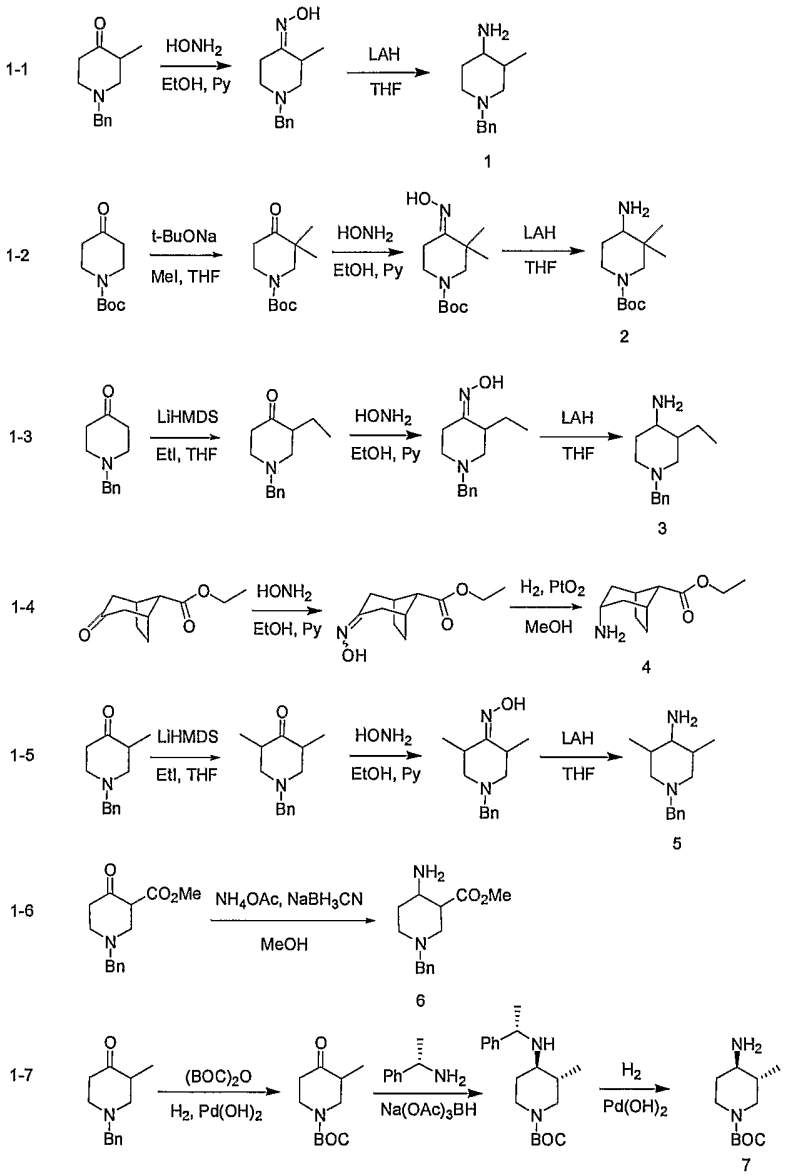
HP1100 LC Pump Gradient Timetable

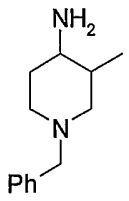
The gradient Timetable contains 5 entries which are:

Time	A%	B%	C%	D%	Flow	Pressure
0.00	0.0	0.0	95.0	5.0	3.500	400
3.50	0.0	0.0	0.0	100.0	3.500	400
4.30	0.0	0.0	0.0	100.0	3.500	400
4.40	0.0	0.0	95.0	5.0	4.000	400
5.00	0.0	0.0	95.0	5.0	4.000	400

LC-MS data were acquired using the "Formic acid-Standard" method unless otherwise noted.

Scheme 1: Preparation of amine intermediates

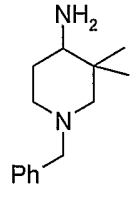




1-Benzyl-3-methyl-piperidin-4-ylamine (1)

To a solution of 1-benzyl-3-methyl-piperidin-4-one (2.04 g, 10 mmol) in EtOH (20 mL), was added pyridine (20 mL, 0.25 mol) and hydroxylamine hydrochloride (0.70 g, 10 mmol). After being stirred at 90 °C overnight, the resultant solution was concentrated *in vacuo* to give the crude product 1-benzyl-3-methyl-piperidin-4-one oxime. LCMS *m/z*: 219 $(M + H)^+$. This material was used without further purification.

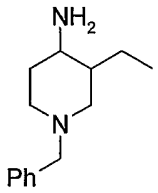
To a 25 °C solution of 1-benzyl-3-methyl-piperidin-4-one oxime in anhydrous THF (20 mL) was added LAH (1.0 M solution THF), (15 mL, 15 mmol). After being stirred at 50 °C overnight, the resultant mixture was quenched with 20% KOH solution. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude mixture ((±)-*cis* : (±)-*trans* = 1:1) 1-benzyl-3-methyl-piperidin-4-ylamine (**1**). LCMS *m/z*: 205 $(M + H)^+$. This material was used without further purification.



(±)-1-Benzyl-3,3-dimethyl-piperidin-4-one (2)

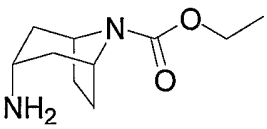
To a solution of 1-benzyl-3-methyl-piperidin-4-one (7.0 g, 34 mmol) and MeI (2.4 mL) in THF (100 mL) was added NaOt-Bu (4.2 g, 44 mmol) at 0 °C. The reaction was slowly allowed to warm to room temperature and stirred overnight. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to

give the crude product. Flash column chromatography (Hexane/EtOAc, gradient) of the residue gave 1-benzyl-3,3-dimethyl-piperidin-4-one, which was converted into 1-benzyl-3,3-dimethyl-piperidin-4-ylamine (**2**) using the same procedure as in Scheme 1-1. LCMS *m/z* : 220 $(M + H)^+$. This material was used without further purification.



1-Benzyl-3-ethyl-piperidin-4-one (3)

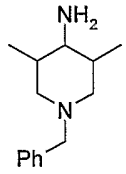
To a -78 °C solution of 1-benzyl-piperidin-4-one (3.79 g, 20 mmol) in anhydrous THF (20 mL) was added lithium hexamethyldisilazide (21 mL, 21 mmol of a 1.0 M solution in THF). After being stirred at -78 °C for 30 min, a solution of iodoethane (1.7 mL, 21 mmol) in THF (5 mL) was added to the reaction mixture. The resultant solution was stirred at 25°C for 2h and quenched with water. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product. The crude material was purified by flash column chromatography (hexane/EtOAc) to provide 0.51 g (11.5% yield) of 1-benzyl-3-ethyl-piperidin-4-one, which was converted into 1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) using the same procedure as in Scheme 1-1. ((±)-*cis* : (±)-trans = 1:1) LCMS *m/z* : 219 $(M + H)^+$. This material was used without further purification.



***cis*-3-Amino-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (4)**

The titled compound was made following the procedure in Scheme 1-1. The oxime (prepared as detailed in Scheme 1-1) (2.5 g) was dissolved in MeOH (10 mL) and AcOH (2 mL) and PtO_2 (100 mg) were added at the resultant mixture stirred at room temperature. The reaction mixture was shaken for 2 days at 60 psi under an atmosphere of H_2. The resultant solution was filtered and concentrated to give the

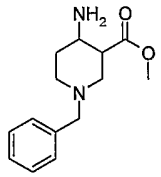
crude product of racemic 3-amino-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester. It was used without further purification.



1-Benzyl-3,5-dimethyl-piperidin-4-ylamine (5)

To a -78 °C solution of 1-benzyl-3-methyl-piperidin-4-one (4.06 g, 20 mmol) in anhydrous THF (20 mL) was added lithium hexamethyldisilazide (21 mL, 21 mmol of a 1.0 M solution THF). After being stirred at -78 °C for 30 min, a solution of iodomethane (1.31 mL, 21 mmol) in THF (5 mL) was added into the reaction mixture. The resultant solution was stirred at 25 °C for 2h and quenched with water. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product. The crude material was purified by flash column chromatography (hexane/EtOAc) to provide 1.37 g (31.5% yield) of 1-benzyl-3,5-dimethyl-piperidin-4-one.

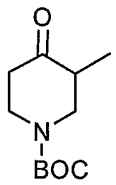
Following the same procedure as in Scheme 1-1, the crude product 1-benzyl-3,5-dimethyl-piperidin-4-ylamine (**5**) was prepared as a mixture of diastereomers. LCMS *m/z*: 219 $(M + H)^+$. This material was used without further purification.



4-Amino-1-benzyl-piperidine-3-carboxylic acid methyl ester (6)

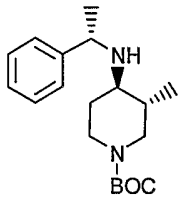
To a 25 °C solution of 1-benzyl-4-oxo-piperidine-3-carboxylic acid methyl ester hydrochloride (2.97 g, 10 mmol) in MeOH (10 mL) was added MP-Carbonate (12 g, 30 mmol, 2.54 mmol/g). After shaking at 25 °C for 1h, the solution was filtered. To the resultant solution was added ammonium acetate (7.71 g, 100 mmol). After stirring at 65 °C overnight, sodium cyanoborohydride (610 mg, 10 mmol) was added

into the resultant mixture and the mixture further stirred for 2h at 50 °C. The solution was then concentrated *in vacuo to* give a solid. The resultant solid was dissolved in water (100 mL) and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product 4-amino-1-benzyl-piperidine-3-carboxylic acid methyl ester (**6**) as a mixture of diastereomers. LCMS showed *m/z*: 249 $(M + H)^+$. This material was used without further purification.



(±)-3-Methyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester

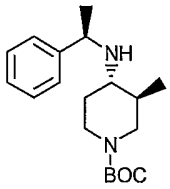
1-Benzyl-3-methyl-piperidin-4-one (6.5 g, 32.0 mmol) was dissolved in methanol (30 mL). Di-*tert*-butyl dicarbonate (10.46 g, 48.0 mmol) was added followed by palladium hydroxide (20%, 100 mg) and the reaction shaken overnight at 55 psi under a hydrogen atmosphere. The reaction was filtered and concentrated *in vacuo* to give a clear oil. Flash column chromatography (75:25 hexanes/ethyl acetate) afforded the title compound as a white solid. Wt.: 5.5 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.25 (m, 1H), 2.84 (m, 1H), 2.53 (m, 1H), 2.43 (m, 2H), 1.50 (s, 9H), 1.05 (d, 3H).



(*3R, 4R*)-3-methyl-4-(1-(*S*)-phenyl-ethylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

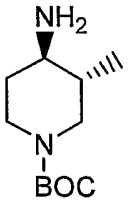
(±)-3-Methyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (5.4 g, 25.3 mmol) was dissolved in dichloromethane (75 mL). *S*-(-)-□-Methylbenzylamine (3.1 g, 3.2 mL, 25.3 mmol) was added followed by sodium triacetoxyborohydride (10.7 g, 50.6 mmol). The reaction was stirred at room temperature overnight. LC/MS analysis revealed four components, with only one component clearly separated. The reaction

was diluted with dichloromethane (150 mL) and extracted water (2x), brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to afford a white foam that was purified by flash column chromatography (84.5:15:0.5 dichloromethane:acetonitrile:NH_4OH) to afford a clear oil. This material was rechromatographed (89.5:10:0.5 dichloromethane:acetonitrile:NH_4OH) to afford the title compound as a clear oil. Wt.: 820 mg (10%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.22 (m, 2H), 3.85 (m, 3H), 2.68 (m, 1H), 2.46 (m. 1H), 2.17 (m, 1H), 1.67 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H), 1.08 (m, 2H), 0.97 (d, 3H); LC/MS *m/z* 319 $(M + H)^+$.



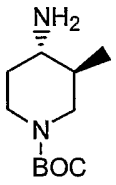
(3S, 4S)-3-methyl-4-(1-(*R*)-phenyl-ethylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

(±)-3-Methyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (5.4 g, 25.3 mmol) was dissolved in dichloromethane (75 mL). *R*-(+)-□-Methylbenzylamine (3.1 g, 3.2 mL, 25.3 mmol) was added followed by sodium triacetoxyborohydride (10.7 g, 50.6 mmol). The reaction was stirred overnight at room temperature. LC/MS analysis revealed four components, with only one component clearly separated. The reaction was diluted with dichloromethane (150 mL) and extracted twice with water, once with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a white foam that was purified by flash column chromatography (84.5:15:0.5 CH_2Cl_2:acetonitrile:NH_4OH) to afford a clear oil. The material was rechromatographed (89.5:10:0.5 CH_2Cl_2:acetonitrile:NH_4OH) to afford the title compound as a clear oil. Wt.: 547 mg (7%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.22 (m, 2H), 3.85 (m, 3H), 2.68 (m, 1H), 2.46 (m. 1H), 2.17 (m, 1H), 1.67 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H), 1.08 (m, 2H), 0.97 (d, 3H); LC/MS *m/z* 319 $(M + H)^+$.



(*3R, 4R*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (7)

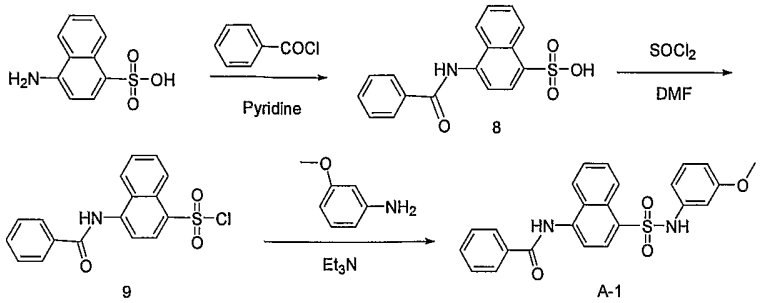
(3R, 4R)-3-Methyl-4-(1-(*S*)-phenyl-ethylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (810 mg, 2.55 mmol) was dissolved in methanol (15 mL). Palladium hydroxide (20%, 100 mg) was added and the mixture was shaken under a hydrogen atmosphere overnight at 55 psi. The reaction was filtered and concentrated *in vacuo* to give the title compound as a clear oil. Wt.: 500 mg (92%). NMR (300 MHz, $CDCl_3$) δ 4.06 (m, 1H), 3.96 (m, 1H), 2.73 (m, 1H), 2.34 (m, 2H), 1.77 (m, 1H), 1.43 (s, 9H), 1.27 (m, 2H), 0.94 (d, 3H); LC/MS *m/z* 215 $(M + H)^+$.



***(3S, 4S)*-4-amino-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (single enantiomer, absolute configuration undetermined)**

(3S, 4S)-3-Methyl-4-(1-(*R*)-phenyl-ethylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (510 mg, 1.60 mmol) was dissolved in methanol (15 mL). Palladium hydroxide (20%, 100 mg) was added and the mixture was shaken under a hydrogen atmosphere overnight at 55 psi. The reaction was filtered and concentrated *in vacuo* to provide the title compound as a clear oil. Wt.: 320 mg (88%). NMR (300 MHz, $CDCl_3$) δ 4.06 (m, 1H), 3.96 (m, 1H), 2.73 (m, 1H), 2.34 (m, 2H), 1.77 (m, 1H), 1.43 (s, 9H), 1.27 (m, 2H), 0.94 (d, 3H); LC/MS *m/z* 215 $(M + H)^+$.

Scheme 2

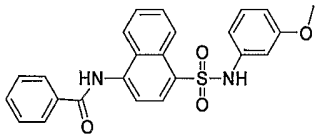


4-Benzoylamino-naphthalene-1-sulfonic acid (8)

To a solution of 4-amino-naphthalene-1-sulfonic acid (2.3 g, 10.0 mmol) in pyridine (15 mL), was added benzoyl chloride (1.4 mL, 12.0 mmol) and the resultant solution was heated at 100 °C and stirred overnight. The solvent was removed *in vacuo* and the crude material was recrystallized from MeOH (2x) to give the pyridinium salt of 4-benzoylamino-naphthalene-1-sulfonic acid (2.0 g) as a gray colored solid. ^{1}H NMR (300 MHz, DMSO) δ 8.92 (m, 3H), 8.60 (t, 1H), 8.00 (m, 6H), 7.55 (m, 6H); LC/MS *m/z* 327 $(M - H)^-$.

4-Benzoylamino-naphthalene-1-sulfonyl chloride (9)

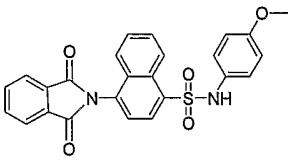
To a solution of the pyridinium salt of 4-benzoylamino-napthalene-1-sulfonic acid (2.4 g, 5.9 mmol) in DMF (10 mL), was added thionyl chloride (0.6 mL, 8.8 mmol). The resultant solution was stirred at 25 °C for 3 hours. The reaction mixture was quenched by pouring into ice water and filtered to give the title compound (1.8 g) a pale white solid. This material was used without further purification.^{1}H NMR (300 MHz, DMSO) δ 8.88 (d, 1H), 8.09 (d, 2H), 7.97 (d, 2H), 7.55 (m, 6H).



***N*-[4-(3-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (A-1)**

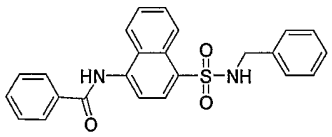
To a solution of 4-benzoylamino-naphthalene-1-sulfonyl chloride (320 mg, 0.93 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.26 mL, 1.85 mmol) and *m*-anisidine (137 mg, 1.11 mmol). The resultant solution was stirred at 25 °C

overnight. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to provide the crude product as yellow viscous oil. HPLC purification of the residue gave the title compound (190 mg) as a pale white solid. ^1H NMR (300MHz, DMSO) δ 8.72 (d, 1H), 8.26 (d, 1H), 8.15 (d, 1H), 8.02 (d, 2H), 7.78 (d, 1H), 7.60 (m, 5H), 7.00 (t, 1H), 6.55 (m, 2H), 6.46 (d, 1H), 3.56 (s, 3H); LC/MS m/z 433 $(M + H)^+$.



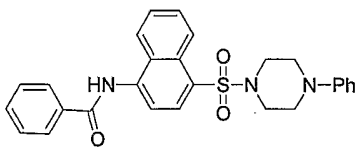
4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (4-methoxyphenyl)-amide (A-2)

The title compound was made following the general procedure detailed in Scheme 2, substituting phthalic anhydride for benzoyl chloride and benzylamine for *m*-anisidine. ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H), 8.20 (d, 1H), 8.02 (m, 2H), 7.87 (m, 2H), 7.66 (m, 3H), 7.42 (d, 1H), 6.86 (d, 2H), 6.69 (d, 2H), 3.72 (s, 3H); LC/MS *m/z* 459 $(M + H)^+$.



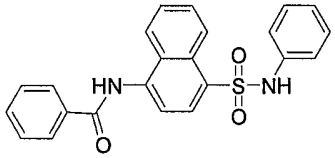
***N*-(4-Benzylsulfamoyl-naphthalen-1-yl)-benzamide (A-3)**

The title compound was made following the general procedure in Scheme 2, substituting benzylamine for *m*-anisidine. ^1H NMR (300 MHz, DMSO) δ 8.71 (d, 1H), 8.18 (m, 2H), 8.11 (d, 2H), 7.90 (d, 1H), 7.60 (m, 5H), 7.40 (m, 5H), 4.05 (s, 2H); LC/MS *m/z* 417 $(M + H)^+$.



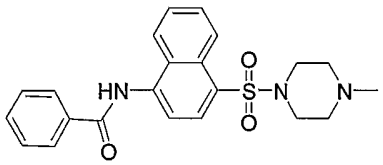
***N*-[4-(4-Phenyl-piperazine-1-sulfonyl)-naphthalen-1-yl]-benzamide (A-5)**

The title compound was made following general procedure in Scheme 2, substituting 1-phenyl-pyrazine for *m*-anisidine.^{1}H NMR (300MHz, DMSO) δ 8.68 (d, 1H), 8.22 (d, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.60 (m, 5H), 7.15 (m, 2H), 6.85 (d, 2H), 6.72 (t, 1H), 3.17 (m, 4H), 3.11 (m, 4H); LC/MS m/z 472 $(M + H)^+$.



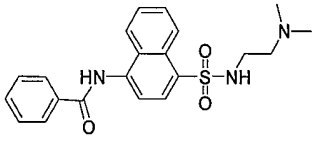
***N*-(4-Phenylsulfamoyl-naphthalen-1-yl)-benzamide (A-7)**

The title compound was made following the general procedure in Scheme 2, substituting aniline for *m*-anisidine. ^{1}H NMR (300MHz, MeOD) δ 8.76 (d, 1H), 8.16 (d, 1H), 8.05 (d, 1H), 7.96 (d, 2H), 7.60 (m, 6H), 7.00 (m, 5H), LC/MS m/z 403 $(M + H)^+$.



***N*-[4-(4-Methyl-piperazine-1-sulfonyl)-naphthalen-1-yl]-benzamide (A-8)**

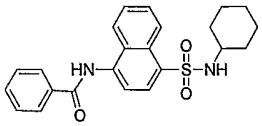
The title compound was made following general procedure in Scheme 2, substituting 1-methyl-pyrazine for *p*-anisidine. ^{1}H NMR (300MHz, MeOD) δ 8.74 (d, 1H), 8.37 (d, 1H), 8.15 (m, 2H), 8.08 (d, 2H), 7.86 (d, 1H), 7.55 (m, 5H), 3.36 (m, 4H), 2.86 (m, 4H), 2.50 (s, 3H); LC/MS m/z 410 $(M + H)^+$.



***N*-[4-(2-Dimethylamino-ethylsulfamoyl)-naphthalen-1-yl]-benzamide (A-9)**

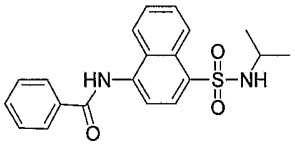
The title compound was made following general procedure in Scheme 2, substituting 2-dimethylamino-ethylamine for *m*-anisidine. ^{1}H NMR (300MHz, MeOD) δ 8.74

(d, 1H), 8.45 (s, 1H), 8.30 (d, 1H), 8.22 (d, 1H), 8.08 (d, 2H), 7.85 (d, 1H), 7.65 (m, 5H), 3.10 (m, 4H), 2.74 (s, 6H); LC/MS m/z 398 $(M + H)^+$.



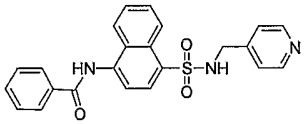
***N*-(4-Cyclohexylsulfamoyl-naphthalen-1-yl)-benzamide (A-10)**

The title compound was made following general procedure in Scheme 2, substituting cyclohexylamine for *m*-anisidine. ^{1}H NMR (300MHz, MeOD) δ 8.80 (d, 1H), 8.33 (d, 1H), 8.20 (d, 1H), 8.08 (d, 2H), 7.85 (d, 1H), 7.66(m, 5H), 3.05 (br s, 1H), 1.60 (m, 3H), 1.48 (m, 1H), 1.35 (m, 1H), 1.25 (m, 5H); LC/MS m/z 409 $(M + H)^+$.



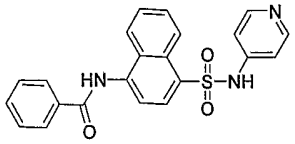
***N*-(4-Isopropylsulfamoyl-naphthalen-1-yl)-benzamide (A-11)**

The title compound was made following general procedure in Scheme 2, substituting isopropylamine for *m*-anisidine.^{1}H NMR (300MHz, DMSO) δ 8.69 (d, 1H), 8.19 (d, 2H), 8.09 (d, 2H), 8.02 (d, 2H), 7.81 (d, 1H), 7.60 (m, 5H), 3.07 (m, 1H), 0.88 (m, 6H); LC/MS m/z 369 $(M + H)^+$.



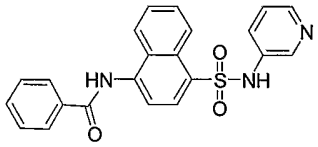
***N*-{4-[(Pyridin-4-ylmethyl)-sulfamoyl]-naphthalen-1-yl}-benzamide (A-13)**

The title compound was made following general procedure in Scheme 2, substituting 4-aminomethyl pyridine for *m*-anisidine. ^{1}H NMR (300MHz, MeOD) δ 8.76 (d, 1H), 8.22 (d, 2H), 8.14 (d, 1H), 8.09 (d, 2H), 7.74 (d, 1H), 7.60 (m, 5H), 7.08 (d, 2H), 4.10 (s, 2H); LC/MS m/z 418 $(M + H)^+$.



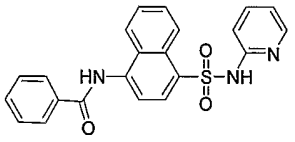
***N*-[4-(Pyridin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (A-14)**

The title compound was made following general procedure in Scheme 2, substituting 4-aminopyridine for *m*-anisidine. ^{1}H NMR (300MHz, DMSO) δ 8.83 (d, 1H), 8.26 (d, 1H), 8.08 (m, 3H), 7.93 (d, 2H), 7.75 (d, 1H), 7.60 (m, 5H), 6.91 (d, 2H); LC/MS m/z 404 $(M + H)^+$.



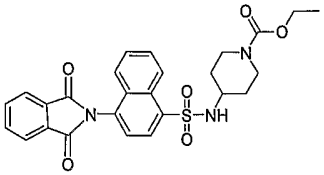
***N*-[4-(Pyridin-3-ylsulfamoyl)-naphthalen-1-yl]-benzamide (A-16)**

The title compound was made following general procedure in Scheme 2, substituting 3-aminopyridine for *m*-anisidine. ^{1}H NMR (300MHz, DMSO) δ 8.85 (d, 1H), 8.34 (d, 1H), 8.10 (m, 3H), 7.82 (m, 1H), 7.76 (d, 1H), 7.58 (m, 6H), 7.18 (d, 1H), 6.71 (t, 1H); LC/MS m/z 404 $(M + H)^+$.



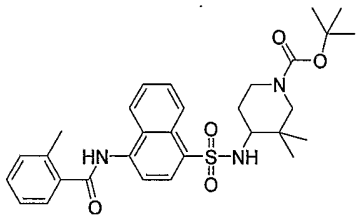
***N*-[4-(Pyridin-3-ylsulfamoyl)-naphthalen-1-yl]-benzamide (A-17)**

The title compound was made following the general procedure in Scheme 2, substituting 2-aminopyridine for *m*-anisidine. ^{1}H NMR (300MHz, DMSO) δ 8.76 (d, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 8.10 (d, 2H), 8.06 (d, 2H), 7.65 (m, 6H), 7.41 (d, 1H), 7.10 (dd, 1H); LC/MS m/z 404 $(M + H)^+$.



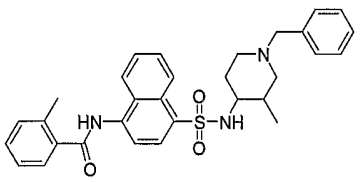
4-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (A-18)

The title compound was made following the general procedure in Scheme 2, substituting phthalic anhydride for benzoyl chloride, and 4-amino-piperidine-1-carboxylic acid ethyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.71 (d, 1H), 8.39 (d, 1H), 8.03 (m, 2H), 7.89 (m, 2H), 7.58 (m, 4H), 5.10 (br s, 1H), 4.07 (q, 2H), 3.94 (m, 2H), 3.36 (br s, 1H), 3.08 (m, 1H), 2.78 (m, 2H), 1.75 (m, 2H), 1,33 (m, 2H), 1.21 (t, 3H); LC/MS *m/z* 508 $(M + H)^+$.



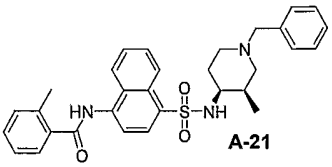
(±)-3,3-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester (A-19)

The title compound was made following general procedure in Scheme 2, substituting 2-methyl-benzoyl chloride for benzoyl chloride and 4-amino-3,3-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine.^{1}H NMR (300 MHz, MeOD) δ 8.83 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.40 (m, 3H), 3.76 (d, 1H), 3.55 (d, 1H), 2.97 (m, 1H), 2.54 (s, 6H); 1.38 (s, 3H), 1.14 (m, 1H), 0.77 (s, 3H), 0.61 (s, 3H); LC/MS *m/z* 552 $(M + H)^+$.

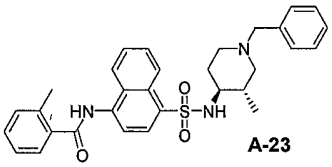


***N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-20)**

The title compounds (~1:1 mixture) were made following general procedure in Scheme 2, substituting 2-methyl-benzoyl chloride for benzoyl chloride and 4-amino-1-benzyl-3-methyl-piperidine for *m*-anisidine. LC/MS *m/z* 528 $(M + H)^+$.



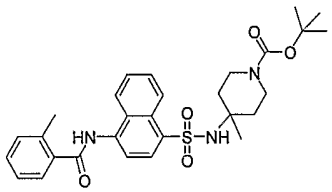
A-21



A-23

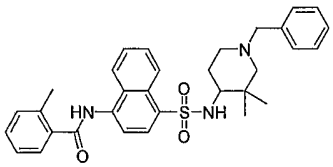
(±)-*cis*-*N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-21) and (±)-trans-*N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-23)

The title compounds were made following general procedure in Scheme 2, substituting 2-methyl-benzoyl chloride for benzoyl chloride and 4-amino-1-benzyl-3-methyl-piperidine for *m*-anisidine. Flash column chromatography of the mixture gave both title compounds respectively. **A-21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, 1H), 8.35 (m, 2H), 8.11 (s, 1H), 7.93 (d, 1H), 7.65 (m, 3H), 7.44 (m, 1H), 7.33 (d, 2H), 7.23(m, 5H), 4.70 (d, 1H), 3.38 (q, 2H), 3.29 (m, 1H), 2.58 (s, 3H), 2.25 (br s, 2H), 1.75 (m, 1H), 1.48 (m, 2H), 0.97 (d, 1H); 0.65 (d, 3H); LC/MS *m/z* 528 $(M + H)^+$. **A-23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 1H), 8.32 (s, 1H), 8.25 (s, 2H), 7.93 (d, 1H), 7.60 (m, 3H), 7.40 (m, 1H), 7.25 (m, 6H), 4.78 (d, 1H), 3.38 (q, 2H), 2.72 (m, 2H), 2.55 (s, 3H), 2.24 (m, 1H), 1.86 (m, 1H), 1.63 (m, 3H), 1.35 (m, 2H); 0.57 (d, 3H); LC/MS *m/z* 528 $(M + H)^+$.



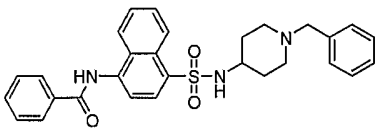
4-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (A-22)

The title compound was made following general procedure in Scheme 2, substituting 2-methyl-benzoyl chloride for benzoyl chloride and 4-amino-4-methyl-piperidine-1-carboxylic acid tert-butyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.380 (m, 2H), 8.19 (d, 1H), 7.95 (d, 2H), 7.68 (m, 3H), 7.44 (m, 1H), 7.35 (m, 2H), 4.78 (s, 1H), 3.40 (m, 2H), 3.03 (m, 2H), 2.68 (s, 3H), 1.72 (m, 2H), 1.470 (m, 2H), 1.38 (s, 9H), 1.18 (s, 3H); LC/MS *m/z* 524 $(M + H)^+$.



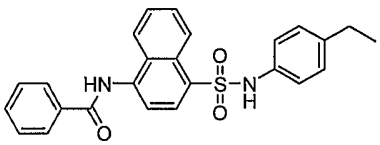
(±)-*N*-[4-(1-Benzyl-3,3-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-24)

The title compound was made following general procedure in Scheme 2, substituting 2-methyl-benzoyl chloride for benzoyl chloride and 4-amino-1-benzyl-3,3-dimethyl-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.77 (d, 1H), 8.22 (dd, 2H), 7.91 (d, 1H), 7.70 (m, 4H), 7.35 (m, 3H), 7.22 (m, 5H), 3.30 (q, 2H), 2.67 (m, 1H), 2.57 (m, 1H), 2.47 (s, 3H), 2.25 (d, 1H), 1.68 (t, 1H), 1.56 (d, 1H), 1.47 (m, 1H), 1.04 (m, 1H); 0.85 (s, 3H), 0.45(s, 3H); LC/MS *m/z* 542 $(M + H)^+$.



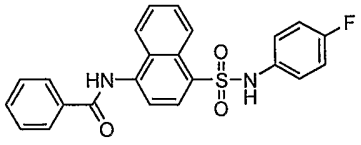
***N*-[4-(1-Benzyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (A-25)**

The title compound was prepared following the general procedure in Scheme 2, substituting 4-amino-1-benzyl-piperidine for *m*-anisidine.



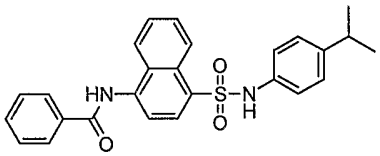
***N*-[4-(4-Ethyl-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (A-26)**

The title compound was prepared following the general procedure in Scheme 2, substituting 4-ethyl-phenylamine for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.76 (d, 1H), 8.21 (d, 1H), 8.16 (d, 1H), 8.07 (s, 1H), 8.04 (m, 1H), 7.78 (d, 1H), 7.76 (m, 5H), 6.94 (m, 4H), 2.4 (m, 2H), 1.03 (t, 3H); LC/MS $(M + H)^+$ *m/z* 431.



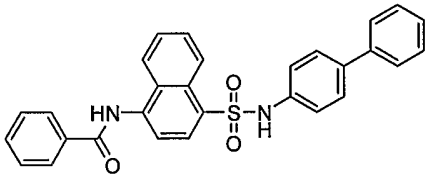
2- Methyl-penta-2,4-dienoic acid [4-(4-fluoro-phenylsulfamoyl)-naphthalen-1-yl]-amide (A-27)

The title compound was prepared following the general procedure in Scheme 2, substituting 4-fluoro-phenyl-amine for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.74 (d, 1H), 8.18 (m, 3H), 8.06 (d, 2H), 7.67 (m, 7H), 7.0 (m, 4H); LC/MS $(M + H)^+$ *m/z* 421.



***N*-[4-(4-Isopropyl-phenylsulfamoyl)-naphthalene-1-yl]- benzamide (A-28)**

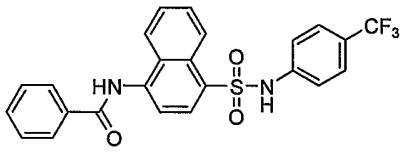
The title compound was prepared following the general procedure in Scheme 2, substituting 4-isopropyl-phenylamine for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.76 (d, 1H), 8.25 (d, 1H), 8.18 (d, 1H), 8.05 (m, 2H), 7.8 (d, 1H), 7.65 (m, 5H), 6.95 (m, 4H), 2.7 (m, 1H), 1.05 (d, 6H); LC/MS $(M + H)^+$ *m/z* 445.



***N*-[Biphenyl-4-yl sulfamoyl)-naphthalen-1-yl]-benzamide (A-29)**

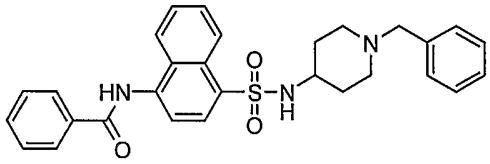
The title compound was prepared following the general procedure in Scheme 2, substituting biphenyl-4-yl amine for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.79 (d, 1H), 8.31 (d, 1H), 8.18 (d, 1H), 8.05 (s, 1H), 8.03 (s, 1H), 7.82 (d, 1H), 7.76

(m, 1H), 7.6 (m, 8H), 7.36 (t, 2H), 7.26 (m, 1H), 7.13 (s, 1H), 7.11 (s, 1H); LC/MS $(M + H)^+$ *m/z* 479.



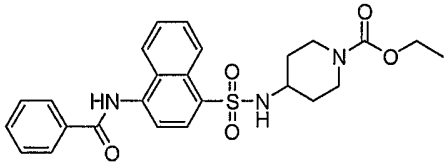
***N*-[4-(4-Trifluoromethyl-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (A-30)**

The title compound was prepared following the general procedure in Scheme 2, substituting 4-trifluoromethyl-phenylamine for *m*-anisidine. ^{1}H NMR (300 MHz, DMSO) δ 8.27 (d, 1H), 8.11 (d, 1H), 8.08 (s, 1H), 8.05 (d, 2H), 7.77 (d, 1H), 7.58 (m, 5H), 7.42 (d, 2H), 7.12 (d, 2H); LC/MS $(M + H)^+$ *m/z* 469.



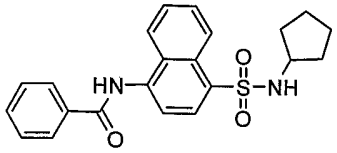
***N*-[4-(1-Benzyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (A-31)**

The title compound was prepared following the general procedure in Scheme 2, substituting 1-benzyl-piperidin-4-yl amine for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.73 (d, 1H), 8.30 (d, 1H), 8.18 (d, 1H), 8.09 (s, 1H), 8.07 (m, 1H), 7.80 (d, 1H), 7.65 (m, 5H), 7.42 (m, 5H), 4.17 (s, 2H), 3.34 (m, 2H), 2.92 (m, 2H), 1.86 (d, 3H), 1.64 (m, 2H); LC/MS $(M + H)^+$ *m/z* 500.



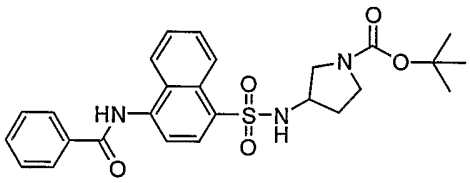
4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (A-34)

The title compound was prepared following the general procedure in Scheme 2, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 1H), 8.11 (m, 1H), 8.09 (m, 1H), 8.07 (m, 1H), 7.82 (d, 1H), 7.65 (m, 5H), 4.03 (m, 2H), 3.82 (m, 2H), 2.78 (m, 2H), 1.56 (m, 2H), 1.28 (m, 2H), 1.19 (t, 3H); LC/MS $(M + H)^+$ *m/z* 480.



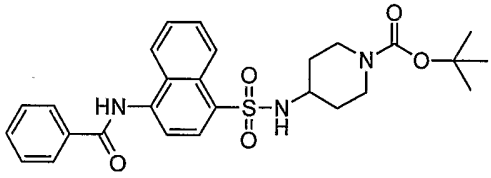
***N*-(4-Cyclopentysulfamoyl-naphthalen-1-yl)-benzamide (A-35)**

The title compound was prepared following the general procedure in Scheme 2, substituting cyclopentylamine for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.29 (d, 1H), 8.19 (d, 1H), 8.10 (m, 1H), 8.07 (m, 1H), 7.82 (d, 1H), 7.65 (m, 5H), 3.51 (m, 1H), 1.56 (m, 4H), 1.34 (m, 5H); LC/MS $(M + H)^+$ *m/z* 395.



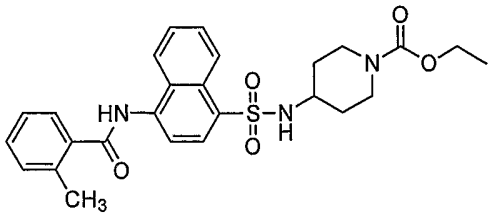
3-(4-Benzoylamino-naphthalene-1-sulfonylamino)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (A-37)

The title compound was prepared following the general procedure in Scheme 2, substituting 3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.79 (d, 1H), 8.35 (d, 1H), 8.25 (d, 1H), 8.11 (d, 2H), 7.89 (m, 1H), 7.69 (m, 5H), 3.78 (m, 1H), 3.03 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.41 (d, 9H); LC/MS $(M + H)^+$ *m/z* 496.



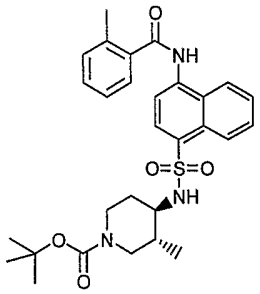
4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (A-38)

The title compound was prepared following the general procedure in Scheme 2, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 1H), 8.19 (d, 1H), 8.09 (m, 1H), 8.07 (m, 1H), 7.82 (d, 1H), 7.65 (m, 5H), 3.78 (m, 2H), 2.73 (m, 2H), 1.52 (m, 3H), 1.39 (s, 9H), 1.28 (m, 2H); LC/MS $(M + H)^+$ *m/z* 510.



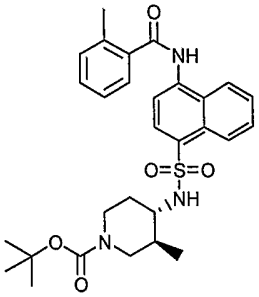
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (A-40)

The title compound was prepared following the general procedure in Scheme 2, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *m*-anisidine and 2-methyl benzoyl chloride for benzoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (d, 1.H), 8.31 (d, 1H), 8.23 (d, 1H), 7.92 (d, 1H), 7.72 (m, 3H), 7.39 (m, 3H), 4.04 (q, 2H), 3.83 (m, 2H), 3.25 (m, 1H), 2.78 (m, 2H), 2.55 (s, 3H), 1.56 (m, 2H), 1.28 (m, 2H), 1.18 (t, 3H); LC/MS $(M + H)^+$ *m/z* 496.



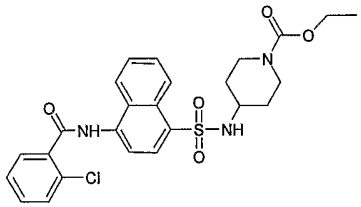
***(3R, 4R)*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (A-41)**

The title compound was prepared according to the general procedure in Scheme 2, substituting *(3R, 4R)*-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine, and 2-methylbenzoyl chloride for benzoyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.69 (d, 1H), 8.40 (m, 1H), 8.32 (m, 1H), 8.12 (s, 1H), 7.69 (m, 1H), 7.63 (m, 2H), 7.43 (m, 1H), 7.32 (m, 2H), 4.48 (d, 1H), 3.87 (m, 2H), 2.82 (m, 1H), 2.57 (s, 3H), 2.28 (m, 1H), 1.64 (m, 1H), 1.17 (m, 2H), 0.58 (m, 3H); LC/MS *m/z* 538 $(M + H)^+$.



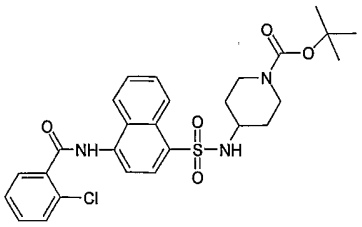
(3S, 4S)-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (A-42)

The title compound was prepared according to the general procedure in Scheme 2, substituting (*3S, 4S*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine, and 2-methylbenzoyl chloride for benzoyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ8.69 (d, 1H), 8.40 (m, 1H), 8.32 (m, 1H), 8.12 (s, 1H), 7.69 (m, 1H), 7.63 (m, 2H), 7.43 (m, 1H), 7.32 (m, 2H), 4.48 (d, 1H), 3.87 (m, 2H), 2.82 (m, 1H), 2.57 (s, 3H), 2.28 (m, 1H), 1.64 (m, 1H), 1.17 (m, 2H), 0.58 (m, 3H); LC/MS *m/z* 538 $(M + H)^+$.



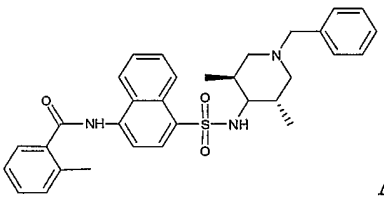
4-[4-(2-Chloro-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (A-43)

The title compound was made following general procedure in Scheme 2, substituting 4-(2-chloro-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine and substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 2H), 7.98 (d, 2H), 7.73 (m, 3H), 7.53 (m, 3H), 4.02 (q, 2H), 3.72 (d, 2H), 3.42 (m, 1H), 2.75 (m, 2H), 1.55 (m, 2H), 1.25 (m, 2H), 1.15 (t, 3H); LC/MS *m/z* 516 $(M + H)^+$

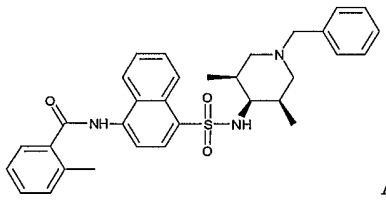


4-[4-(2-Chloro-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester (A-44)

The title compound was made following general procedure in Scheme 2, substituting 4-(2-chloro-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine and substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *m*-anisidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (m, 2H), 8.36 (m, 2H), 8.08 (d, 1H), 7.90 (m, 1H), 7.67 (m, 2H), 7.48 (m, 3H), 4.80 (d, 1H), 3.82 (m, 2H), 3.25 (m, 1H), 2.70 (t, 2H), 1.65 (m, 3H), 1.35 (s, 9H), 1.20 (m, 2H); LC/MS *m/z* 544 $(M + H)^+$



A-45

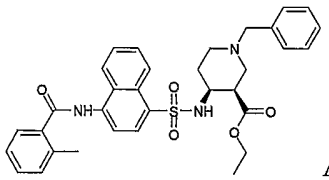


A-46

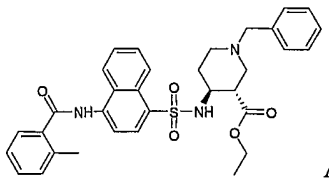
(±)-(*cis*, *trans*)-*N*-[4-(1-Benzyl-3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-45) and (±)-(*cis*, *cis*)-*N*-[4-(1-Benzyl-3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-46)

The title compounds were made following general procedure in Scheme 2, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine and substituting 1-benzyl-3,5-dimethyl-piperidin-4-ylamine **6** for *m*-anisidine. After flash column separation, **A-45** and **A-46** were obtained. **A-45**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77(d, 1H), 8.36 (m, 2H), 8.10 (s, 1H), 7.92 (d, 1H), 7.66 (m, 3H), 7.44 (m, 1H), 7.34 (m, 1H), 7.22 (m, 6H), 4.65 (d, 1H), 3.34 (dd, 2H), 2.90 (m, 1H), 2.59 (s, 3H), 2.35 (m, 1H), 2.05 (d, 1H), 1.70 (s, br, 3H), 1.57 (s, 1H), 0.75 (d, 3H), 0.60 (d, 3H); LC/MS *m/z* 543 $(M + H)^+$; **A-46**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25(d, 1H), 8.34

(m, 4H), 7.98 (d, 1H), 7.64 (m, 3H), 7.43 (m, 1H), 7.31 (m, 6H), 6.15 (d, 1H), 3.84 (s, 2H), 3.40 (d, 1H), 2.80 (d, 3H), 2.56 (s, 3H), 2.30 (t, 2H), 2.10 (s, br, 2H), 0.42 (d, 6H); LC/MS *m/z* 543 $(M + H)^+$



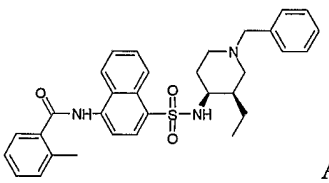
A-47



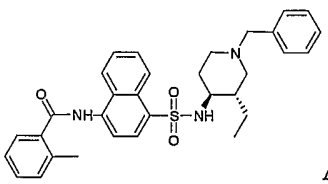
A-48

(±)-(*cis*)-1-Benzyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (A-47) and (±)-(*trans*)-1-Benzyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (A-48)

The title compounds were made following general procedure in Scheme 2, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine and substituting 4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester **5** for *m*-anisidine. After flash column separation, **A-47** and **A-48** were obtained. **A-47**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 1H), 8.32 (m, 2H), 8.30 (s, 1H), 7.88 (d, 1H), 7.64 (m, 3H), 7.42 (t, 1H), 7.32 (m, 2H), 7.20 (m, 5H), 6.18 (d, 1H), 3.85 (m, 2H), 3.45 (m, 1H), 3.25 (m, 2H), 3.00 (d, 1H), 2.65 (s, 1H), 2.55 (s, 3H), 2.35 (s, 1H), 1.80 (m, 3H), 1.42 (m, 1H), 1.00 (t, 3H); LC/MS *m/z* 586 $(M + H)^+$; **A-48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, 1H), 8.36 (m, 2H), 8.10 (s, 1H), 7.90 (d, 1H), 7.65 (m, 3H), 7.42 (t, 1H), 7.32 (m, 2H), 7.24 (m, 5H), 4.95 (d, 1H), 3.50 (m, 4H), 2.86 (d, 1H), 2.70 (m, 2H), 2.51 (s, 3H), 2.20 (t, 1H), 2.02 (t, 1H), 1.88 (m, 3H), 1.48 (m, 1H), 1.00 (t, 3H); LC/MS *m/z* 586 $(M + H)^+$



A-49

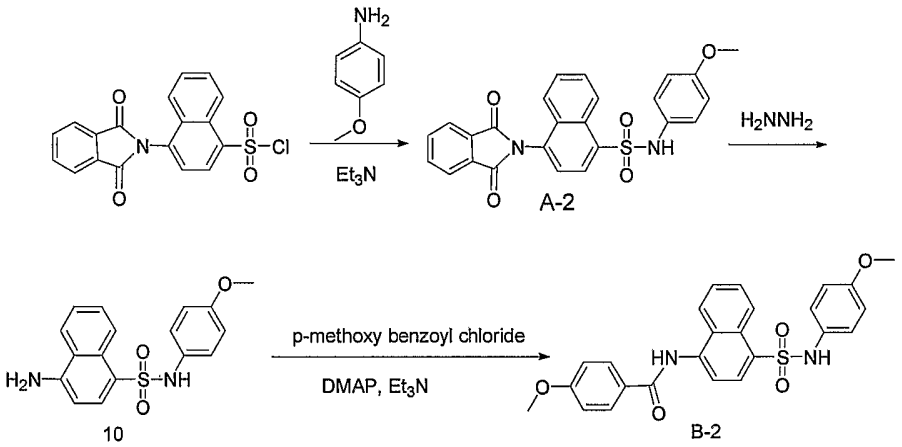


A-50

(±)-(*cis*)-*N*-[4-(1-Benzyl-3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-49) and (±)-(trans)-*N*-[4-(1-Benzyl-3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (A-50)

The title compounds were made following general procedure in Scheme 2, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine and substituting 1-benzyl-3-ethyl-piperidin-4-ylamine **3** for *m*-anisidine. After flash column separation and further HPLC purification, **A-49** and **A-50** formic acid salts were obtained. **A-49**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.42 (d, 1H), 8.18 (s, 1H), 8.00 (d, 2H), 7.65 (d, 1H), 7.30 (m, 3H), 7.05 (t, 1H), 6.95 (m, 8H), 5.30 (s, br, 1H), 3.50 (s, br, 1H), 3.20 (q, 2H), 3.08 (s, 1H), 2.21 (s, 3H), 2.05 (m, 3H), 1.20 (m, 3H), 0.60 (m, 2H), 0.05 (t, 3H); LC/MS *m/z* 542 $(M+H)^+$; **A-50**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 1H), 8.30 (m, 2H), 8.20 (s, 1H), 7.90 (d, 1H), 7.60 (m, 3H), 7.42 (t, 1H), 7.25 (m, 8H), 4.75 (d, 1H), 3.45 (dd, 2H), 2.85 (m, 2H), 2.60 (m, 1H), 2.55 (s, 3H), 1.85 (t, 1H), 1.75 (t, 1H), 1.40 (m, 4H), 0.85 (m, 1H), 0.55 (t, 3H); LC/MS *m/z* 542 $(M+H)^+$

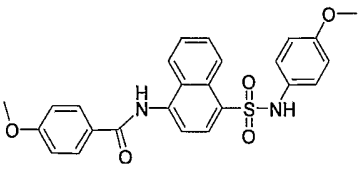
Scheme 3



4-Amino-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide (10)

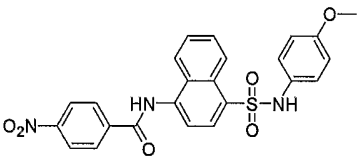
To a solution of sulfonamide (**A-2**) (0.75 g, 1.64 mmol) in methanol (10 mL) was added hydrazine (1mL). The resultant solution was stirred at 55 °C for 2 hr. A precipitate formed which was filtered and washed with a small amount of methanol. The filtrate was collected and solvent was removed *in vacuo* to give the title

compound as white solid (0.7 g). ^{1}H NMR (300 MHz, DMSO) δ 9.84 (br s, 1H), 8.55 (d, 1H), 8.16 (d, 1H), 7.80 (d, 1H), 7.60 (t, 1H), 7.47 (t, 1H), 6.82 (d, 2H), 6.71 (m, 3H), 6.53 (d, 1H), 3.58 (s, 3H); LC/MS *m/z* 329 $(M + H)^+$.



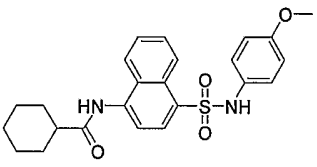
4-Methoxy-*N*-[4-(4-methoxy-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (B-2)

To a solution of naphthalenyl amine (**10**) (65 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added *p*-methoxybenzoyl chloride (45 uL, 0.24 mmol) and Et_3N (50 uL, 0.4 mmol). The resultant solution was stirred at 25 °C overnight. The solvent was removed *in vacuo* and the residue was purified using HPLC to give the title compound (30 mg) as pale yellow solid.. ^{1}H NMR (300MHz, MeOD) δ 8.73 (d, 1H), 8.08 (m, 4H), 7.70 (m, 3H), 7.10 (d, 2H), 6.90 (d, 2H), 6.70 (d, 2H), 3.84 (s, 3H), 3.60 (s, 3H); LC/MS m/z 463 $(M + H)^+$.



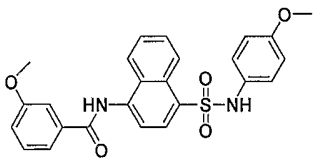
***N*-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-4-nitro-benzamide (B-3)**

The title compound was made following general procedure in scheme 3, substituting *p*-nitrobenzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 8.24 (d, 2H), 8.02 (m, 3H), 7.55 (d, 2H), 7.48 (m, 1H), 7.18 (d, 2H), 6.83 (d, 2H), 6.69 (d, 1H), 3.69 (s, 3H); LC/MS *m/z* 478 $(M + H)^+$.



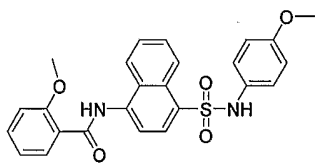
Cyclohexanecarboxylic acid [4-(4-methoxy-phenylsulfamoyl)-naphthalen-1-yl]-amide (B-4)

The title compound was made following general procedure in Scheme 3, substituting cyclohexyl carboxyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 10.28 (s, 1H), 10.05 (s, 1H), 8.74 (d, 1H), 8.25 (d, 1H), 8.08 (d, 1H), 7.85 (d, 1H), 7.70 (m, 2H), 6.86 (d, 2H), 6.67 (d, 2H), 3.60 (s, 3H), 2.60 (m, 1H), 1.50 (m, 10H); LC/MS m/z 439 $(M + H)^+$.



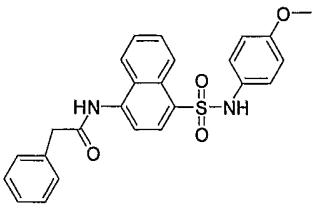
3-Methoxy-*N*-[4-(4-methoxy-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (B-5)

The title compound was made following general procedure in Scheme 3, substituting 3-methoxy-benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 10.67 (s, 1H), 10.32 (br s, 1H), 8.79 (d, 1H), 8.22 (d, 1H), 8.19 (s, 2H), 7.90 (d, 1H), 7.79 (d, 2H), 7.62 (t, 1H), 7.31 (m, 1H), 7.18 (t, 1H), 6.92 (d, 2H), 6.76 (d, 2H), 3.63 (s, 3H), 3.37 (s, 3H); LC/MS m/z 463 $(M + H)^+$.



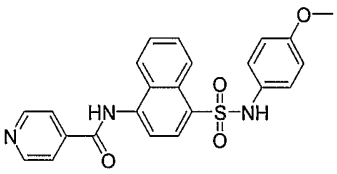
2-Methoxy-*N*-[4-(4-methoxy-phenylsulfamoyl)-naphthalen-1-yl]-benzamide (B-6)

The title compound was made following general procedure in Scheme 3, substituting 2-methoxy benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 10.60 (s, 1H), 10.2 (br s, 1H), 8.87 (d, 1H), 8.40 (d, 1H), 8.11 (s, 2H), 7.84 (d, 1H), 7.76 (d, 2H), 7.55 (t, 1H), 7.45 (d, 1H), 7.12 (t, 1H), 6.88 (d, 2H), 6.70 (d, 2H), 3.60 (s, 3H), 3.34 (s, 3H); LC/MS m/z 463 $(M + H)^+$.



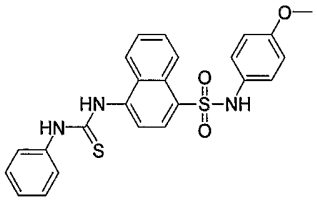
N-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-2-phenyl-acetamide (B-7)

The title compound was made following general procedure in Scheme 3, substituting phenylacetyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 10.30 (s, 1H), 10.18 (s, 1H), 8.67 (d, 1H), 8.24 (d, 1H), 8.05 (s, 1H), 7.84 (d, 1H), 7.66 (m, 2H), 7.30 (m, 5H), 6.82 (d, 2H), 6.67 (d, 2H), 3.81 (s, 2H), 3.55 (s, 3H), 3.29 (s, 3H); LC/MS m/z 447 $(M + H)^+$.



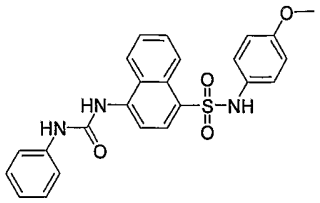
N-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-isonicotinamide (B-8)

The title compound was made following general procedure in Scheme 3, substituting isonicotinoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 8.82 (d, 2H), 8.78 (d, 1H), 8.22 (d, 1H), 8.17 (d, 1H), 7.98 (d, 2H), 7.80 (d, 2H), 7.72 (m, 1H), 6.92 (d, 2H), 6.74 (d, 2H), 3.62 (s, 3H); LC/MS m/z 434 $(M + H)^+$.



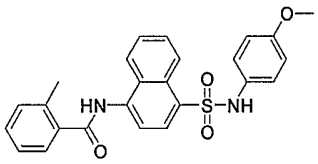
4-(3-Phenyl-thioureido)-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide (B-9)

The title compound was made following general procedure in Scheme 3, substituting phenyl isothionitrile for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 8.73 (d, 1H), 8.10 (d, 1H), 8.08 (d, 1H), 7.70 (m, 3H), 7.50 (d, 2H), 7.32 (t, 2H), 7.13 (t, 1H), 6.90 (d, 2H), 6.70 (d, 2H), 3.60 (s, 3H); LC/MS m/z 464 $(M + H)^+$.



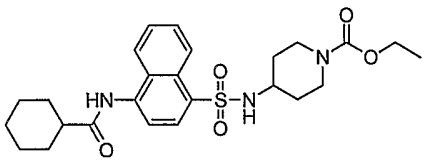
4-(3-Phenyl-ureido)-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide (B-10)

The title compound was made following general procedure in Scheme 3, substituting phenyl isocyanate for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300MHz, DMSO) δ 8.58 (d, 1H), 8.05 (m, 3H), 7.48 (m, 2H), 7.40 (d, 2H), 7.22 (m, 2H), 6.96 (t, 1H), 6.75 (d, 2H), 6.65 (d, 2H), 3.58 (s, 3H); LC/MS m/z 448 $(M + H)^+$.



***N*-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (B-11)**

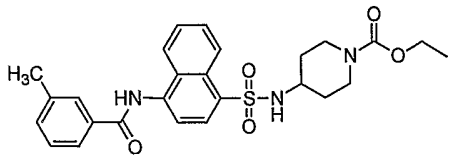
The title compound was made following general procedure in Scheme 3, substituting *o*-tolyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 8.75 (d, 1H), 8.24 (d, 1H), 8.14 (d, 1H), 7.86 (d, 1H), 7.71 (m, 3H), 7.42 (m, 1H), 7.36 (m, 2H), 6.90 (d, 2H), 6.70 (d, 2H); 3.60 (s, 3H), 2.45 (s, 3H); LC/MS *m/z* 447 $(M + H)^+$.



4-[4-(Cyclohexanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (B-12)

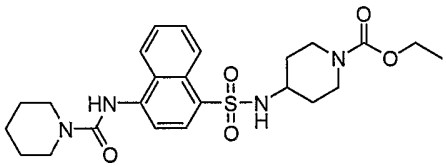
The title compound was prepared following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *p*-anisidine and cyclohexane carbonyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.05 (s, 1H), 8.65 (d, 1H), 8.26 (d, 1H), 8.14 (d, 1H), 8.04 (d, 1H), 7.92

(d, 1H), 7.71 (m, 2H), 3.95 (m, 3H), 3.68 (m, 2H), 1.93 (m, 2H), 1.80 (m, 2H), 1.31 (m, 13H), 1.13 (t, 3H); LC/MS $(M + H)^+$ *m/z* 488.



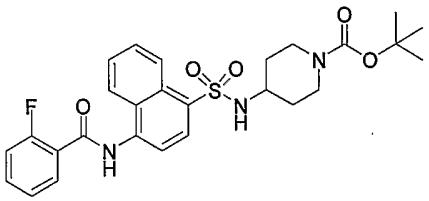
4-[4-(3-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (B-13)

The title compound was prepared following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *p*-anisidine and 3-methyl benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.30 (d, 1H), 8.18 (d, 1H), 7.80 (m, 5H), 7.46 (m, 2H), 4.03 (q, 2H), 3.83 (d, 2H), 3.23 (m, 1H), 2.78 (m, 2H), 2.47 (s, 3H), 1.56 (m, 2H), 1.28 (m, 2H), 1.19 (t, 3H); LC/MS $(M + H)^+$ *m/z* 496.



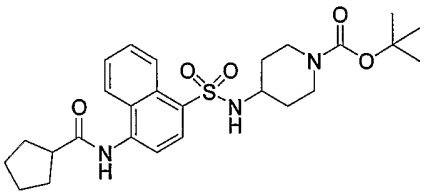
4-{4-[(Piperidine-1-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (B-14)

The title compound was prepared following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *p*-anisidine and 1-piperidine carbonyl chloride for *p*-methoxy-benzoyl chloride.



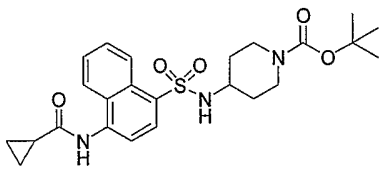
4-[4-(2-Fluoro-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (B-15)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine and 2-fluorobenzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.72(s, 1H), 8.67(d, 1H), 8.30(d, 1H), 8.20(d, 1H), 8.10(d, 1H), 8.01(d, 1H), 7.83(t, 1H), 7.74(t, 2H), 7.65(m, 1H), 7.41(q, 2H), 3.67(d, 2H), 3.18(m, 1H), 2.70(m, 2H), 1.43(m, 2H), 1.33(s, 9H), δ 1.18(m, 2H). LC/MS *m/z* 527 $(M - H)^-$, 529 $(M + H)^+$



4-[4-(Cyclopentanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (B-16)

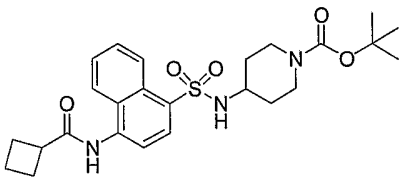
The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, and cyclopentanecarbonyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.11(s, 1H), 8.64(d, 1H), 8.25(d, 1H), 8.13(d, 1H), 8.01(d, 1H), 7.92(d, 1H), 7.89(m, 1H), 7.70(m, 2H), 3.61(d, 2H), 3.11(m, 2H), 1.94(m, 2H), 1.84-1.60 (m, 7H), 1.38(d, 2H), 1.33(s, 9H), 1.12(m, 2H). LC/MS *m/z* 500 $(M - H)^-$, 502 $(M + H)^+$



4-[4-(Cyclopropanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (B-17)

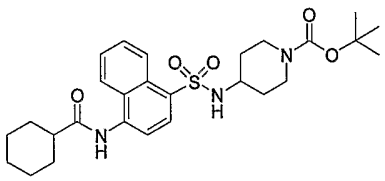
The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, and cyclopropanecarbonyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.43 (s, 1H), 8.65 (d, 1H), 8.34 (d, 1H), 8.12 (d, 1H), 7.99(t, 2H), 7.73 (m, 2H), 3.61 (d, 2H), 3.13 (m, 1H), 2.68 (m, 2H), 2.16 (m, 2H), 2.16 (m, 1H),

1.39 (d, 2H), 1.33 (s, 9H), 1.12 (m, 2H), 0.88 (d, 4H); LC/MS *m/z* 472 $(M - H)^-$, 474 $(M + H)^+$



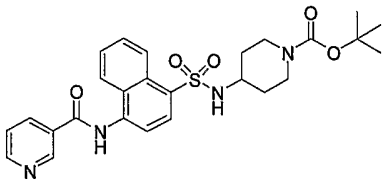
4-[4-(Cyclobutanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (B-18)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, and cyclobutanecarbonyl chloride for *p*-methoxy-benzoyl chloride. ^1H NMR (300 MHz, DMSO) δ 9.98 (s, 1H), 8.62 (d, 1H), 8.21 (d, 1H), 8.12 (d, 1H), 7.99 (d, 1H), 7.95 (d, 1H), 7.70 (m, 2H), 3.59 (d, 2H), 3.51 (t, 1H), 3.13 (m, 1H), 2.67 (m, 2H), 2.32-2.16 (m, 4H), 1.99 (m, 1H), 1.84 (m, 1H), 1.37 (d, 2H), 1.31 (s, 9H), 1.10(m, 2H); LC/MS *m/z* 486 $(M - H)^-$, 488 $(M + H)^+$



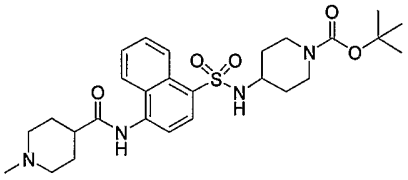
4-[4-(Cyclohexanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (B-19)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine and cyclohexanecarbonyl chloride for *p*-methoxy-benzoyl chloride. ^1H NMR (300 MHz, DMSO) δ 10.05 (s, 1H), 8.64 (d, 1H), 8.25 (d, 1H), 8.12 (d, 1H), 8.00 (d, 1H), 7.91 (d, 1H), 7.71 (m, 2H), 3.61 (d, 2H), 3.43 (m, 1H), 3.15 (m, 1H), 2.65 (m, 2H), 1.90 (d, 2H), 1.77 (d, 2H), 1.69 (m, 1H), 1.54-1.33 (m, 5H), 1.32 (s, 9H), 1.30-1.12 (m, 4H); LC/MS *m/z* 486 $(M - H)^-$, 488 $(M + H)^+$



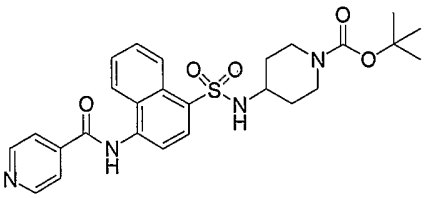
4-{4-[(Pyridine-3-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid *tert*-butyl ester (B-20)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, and nicotinoyl chloride hydrochloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.83 (s, 1H), 9.23 (d, 1H), 8.81 (d, 1H), 8.67 (dd, 1H), 8.11 (dt, 1H), 8.27 (dd,1 H), 8.27 (dd, 1H), 8.20 (d, 1H), 8.09 (d, 1H), 7.85 (d, 1H), 7.75 (m, 2H), 7.6 (m, 1H), 3.62 (d, 2H), 3.18 (m, 1H), 2.69 (m, 2H), 1.45-1.37 (m, 2H), 1.30 (s, 9H), 1.14 (m, 2H); LC/MS *m/z* 509 $(M - H)^-$, 511 $(M + H)^+$



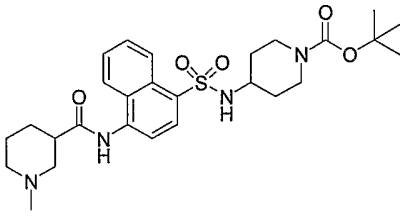
4-{4-[(1-Methyl-piperidine-4-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid *tert*-butyl ester (B-21)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, *N*-methyl-piperdine-4-carboxylic acid hydrochloride for *p*-methoxy-benzoyl chloride and reagents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole hydrate (HOBt) and pyridine for dimethylamino pyridine (DMAP) and triethylamine. ^{1}H NMR (300 MHz, DMSO) δ 10.39 (s, 1H), 8.64 (dd, 1H), 8.29 (dd, 1H), 8.14 (d, 1H), 8.05 (d, 1H), 7.89 (d, 1H), 7.72 (m, 2H), 3.62 (d, 2H), 3.40 (m, 2H), 3.15 (m, 1H), 2.95 (m, 2H), 2.78-2.67 (m, 6H), 2.09 (m, 2H), 2.0 (m, 2H), 1.84 (m, 1H), 1.39 (m, 1H), 1.32 (s, 9H), 1.18 (m, 2H); LC/MS *m/z* 484 $(M - H)^-$, 486 $(M + H)^+$



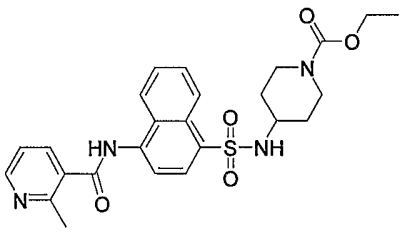
4-{4-[(Pyridine-4-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid *tert*-butyl ester (B-22)

The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine and isonicotinoylchloride hydrochloride for *p*-methoxy-benzoyl chloride. LC/MS *m/z* 511 $(M + H)^+$



4-{4-[(1-Methyl-piperidine-3-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid *tert*-butyl ester (B-23)

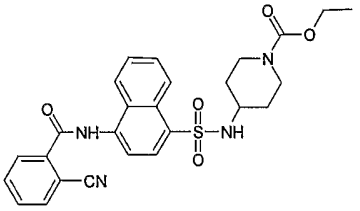
The title compound was made following the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine, *N*-methyl-piperidine-3-carbonyl chloride (prepared in situ from *N*-methyl-piperidine-3-carboxylic acid, oxalyl chloride (1.2eq) and triethylamine (1 eq)) for *p*-methoxy-benzoyl chloride. LC/MS *m/z* 531 $(M + H)^+$



4-{4-[(2-Methyl-pyridine-3-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (B-24):

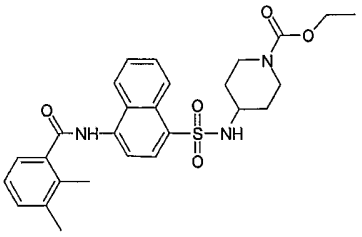
To a suspension of 4-(4-Amino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (0.26 g, 0.71 mmol) (prepared following the general

procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid ethyl ester for *p*-anisidine) in CH_2Cl_2 (10 mL) and aqueous saturated sodium bicarbonate solution (4 mL) was added 2-methyl nicotinic chloride (0.16 g, 1.07 mmol) and the resulting mixture was stirred at room temperature overnight. The organic layer was separated, dried over sodium sulfate and concentrated. Purification of the residue by column chromatography (2-5% MeOH/CH_2Cl_2) provided the **B-24** (0.09g, 26%). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.61-8.66 (m, 2H), 8.34 (s, 1H), 8.19-8.28 (m, 1H), 7.94 (d, 2H), 7.60-7.70 (m, 2H), 7.28-7.31(m, 1H), 4.91(d, 1H), 4.03 (q, 2H), 3.85 (d, 2H), 3.20-3.32 (m, 1H), 2.80 (s, 2H), 2.63-2.74 (m, 2H), 1.67 (br s, 4H), 1.16-1.21 (m, 5H). LC/MS m/z 497 $(M + H)^+$.



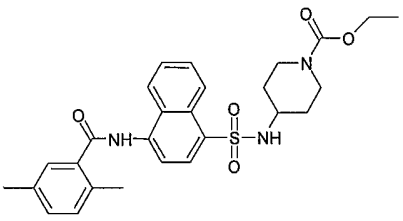
4-[4-(2-Cyano-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (B-26)

A solution of 2-cyano-benzoic acid (294 mg, 2 mmol) in thionyl chloride (5 mL) was heated to reflux where the mixture was stirred for 3 h and then concentrated *in vacuo*. The crude material, 2-cyano-benzoyl chloride was used without purification. The title compound was made following the general procedure in scheme 3, substituting 4-(4-amino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester for 4-amino-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide and substituting 2-cyano-benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.05 (dd, 1H), 8.36 (d, 1H), 8.05 (m, 2H), 7.92 (m, 2H), 7.83 (m, 1H), 7.75 (m, 1H), 7.64 (d, 2H), 6.89 (td, 1H), 4.05 (q, 2H), 3.85 (d, 2H), 3.30 (m, 1H), 2.80 (m, 2H), 1.60 (m, 2H), 1.30 (m, 2H), 1.20 (t, 3H); LC/MS *m/z* 508 $(M + H)^+$



4-[4-[4-(2,3-Dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (B-27)

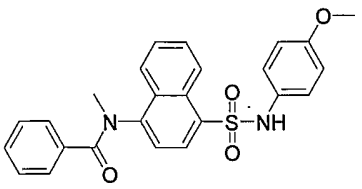
The title compound was made following general procedure in Scheme 3, substituting 4-(4-amino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester for 4-amino-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide and substituting 2,3-dimethyl-benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, MeOD/$CDCl_3$) δ 8.63 (d, 1H), 8.24 (m, 2H), 7.97 (d, 1H), 7.60 (m, 2H), 7.38 (m, 1H), 7.30 (m, 2H), 4.00 (q, 2H), 3.81 (d, 2H), 3.20 (m, 1H), 2.75 (m, 2H), 2.40 (s, 3H), 2.30 (s, 3H), 1.58 (m, 2H), 1.20 (m, 2H), 1.12 (t, 3H); LC/MS *m/z* 510 $(M + H)^+$



4-[4-(2,5-Dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (B-28)

A solution of 2,5-dimethyl-benzoic acid (300 mg, 2 mmol) in thionyl chloride (5 mL) was refluxed for 3 h and then concentrated in vacuo. The crude material was used without purification as 2,5-dimethyl-benzoyl chloride. The title compound was made following general procedure in Scheme 3, substituting 4-(4-amino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester for 4-amino-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide and substituting 2,5-dimethyl-benzoyl chloride for *p*-methoxy-benzoyl chloride. ^{1}H NMR (300 MHz, MeOD/$CDCl_3$) δ 8.60 (dd, 1H), 8.22 (d, 1H), 8.10 (m, 1H), 7.98 (m, 1H), 7.58 (m, 2H), 7.35 (s, 1H), 7.14 (m, 2H), 3.98 (q, 2H), 3.78 (d, 2H), 3.15 (m, 1H), 2.68 (m,

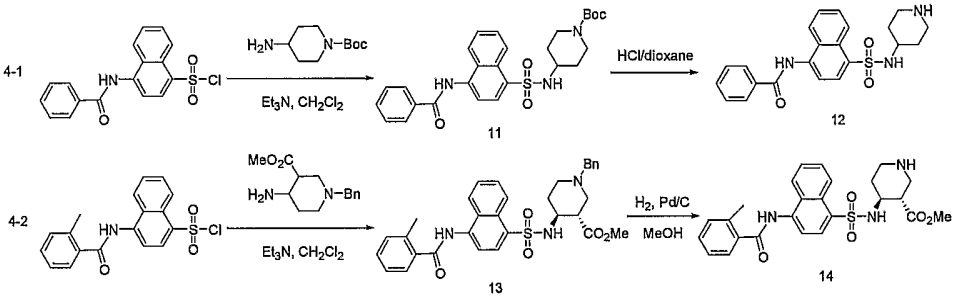
2H), 2.42 (s, 3H), 2.32 (s, 3H), 1.55 (m, 2H), 1.20 (m, 2H), 1.12 (t, 3H); LC/MS *m/z* 510 $(M + H)^+$



***N*-[4-(4-Methoxy-phenylsulfamoyl)-naphthalen-1-yl]-*N*-methyl-benzamide (B-33)**

The title compound was made from **B-30** following the general procedure in Scheme 3. ^1H NMR (300 MHz, DMSO) δ 8.23 (t, 2H), 8.10 (d, 3H), 7.87 (d, 1H), 7.60 (m, 5H), 7.03 (d, 2H), 6.82 (d, 2H), 3.72 (s, 3H), 3.18 (s, 3H); LC/MS *m/z* 445 $(M - H)^-$.

Scheme 4: General procedures for amine deprotections



***N*-[4-(Piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (12)**

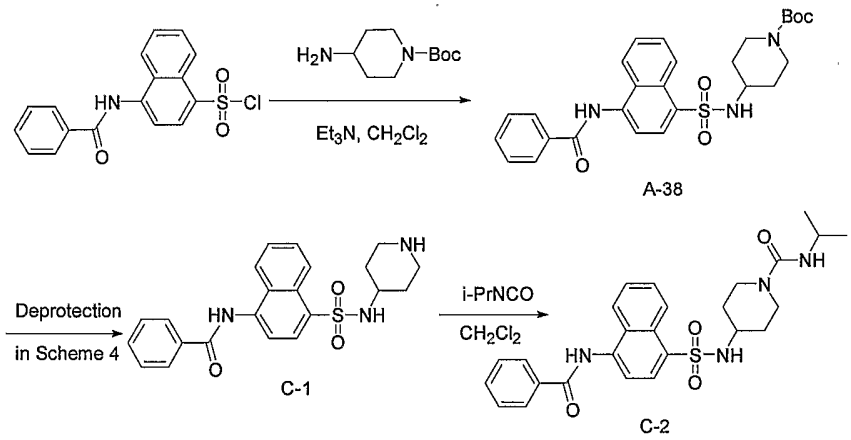
4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**11**) was prepared following the general procedure in Scheme 2. To a solution of 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**11**) in MeOH was added a solution of 4 N HCl in dioxane. The reaction mixture was stirred at 25 °C for 5 h and then concentrated *in vacuo*. The crude material was purified by reverse phase HPLC to provide the title compound. ^1H NMR (300 MHz, MeOH) δ 8.75 (d, 1H), 8.46 (s, 1H), 8.33 (d, 1H), 8.21 (d, 1H), 8.10 (m, 1H), 8.07 (m, 1H), 7.83 (d, 1H), 7.69 (m, 5H), 3.21 (m, 3H), 2.92 (m, 2H), 1.82 (m, 2H), 1.60 (m, 2H); LC/MS $(M + H)^+$ *m/z* 410.

(±)-(*trans*)-4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (14)

(±)-(*trans*)-1-Benzyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid methyl ester **13** was made following general procedure in Scheme 2, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for *m*-anisidine and 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride benzylamine.

To a solution of 1-benzyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid methyl ester **13** (170 mg, 0.29 mmol) in MeOH was added $Pd(OH)_2/C$ 20% wet (80mg). The reaction mixture was stirred at 25 °C under an hydrogen atmosphere overnight. The resultant mixture was filtered and the solvent was concentrated *in vacuo* to provide the title compound **14**. This material was not further purified and used directly in the next reaction.

Scheme 5



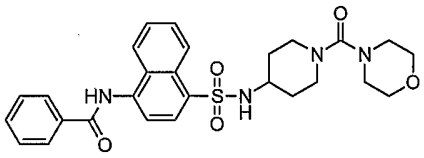
***N*-[4-(Piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-1)**

4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-38**) was prepared following the general procedure in Scheme 2. Deprotection was achieved following the procedure in Scheme 4-1. The reaction mixture was stirred at 25 °C for 5 h and then concentrated *in vacuo*. The crude material was purified by reverse phase HPLC to provide the title compound. ^1H NMR (300 MHz, MeOH) δ 8.75 (d, 1H), 8.46 (s, 1H), 8.33 (d, 1H), 8.21 (d, 1H),

8.10 (m, 1H), 8.07 (m, 1H), 7.83 (d, 1H), 7.69 (m, 5H), 3.21 (m, 3H), 2.92 (m, 2H), 1.82 (m, 2H), 1.60 (m, 2H); LC/MS $(M + H)^+$ *m/z* 410.

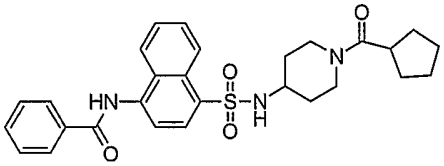
4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid isopropyl amide (C-2)

To a 25 °C solution of *N*-[4-(piperidin-4-yl sulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) in CH_2Cl_2 was added Et_3N followed by 2-isocyanato-propane. The reaction mixture was stirred at 25° C overnight. Aqueous work-up followed by purification using reverse phase HPLC provided the title compound. ^1H NMR (300 MHz, MeOD) δ 8.74 (d, 1H), 8.29 (d, 1H), 8.17 (d, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 7.81 (d, 1H), 7.63 (m, 5H), 3.75 (m, 3H), 3.21 (m, 1H), 2.68 (t, 2H), 1.51 (m, 2H), 1.26 (m, 2H), 1.05 (d, 6H); LC/MS $(M + H)^+$ *m/z* 495.



***N*-{4-[1-(Morpholine-4-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-4)**

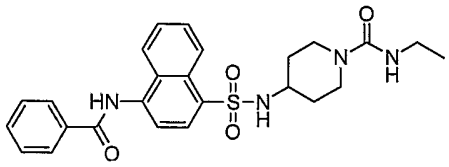
The title compound was made following general procedure in Scheme 5, substituting 4-isocyanato-tetrahydro-pyran for 2-isocyanato-propane. ^1H NMR (300 MHz, MeOD) δ 8.74 (d, 1H), 8.29 (d, 1H), 8.17 (d, 1H), 8.07 (m, 1H), 8.05 (m, 1H), 7.81 (d, 1H), 7.63 (m, 5H), 3.57 (m, 4H), 3.48 (m, 2H), 3.13 (m, 3H), 2.73 (t, 2H), 2.54 (m, 2H), 1.32 (m, 2H); LC/MS $(M + H)^+$ *m/z* 523.



***N*-[4-(1-Cyclopentanecarbonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-5)**

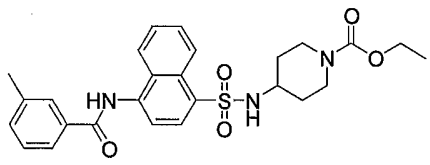
The title compound was prepared following general procedure in Scheme 5, substituting cyclopentanecarbonyl chloride for 2-isocyanato-propane to afford the

title compound as a cream colored solid. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 1H), 8.19 (d, 1H), 8.09 (m, 1H), 8.07 (d, 1H), 7.82 (d, 1H), 7.65 (m, 6H), 4.17 (d, 1H), 3.83 (d, 1H), 2.97 (m, 2H), 2.65 (m, 1H), 1.65 (m, 11H), 1.29 (m, 2H); LC/MS $(M + H)^+$ *m/z* 506.



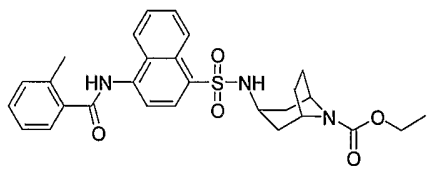
4-(4-Benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethylamide (C-7)

The title compound was prepared following general procedure in Scheme 5, substituting isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.30 (d, 1H), 8.19 (d, 1H 8.08 (d, 2H), 7.82 (d, 1H), 7.65 (m, 5H), 3.74 (d, 2H), 3.23 (m, 1H), 3.10 (m, 2H), 2.70 (t, 2H), 1.53 (m, 2H), 1.28 (m, 2H), 1.04 (t, 3H); LC/MS $(M + H)^+$ *m/z* 481.



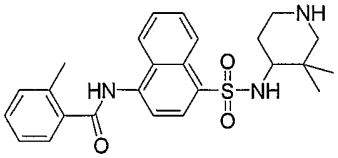
4-[4-(3-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-9)

The title compound was made following general procedure in Scheme 5, substituting 4-aminopiperidine-1-carboxylic acid ethyl ester for 4-aminopiperidine-1-carboxylic acid *tert*-butyl ester and m-tolyl chloride for benzoyl chloride.



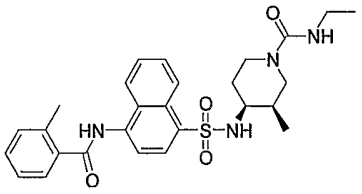
***cis*-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (C-10)**

The title compound was made following general procedure in Scheme 5, substituting *cis*-3-amino-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester for 4-aminopiperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 8.75 (d, 1H), 8.27 (d, 1H), 8.14 (d, 1H), 7.75 (d, 1H), 7.65 (m, 4H), 7.41 (m, 1H), 7.35 (m, 2H), 3.94 (m, 4H), 3.25 (br s, 1H); 2.50 (s, 3H), 1.92 (d, 2H), 1.67 (m, 4H), 1.07 (t, 3H); LC/MS *m/z* 523 $(M + H)^+$.



(±)-*N*-[4-(3,3-Dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-11)

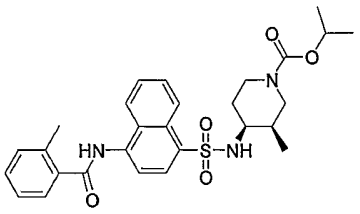
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride and 4-amino-3,3-dimethyl-piperidine-1-carboxylic acid tert-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.82 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.68 (m, 3H), 7.40 (m, 3H), 3.18 (m, 3H), 3.00 (d, 1H), 2.85 (m, 2H); 2.54 (s, 3H), 1.60 (m, 3H), 0.95 (s, 3H), 0.70 (s, 3H); LC/MS *m/z* 452 $(M + H)^+$.



(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-12)

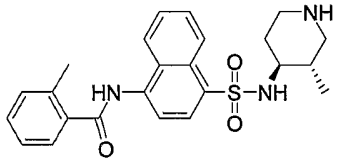
The title compounds were made following general procedure in Scheme 5 and deprotection in scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, 1H), 8.40 (s, 1H), 8.28 (s, 2H), 7.98 (d, 1H), 7.68 (m, 3H), 7.41 (m, 1H), 7.30

(m, 2H), 5.21(d, 1H), 4.36 (m, 1H), 3.35 (m, 2H), 3.15 (m, 4H), 2.98 (m, 2H), 2.57 (s, 3H), 1.71 (m, 2H), 1.40 (m, 2H), 1.10 (m, 1H), 1.03 (t, 3H) 0.63 (d, 3H); LC/MS *m/z* 509 $(M + H)^+$.



(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-13)

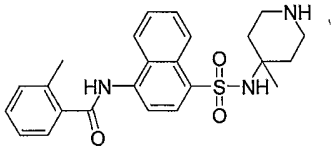
The title compounds were made following the general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isopropyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, 1H), 8.43 (d, 1H), 8.35 (d, 1H), 8.12 (d, 1H), 7.95 (d, 2H), 7.72 (m, 3H), 7.46 (m, 1H), 7.35(d, 2H), 4.85 (m, 1H), 4.66 (d, 1H), 3.55 (m, 1H), 3.37 (m, 1H), 3.17 (m, 2H), 2.59 (s, 3H), 1.74 (m, 1H), 1.58 (m, 1H), 1.40 (m, 2H) 1.18 (dd, 6H), 0.67 (m, 3H); LC/MS *m/z* 524 $(M + H)^+$.



(±)-*trans*-2-Methyl-*N*-[4-(3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-14)

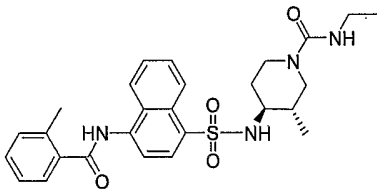
The title compound was made following general procedure in Scheme 5 and flash column chromatography (Hexane/EtOAc, gradient) followed by deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride and (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.77 (d, 1H), 8.48 (s, 1H), 8.32 (d, 1H), 8.24

(d, 1H), 7.94 (d, 1H), 7.75 (m, 3H), 7.40 (m, 3H), 3.25 (m, 1H), 2.90 (m, 2H), 2.55 (s, 3H), 1.60 (m, 3H), 0.65 (d, 3H); LC/MS *m/z* 438 $(M + H)^+$.



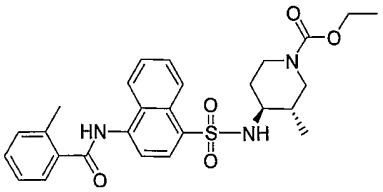
2-Methyl-*N*-[4-(4-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-15)

The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride and 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 8.73 (d, 1H), 8.68 (br s, 1H), 8.28 (d, 1H), 8.23 (d, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.40 (m, 3H), 2.90 (m, 4H), 2.48 (s, 3H), 2.00 (m, 2H), 1.58 (m, 2H), 0.95 (s, 3H); LC/MS *m/z* 438 $(M + H)^+$.



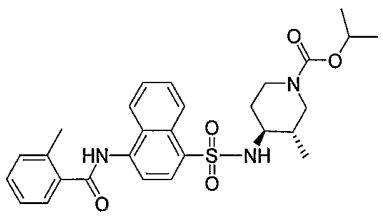
(±)-*trans*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-16)

The title compounds were made following general procedure in Scheme 5 and deprotection in scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.77 (d, 1H), 8.29 (d, 1H), 8.23 (d, 1H), 7.91 (d, 1H), 7.70 (m, 3H), 7.36 (m, 3H), 3.82 (m, 2H), 3.12 (q, 2H), 2.82 (m, 1H), 2.58 (m, 1H), 2.55 (s, 3H), 2.31 (t, 1H), 1.40 (m, 2H), 1.20 (m, 1H), 1.03 (t, 3H), 0.59 (d, 3H); LC/MS *m/z* 509 $(M + H)^+$.



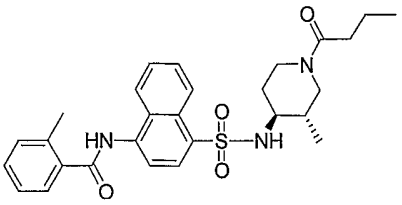
(±)-*trans*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-17)

The title compound was made following general procedure in scheme 5 and deprotection in scheme 4, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and ethyl chloroformate for 2-isocyanato-propane. Flash column chromatography (Hexane/EtOAc, gradient) of the mixture gave **C-17**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.92 (d, 1H), 7.73 (m, 3H), 7.35 (m, 3H), 4.03 (q, 2H), 3.94 (t, 2H), 2.85 (dt, 1H), 2.64 (m, 1H), 2.55 (s, 3H), 2.40 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.20 (t, 3H), 0.59 (d, 3H); LC/MS *m/z* 510 $(M + H)^+$.



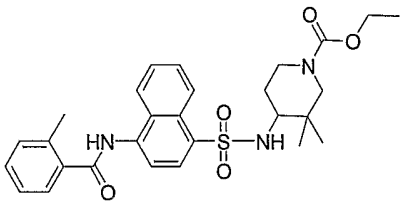
(±)-*trans*-3-methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-18)

The title compounds were made following the general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isopropyl chloroformate for 2-isocyanato-propane. **C-18:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 1H), 8.40 (m, 2H), 8.17 (s, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.44 (m, 1H), 7.34 (m, 2H), 4.80 (m, 1H), 4.58 (d, 1H), 3.90 (d, 2H), 2.87 (m, 1H), 2.60 (m, 1H), 2.59 (s, 3H), 2.33 (m, 1H), 1.65 (m, 1H), 1.32 (m, 1H), 1.18(d, 6H), 0.60 (br s, 3H); LC/MS *m/z* 524 $(M + H)^+$.



(±)-*trans*-*N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-19)

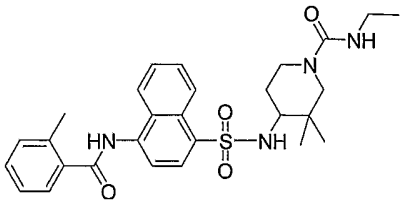
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. Flash column chromatography (Hexane/EtOAc, gradient) of the mixture gave **C-19**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (t, 1H), 8.33 (m, 3H), 7.95 (d, 1H), 7.62 (m, 3H), 7.40 (m, 1H), 7.34 (m, 2H), 5.00 (d, 1H), 4.30 (dd, 1H), 3.63 (m, 1H), 2.85 (m, 1.5H), 2.57 (s, 3H), 2.40 (t, 0.5H), 2.15 (m, 1.5H), 2.09 (m, 0.5H), 1.83 (m, 0.5H), 1.50 (m, 1.5H); LC/MS *m/z* 508 $(M + H)^+$.



(±)-3,3-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-20)

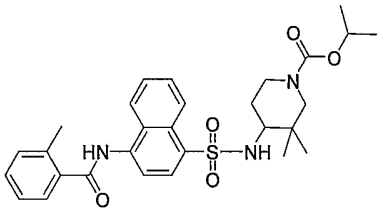
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3,3-dimethyl-piperidine for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.75 (d, 1H), 8.24 (m, 2H), 7.93 (d, 1H), 7.77 (d, 1H), 7.66 (m, 3H), 7.40 (m, 3H), 3.98 (q, 2H), 3.69 (m, 1H), 3.43 (d, 1H), 2.96 (m, 1H), 2.60 (m, 1H), 2.48

(s, 3H), 1.33 (m, 1H), 1.15 (m, 1H), 1.10 (t, 3H), 0.68 (s, 3H), 0.50 (s, 3H); LC/MS *m/z* 524 $(M + H)^+$.



(±)-3,3-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-21)

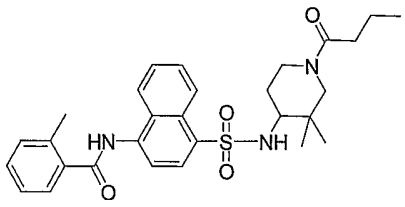
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3,3-dimethyl-piperidine for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.76 (d, 1H), 8.26 (m, 2H), 7.92 (d, 1H), 7.65 (m, 4H), 7.38 (m, 3H), 6.24 (m, 1H), 3.65 (d, 1H), 3.48 (d, 1H), 3.48 (d, 1H), 2.90 (m, 3H), 2.47 (s, 3H), 2.42 (m, 3H), 1.25 (m, 1H), 1.00 (m, 1H), 0.91 (t, 3H), 0.68 (s, 3H), 0.53 (s, 3H); LC/MS *m/z* 523 $(M + H)^+$.



(±)-3,3-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-22)

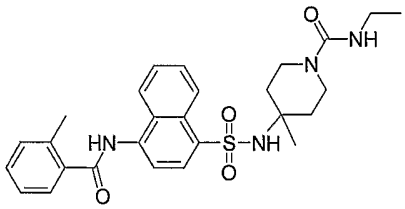
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3,3-dimethyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isopropyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.75 (d, 1H), 8.25 (m, 2H), 7.93 (d, 1H), 7.70 (m, 3H), 7.38 (m, 3H), 4.66 (m, 1H), 3.68 (m, 1H), 3.43 (d, 1H), 2.94 (m, 1H), 2.55 (m, 2H), 2.47 (s,

3H), 1.30 (m, 1H), 1.10 (d, 6H), 0.67 (s, 3H), 0.50 (s, 3H); LC/MS *m/z* 538 (M + H)$^+$.



(±)-*N*-[4-(1-Butyryl-3,3-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-23)

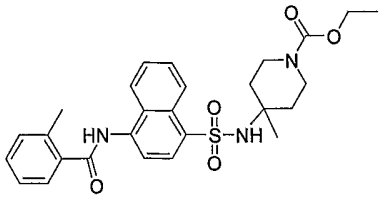
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, (±)-4-amino-1-benzyl-3,3-dimethyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.77 (dd, 1H), 8.25 (m, 2H), 7.93 (d, 1H), 7.70 (m, 4H), 7.38 (m, 3H), 4.06 (d, 0.5H), 3.85 (d, 0.5H), 3.60 (d, 0.5H), 3.37 (d, 0.5H), 2.98 (m, 1H), 2.77 (m, 1H), 2.47 (s, 3H), 2.35 (d, 0.5H), 2.16 (m, 2H), 1.40 (m, 2H), 1.24 (m, 0.5H), 1.11 (m, 0.5H), 0.80 (t, 3H), 0.70 (s, 1.5H), 0.64 (s, 1.5H), 0.55 (s, 3H); LC/MS *m/z* 522 (M + H)$^+$.



4-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-24)

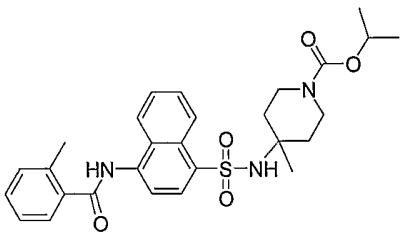
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.76 (d, 1H), 8.24 (m, 2H), 7.93 (d, 1H), 7.38 (m, 3H),

7.70 (m, 4H), 6.26 (t, 1H), 3.18 (m, 2H), 2.93 (m, 2H), 2.78 (m, 2H), 2.47 (s, 3H), 1.69 (m, 2H), 1.24 (m, 2H), 1.09 (s, 3H), 0.90 (t, 3H); LC/MS *m/z* 509 $(M + H)^+$.



4-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-25)

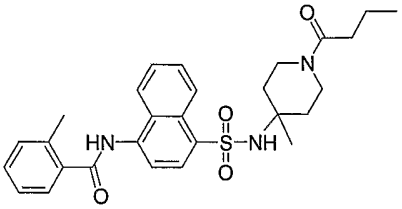
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.80 (d, 1H), 8.29 (m, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.65 (m, 3H), 7.38 (m, 3H), 4.02 (q, 2H), 3.43 (m, 2H), 2.90 (m, 2H), 2.54 (s, 3H), 1.87 (m, 2H), 1.15 (m, 6H); LC/MS *m/z* 510 $(M + H)^+$.



4-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-26)

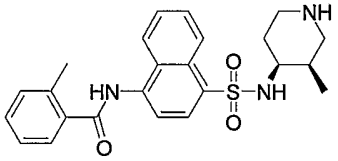
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.80 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.75 (m, 3H), 7.35 (m, 3H), 4.79 (q, 2H), 3.40

(m, 2H), 2.88 (t, 2H), 1.86 (m, 2H), 1.37 (m, 6H), 1.10 (m, 9H); LC/MS *m/z* 524 (M + H)$^+$.



N-[4-(1-Butyryl-4-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-27)

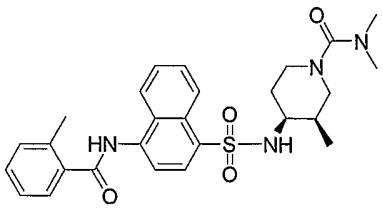
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.76 (d, 1H), 8.26 (m, 2H), 7.95 (d, 1H), 7.70 (m, 3H), 7.34 (m, 3H), 3.54 (m, 1H), 3.31 (m, 1H), 3.04 (m, 1H), 2.76 (m, 1H), 2.47 (s, 3H), 2.09 (t, 3H), 1.82 (m, 2H), 1.30 (m, 6H), 1.07 (s, 3H), 0.77 (t, 3H); LC/MS *m/z* 508 (M + H)$^+$.



(±)-*cis*-2-Methyl-*N*-[4-(3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-28)

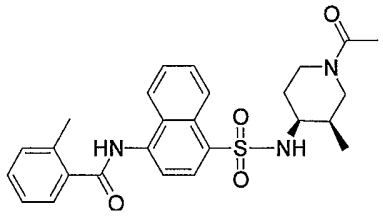
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride and (±)-4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. Purification of the benzyl-protected intermediate by Flash column chromatography (Hexane/EtOAc, gradient) followed by deprotection according to Scheme 4-2 gave **C-28**. ^{1}H NMR (300 MHz, MeOD) δ 8.82 (d, 1H), 8.52 (s, 1H), 8.32 (d, 1H), 8.24 (d, 2H), 7.94 (d, 2H), 7.70

(m, 3H), 7.4 (m, 3H), 3.46 (m, 1H), 3.00 (m, 2H), 2.97 (m, 1H), 2.55 (s, 3H), 1.93 (m, 1H), 1.64 (m, 2H), 0.63 (d, 3H); LC/MS *m/z* 438 $(M + H)^+$.



(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (C-29)

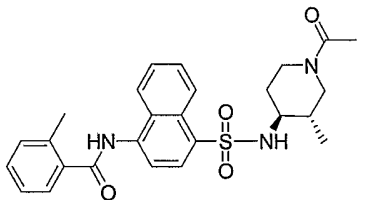
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-2, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and dimethylcarbamyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.97 (d, 1H), 7.62 (m, 3H), 7.41 (m, 1H), 7.28 (m, 2H), 5.27 (d, 1H), 3.38 (m, 1H), 3.11 (m, 1H), 2.99 (dd, 1H), 2.88 (m, 2H), 2.70 (s, 6H), 2.56 (s, 3H), 1.46 (m, 1H), 1.42 (m, 2H), 0.63 (d, 3H); LC/MS *m/z* 509 $(M + H)^+$.



(±)-*cis*-*N*-[4-(1-Acetyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-30)

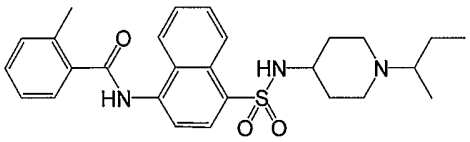
The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-2, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-1-benzyl-3-methyl-piperidine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and acetyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (m, 1H), 8.33 (br s, 3H), 7.98 (d, 1H), 7.63 (m, 3H), 7.42 (m, 1H), 7.26 (m, 2H),

5.29 (d, 1H), 3.78 (m, 0.5H), 3.38 (m, 1.5H), 3.20 (m, 1.5H), 2.97 (m, 0.5H), 2.57 (s, 3H), 2.08 (m, 1.5H), 1.96 (d, 3H), 1.83 (m, 0.5H), 1.45 (m, 2H), 0.72 (d, 1.5H), 0.56 (d, 1.5H); LC/MS *m/z* 480 $(M + H)^+$.



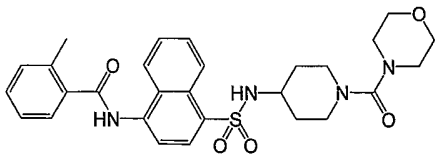
(±)-(*trans*)-*N*-[4-(1-Acetyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-31)

The title compound was made following general procedure in Scheme 5 and deprotection in Scheme 4-1, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-amino-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and acetyl chloride for 2-isocyanato-propane. ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (m, 1H), 8.35 (m, 3H), 7.95 (d, 1H), 7.65 (m, 3H), 7.40 (m, 1H), 7.26 (m, 2H), 5.02 (d, 1H), 4.30 (m, 1H), 3.58 (m, 1H), 2.95 (m, 2H), 2.62 (m, 0.5H), 2.58 (s, 3H), 2.45 (m, 0.5H), 1.98 (s, 3H), 1.75 (m, 1H), 1.25 (m, 2H), 0.70 (d, 1.5H), 0.51 (d, 1.5H); LC/MS *m/z* 480 $(M + H)^+$.



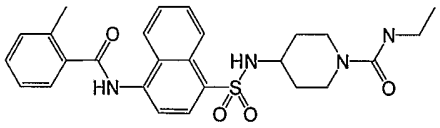
(±)-*N*-[4-(1-*sec*-Butyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-32)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and butan-2-one/sodium triacetoxyborohydride for 2-isocyanato-propane. ^1H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.39 (m, 1H), 3.15 (m, 3H), 2.98 (m, 2H), 2.55 (s, 3H), 1.88 (m, 2H), 1.72 (m, 3H), 1.43 (m, 1H), 1.19 (d, 3H), 0.95 (t, 3H); LC/MS $(M + H)^+$ *m/z* 480.



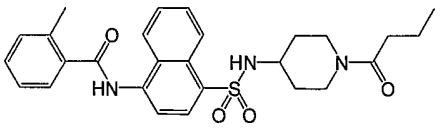
2-Methyl-*N*-{4-[1-(morpholine-4-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-33)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and morpholine-4-carbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.59 (t, 4H), 3.50 (m, 2H), 3.27 (m, 1H), 3.19 (t, 4H), 2.76 (m, 2H), 2.54 (s, 3H), 1.59 (m, 2H), 1.27 (m, 2H); LC/MS $(M + H)^+$ *m/z* 537.



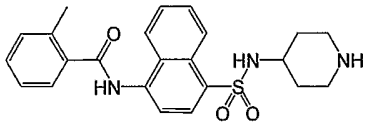
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-34)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.73 (m, 2H), 3.23 (m, 1H), 3.11 (q, 2H), 2.69 (m, 2H), 2.54 (s, 3H), 1.53 (m, 2H), 1.29 (m, 2H), 1.04 (t, 3H); LC/MS $(M + H)^+$ *m/z* 495.



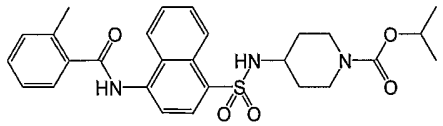
N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-35)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 4.19 (m, 1H), 3.74 (m, 1H), 3.33 (m, 1H), 3.01 (m, 1H), 2.64 (m, 1H), 2.54 (s, 3H), 2.74 (t, 2H), 1.62 (m, 2H), 1.55 (m, 2H), 1.29 (m, 2H), 0.89 (t, 3H); LC/MS $(M + H)^+$ *m/z* 496.



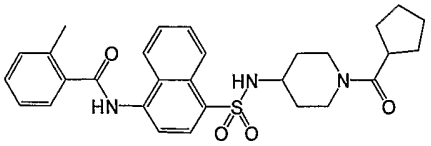
2-Methyl-N-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-36)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.49 (m, 1H), 3.15 (m, 2H), 2.90 (m, 2H), 2.50 (s, 3H), 2.21 (m, 1H), 1.82 (m, 2H), 1.59 (m, 1H)); LC/MS $(M + H)^+$ *m/z* 424.



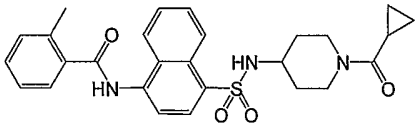
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-37)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and isopropyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 4.80 (m, 1H), 3.83 (m, 2H), 3.25 (m, 1H), 2.79 (m, 2H), 2.54 (s, 3H), 1.58 (m, 2H), 1.29 (m, 2H), 1.20 (t, 3H); LC/MS $(M + H)^+$ *m/z* 510.



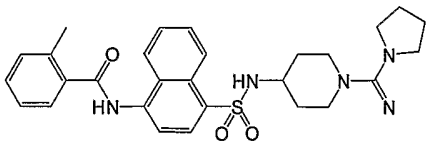
***N*-[4-(1-Cyclopentanecarbonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-38)**

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and cyclopentanecarbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.41 (m, 3H), 4.19 (m, 1H), 3.88 (m, 1H), 3.00 (m, 2H), 2.68 (m, 2H), 2.54 (s, 3H), 1.65 (m, 11H), 1.29 (m, 3H); LC/MS $(M + H)^+$ *m/z* 520.



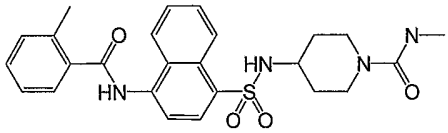
***N*-[4-(1-Cyclopropanecarbonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-39)**

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and cyclopropanecarbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.41 (m, 3H), 4.17 (m, 2H), 3.13 (m, 1H), 2.71 (m, 2H), 2.54 (s, 3H), 1.84 (m, 1H), 1.71 (m, 1H), 1.59 (m, 1H), 1.29 (m, 2H), 0.79 (m, 4H); LC/MS $(M + H)^+$ *m/z* 492.



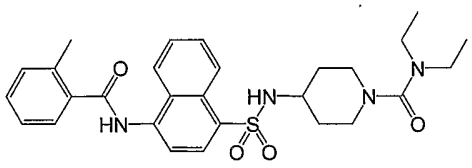
***N*-{4-[1-(Imino-pyrrolidin-1-yl-methyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-40)**

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and pyrrolidine-1-carbonitrile for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.70 (d, 1H), 8.49 (s, 1H), 8.28 (d, 1H), 8.21 (d, 1H), 7.93 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.40 (m, 9H), 2.98 (m, 2H), 2.54 (s, 3H), 1.82 (m, 4H), 1.60 (m, 1H), 1.39 (m, 1H); LC/MS $(M + H)^+$ *m/z* 520.



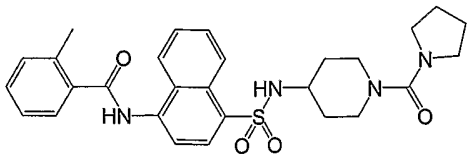
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid methylamide (C-41)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and isocyanatomethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.73 (m, 2H), 3.25 (m, 1H), 2.72 (m, 2H), 2.65 (s, 3H), 2.56 (s, 3H), 1.53 (m, 2H), 1.28 (m, 2H); LC/MS $(M + H)^+$ *m/z* 481.



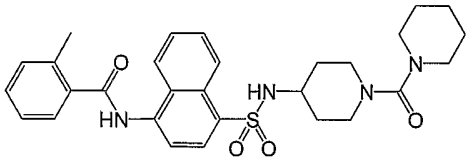
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid diethylamide (C-42)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and diethylcarbamyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.41 (m, 2H), 3.23 (m, 1H), 3.15 (q, 4H), 2.72 (m, 2H), 2.56 (s, 3H), 1.53 (m, 2H), 1.40 (m, 2H), 1.07 (t, 6H); LC/MS $(M + H)^+$ *m/z* 523.



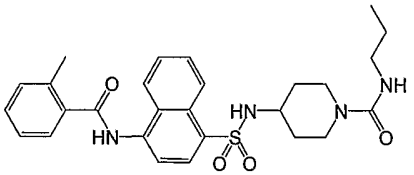
2-Methyl-*N*-{4-[1-(pyrrolidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-43)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and pyrrolidine-1-carbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.55 (m, 2H), 3.25 (m, 5H), 2.72 (m, 2H), 2.56 (s, 3H), 1.72 (m, 4H), 1.59 (m, 2H), 1.38 (m, 2H); LC/MS $(M + H)^+$ *m/z* 521.



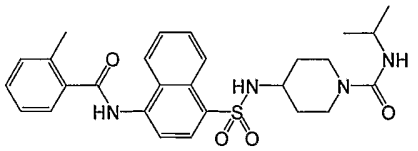
2-Methyl-*N*-{4-[1-(piperidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-44)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and piperidine-1-carbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.39 (m, 3H), 3.41 (m, 4H), 3.15 (m, 5H), 2.72 (m, 2H), 2.56 (s, 3H), 1.58 (m, 8H); LC/MS $(M + H)^+$ *m/z* 535.



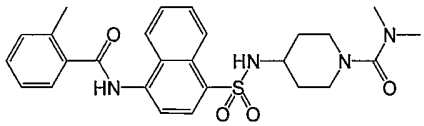
4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid propylamide (C-45)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and 1-isocyanato-propane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.75 (m, 2H), 3.25 (m, 1H), 3.06 (t, 2H), 2.74 (m, 2H), 2.59 (s, 3H), 1.59 (m, 2H), 1.49 (m, 2H), 1.30 (m, 2H), 0.89 (t, 3H); LC/MS $(M + H)^+$ *m/z* 509.



4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropylamide (C-46)

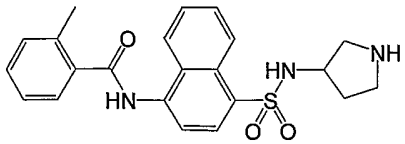
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.76 (m, 2H), 3.25 (m, 2H), 2.71 (m, 2H), 2.57 (s, 3H), 1.59 (m, 2H), 1.30 (m, 2H), 1.05 (d, 6H); LC/MS $(M + H)^+$ *m/z* 509.



4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (C-47)

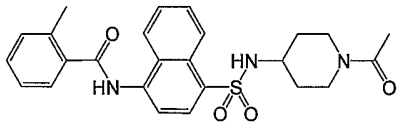
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and dimethylcarbamyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.54 (m, 2H), 3.25 (m, 1H),

2.75 (s, 6H), 2.71 (m, 2H), 2.55 (s, 3H), 1.59 (m, 2H), 1.35 (m, 2H); LC/MS (M + H)$^+$ *m/z* 495.



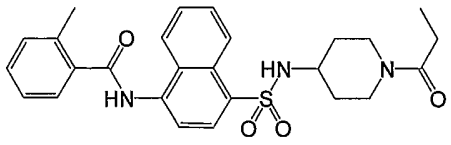
(±)-2-Methyl-*N*-[4-(pyrrolidin-3-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-48)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 8.78 (d, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.69 (m, 1H), 3.88 (m, 3H), 2.61 (m, 1H), 2.48 (s, 3H), 1.74 (m, 1H), 1.49 (m, 1H); LC/MS (M + H)$^+$ *m/z* 410.



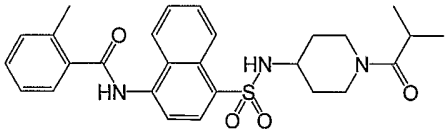
N-[4-(1-Acetyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-49)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and acetyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.15 (m, 1H), 3.69 (m, 1H), 3.25 (m, 1H), 3.03 (m, 1H), 2.69 (m, 1H), 2.55 (s, 3H), 1.98 (s, 3H), 1.59 (m, 2H), 1.31 (m, 2H); LC/MS (M + H)$^+$ *m/z* 466.



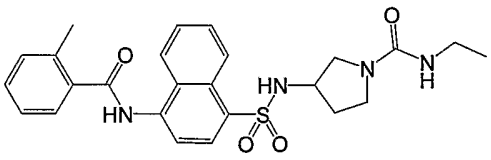
2-Methyl-*N*-[4-(1-propionyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-50)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and propionyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.19 (m, 1H), 3.72 (m, 1H), 3.25 (m, 1H), 3.01 (m, 1H), 2.69 (m, 1H), 2.55 (s, 3H), 2.41 (q, 2H), 1.61 (m, 2H), 1.31 (m, 2H), 1.02 (t, 3H); LC/MS $(M + H)^+$ *m/z* 480.



***N*-[4-(1-Isobutyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-51)**

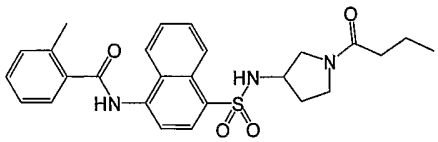
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and isobutyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.20 (m, 1H), 3.72.



(±)-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-pyrrolidine-1-carboxylic acid ethylamide (C-52)

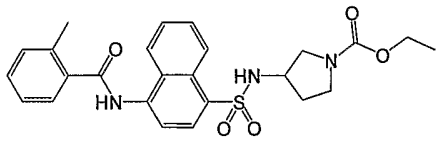
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.80 (m,

1H), 3.19 (m, 1H), 3.11 (q, 2H), 3.09 (m, 3H), 2.55 (s, 3H), 1.89 (m, 1H), 1.73 (m, 1H), 1.03 (t, 3H); LC/MS $(M+H)^+$ *m/z* 481.



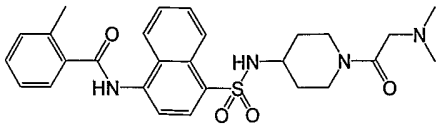
(±)-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-pyrrolidine-1-carboxylic acid ethylamide (C-53)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.85 (m, 1H), 3.40 (m, 3H), 3.15 (m, 1H), 2.53 (s, 3H), 2.19 (t, 1H), 1.95 (t, 1H), 1.85 (m, 2H), 1.50 (m, 2H), 0.88 (m, 3H); LC/MS $(M+H)^+$ *m/z* 480.



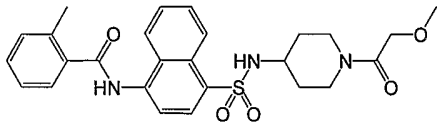
(±)-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-pyrrolidine-1-carboxylic acid ethyl ester (C-54)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl chlorofomate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.06 (m, 2H), 3.80 (m, 1H), 3.38 (m, 1H), 3.25 (m, 1H), 3.09 (m, 2H), 2.55 (s, 3H), 1.89 (m, 1H), 1.73 (m, 1H), 1.20 (m, 3H); LC/MS $(M+H)^+$ *m/z* 483.



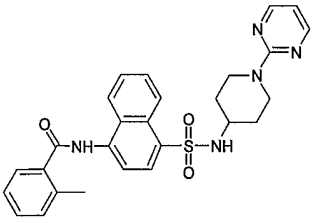
***N*-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-55)**

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and dimethylamino-acetyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.18 (m, 1H), 3.94 (d, 2H), 3.54 (m, 1H), 3.34 (m, 1H), 3.03 (m, 1H), 2.80 (m, 1H), 2.77 (s, 6H), 2.55 (s, 3H), 1.68 (m, 2H), 1.39 (m, 2H); LC/MS $(M + H)^+$ *m/z* 509.



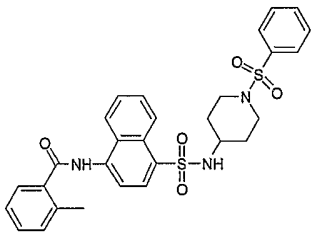
***N*-{4-[1-(2-Methoxy-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-56)**

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and methoxy-acetyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.15 (m, 1H), 4.04 (d, 2H), 3.94 (d, 2H), 3.63 (m, 1H), 3.34 (s, 3H), 3.32 (m, 1H), 3.01 (m, 1H), 2.71 (m, 1H), 2.55 (s, 3H), 1.63 (m, 2H), 1.41 (m, 2H); LC/MS $(M + H)^+$ *m/z* 496.



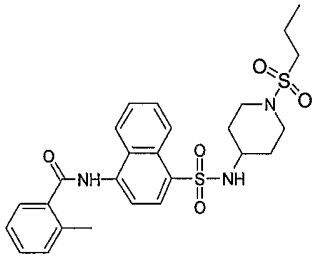
2-Methyl-*N*-[4-(1-pyrimidin-2-yl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-57)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting 2-bromo-pyrimidine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$/MeOD) δ 8.57 (d, 1H), 8.19 (d, 2H), 8.08 (d, 2H), 7.97 (d, 2H), 7.52 (m, 3H), 7.27 (t, 1H), 7.18 (d, 2H), 6.32 (t, 1H), 4.30 (d, 2H), 3.93 (s, 3H), 3.21 (m, 1H), 2.79 (dt, 2H), 2.43 (s, 3H), 1.58 (m, 2H), 1.20 (m, 3H); LC/MS *m/z* 500 $(M - H)^-$



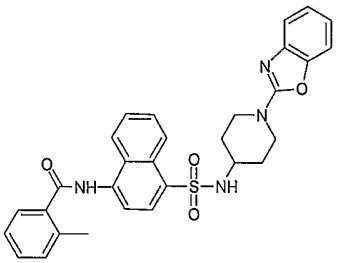
N-[4-(1-Benzenesulfonyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-58)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting benzenesulfonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, 1H), 8.22 (m, 3H), 7.94 (d, 1H), 7.48 (m, 11H), 4.57 (d, 1H), 3.49 (m, 2H), 3.02 (s, br, 1H), 2.55 (s, 3H), 2.28 (t, 2H), 1.60 (m, 2H), 1.40 (m, 2H); LC/MS *m/z* 564 $(M + H)^+$



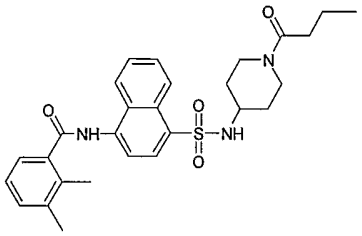
2-Methyl-N-{4-[1-(propane-1-sulfonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-59)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting propane-1-sulfonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD/$CDCl_3$) δ 8.69 (d, 1H), 8.27 (d, 1H), 8.17 (d, 1H), 7.97 (m, 1H), 7.62 (m, 4H), 7.34 (m, 2H), 3.50 (d, 2H), 3.15 (m, 1H), 2.75 (m, 4H), 2.54 (s, 3H), 1.68 (m, 4H), 1.45 (m, 2H), 1.00 (s, 3H); LC/MS *m/z* 528 $(M - H)^-$



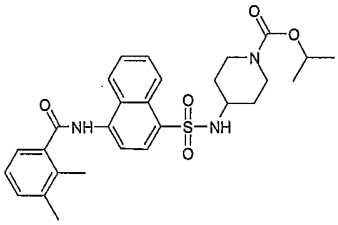
***N*-[4-(1-Benzooxazol-2-yl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-60)**

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting 2-chloro-benzooxazole for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD/$CDCl_3$) δ 8.47 (dd, 1H), 8.08 (d, 1H), 8.94 (m, 1H), 7.80 (m, 1H), 7.44 (m, 3H), 7.12 (m, 3H), 6.98 (t, 2H), 6.89 (td, 1H), 6.76 (td, 1H), 3.75 (d, 2H), 3.10 (m, 1H), 2.75 (td, 2H), 2.30 (s, 3H), 1.50 (m, 2H), 1.25 (m, 2H); LC/MS *m/z* 528 $(M + H)^+$



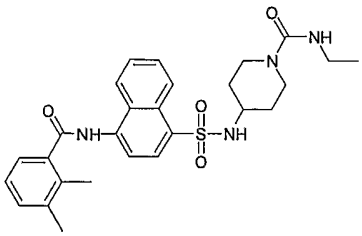
N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2,3-dimethyl-benzamide (C-61)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2,3-dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting butyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.32 (d, 1H), 8.22 (d, 1H), 7.96 (m, 1H), 7.71 (m, 2H), 7.46 (m, 1H), 7.29 (m, 2H), 4.35 (d, 1H), 3.75 (d, 1H), 3.02 (t, 1H), 2.65 (m, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.25 (m, 1H), 1.60 (m, 4H), 1.28 (m, 2H), 2.75 (m, 2H), 0.90 (m, 5H); LC/MS *m/z* 508 $(M + H)^+$



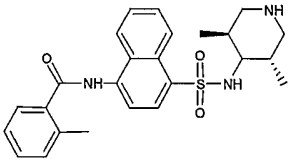
4-[4-(2,3-Dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (C-62)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2,3-dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting isopropyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 1H), 8.22 (d, 1H), 7.96 (m, 1H), 7.71 (m, 2H), 7.46 (m, 1H), 7.29 (m, 2H), 4.78 (m, 1H), 3.82 (d, 2H), 3.25 (m, 1H), 2.75 (m, 2H), 2.45 (s, 3H), 2.35 (s, 3H), 1.50 (m, 2H), 1.25 (m, 2H), 1.15 (d, 6H); LC/MS *m/z* 524 $(M + H)^+$



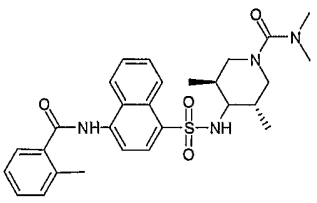
4-[4-(2,3-Dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-63)

The title compound was made following general procedure in Scheme 5, substituting 4-[4-(2,3-dimethyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester for 4-(4-benzoylamino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**A-28**), and substituting isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.31 (d, 1H), 8.22 (d, 1H), 7.96 (m, 1H), 7.71 (m, 2H), 7.46 (m, 1H), 7.29 (m, 2H), 3.75 (d, 2H), 3.82 (d, 2H), 3.25 (m, 1H), 3.10 (q, 2H), 2.72 (t, 2H), 2.45 (s, 3H), 2.35 (s, 3H), 1.55 (m, 2H), 1.25 (m, 2H), 1.05 (t, 3H); LC/MS *m/z* 509 $(M + H)^+$



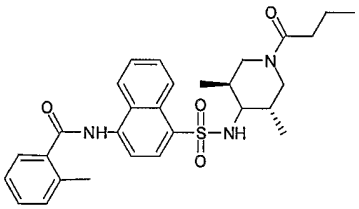
(±)-(*cis,trans*)-*N*-[4-(3,5-Dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-64)

The title compound was made following general procedure in scheme 4-2, substituting (±)-1-benzyl-3,5-dimethyl-piperidin-4-ylamine (**5**) for (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**6**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 1H), 8.35 (s, 1H), 8.18 (d, 1H), 8.05 (m, 2H), 7.55 (m, 3H), 7.30 (m, 1H), 7.20 (m, 2H), 3.85 (s, br, 1H), 3.05 (m, 2H), 2.80 (m, 2H), 2.50 (s, 3H), 2.40 (m, 1H), 1.85 (m, 2H), 0.63 (dd, 6H); LC/MS *m/z* 453 $(M + H)^+$



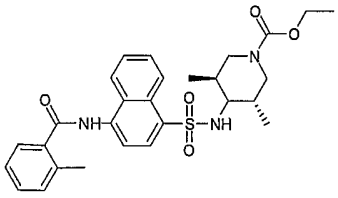
(±)-(*cis,trans*)-3,5-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (C-65)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, trans*)-*N*-[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-64**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting dimethylcarbamyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H), 8.34 (m, 2H), 8.21 (s, 1H), 7.95 (d, 1H), 7.65 (m, 3H), 7.43 (m, 1H), 7.34 (m, 2H), 4.85 (m, 1H), 3.44 (d, 1H), 3.18 (d, 1H), 2.90 (m, 2H), 2.73 (s, 6H), 2.56 (s, 3H), 2.37 (dd, 1H), 1.74 (m, 2H), 0.71 (d, 3H), 0.59 (d, 3H); LC/MS *m/z* 524 $(M + H)^+$



(±)-(*cis,trans*)-*N*-[4-(1-Butyryl-3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-66)

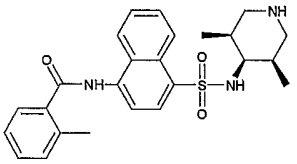
The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, trans)-N*-[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-64**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting butyl chloride for 2-isocyanato-propane.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74(d, 1H), 8.33 (m, 3H), 7.96 (m, 1H), 7.64 (m, 3H), 7.42 (m, 1H), 7.31 (m, 2H), 5.12 (m, 1H), 3.60 (m, 2H), 3.18 (d, 1H), 3.00 (m, 2H), 2.56 (s, 3H), 2.15 (m, 2H), 1.80 (m, 2H), 1.55 (m, 3H), 0.86 (m, 3H), 0.68 (m, 3H), 0.49 (m, 3H); LC/MS *m/z* 523 $(M + H)^+$



(±)-(*cis,trans*)-3,5-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-67)

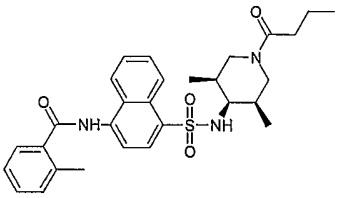
The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, trans)-N*-[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-

methyl-benzamide (**C-64**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H), 8.35 (m, 2H), 8.19 (s, 1H), 7.95 (d, 1H), 7.66 (m, 3H), 7.38 (m, 3H), 4.79 (d, 1H), 4.05 (m, 2H), 3.74 (m, 2H), 2.95 (m, 2H), 2.59 (s, 3H), 2.40 (m, 1H),1.80 (s, br, 2H), 1.18 (t, 3H), 0.62 (m, 6H); LC/MS *m/z* 525 $(M + H)^+$



(±)-(*cis*,*cis*)-*N*-[4-(3,5-Dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-68)

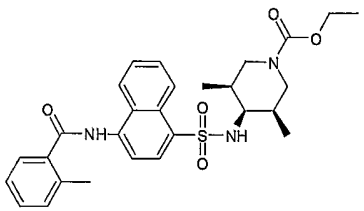
The title compound was made following general procedure in Scheme 4-2, substituting (±)-1-benzyl-3,5-dimethyl-piperidin-4-ylamine (**5**) for (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**6**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H), 8.39 (s, 1H), 8.16 (d, 1H), 8.05 (m, 2H), 7.58 (m, 3H), 7.32 (m, 1H), 7.20 (m, 2H), 3.75 (s, br, 1H), 3.45 (s, 1H), 2.75 (m, 2H), 2.56 (m, 2H), 2.45 (s, 3H), 1.82 (m, 2H), 0.40 (d, 6H); LC/MS *m/z* 453 $(M + H)^+$



(±)-(*cis*,*cis*)-*N*-[4-(1-Butyryl-3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-69)

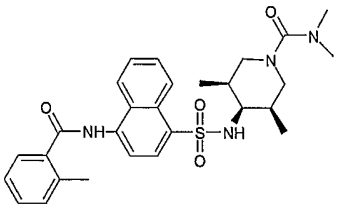
The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, cis*)- *N* -[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-68**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting butyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H), 8.28 (m, 3H), 7.96 (d, 1H), 7.64 (m, 3H), 7.42 (m, 1H), 7.32 (m, 2H), 5.16 (d, 1H), 4.18 (dd, 1H), 3.51 (d, 1H), 3.38 (d, 1H), 2.68

(t, 1H), 2.55 (s, 3H), 2.18 (m, 3H), 1.62 (m, 4H), 0.90 (t, 3H), 0.63 (d, 3H), 0.36 (d, 3H); LC/MS *m/z* 523 $(M + H)^+$



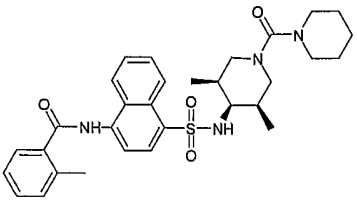
(±)-(*cis,cis*)-3,5-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-70)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, cis*)-*N*-[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-68**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting ethyl chloroformate for 2-isocyanato-propane. ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H), 8.33 (m, 2H), 8.15 (s, 1H), 7.94 (d, 1H), 7.67 (m, 3H), 7.37 (m, 3H), 4.77 (d, 1H), 4.07 (q, 2H), 3.75 (s, br, 2H), 3.48 (m, 2H), 2.58 (s, 3H), 2.37 (m, 1H), 1.72 (m, 2H), 1.22 (t, 3H), 0.48 (s, br, 6H); LC/MS *m/z* 525 $(M + H)^+$



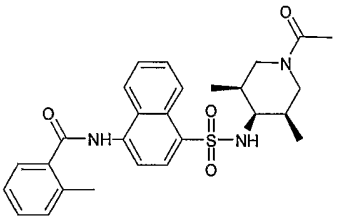
(±)-(*cis,cis*)-3,5-Dimethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (C-71)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis, cis*)- *N* -[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-68**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting dimethylcarbamyl chloride for 2-isocyanato-propane. ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H), 8.26 (m, 3H), 7.95 (d, 1H), 7.65 (m, 3H), 7.34 (m, 3H), 5.20 (d, 1H), 3.51 (m, 1H), 3.20 (d, 2H), 2.76 (s, 6H), 2.56 (s, 3H), 2.40 (t, 2H), 1.78 (m, 2H), 0.44 (dd, 6H); LC/MS *m/z* 524 $(M + H)^+$



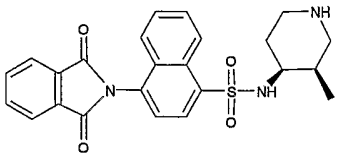
(±)-(*cis*,*cis*)-*N*-{4-[3,5-Dimethyl-1-(piperidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-72)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis*, *cis*)- *N* -[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-68**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting piperidine-1-carbonyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H), 8.33 (s, 1H), 8.25 (m, 2H), 7.95 (d, 1H), 7.63 (m, 3H), 7.32 (m, 3H), 5.08 (d, 1H), 3.49 (d, 1H), 3.18 (dd, 2H), 3.07 (s, br, 4H), 2.55 (s, 3H), 2.39 (t, 2H), 1.75 (m, 2H), 1.50 (s, br, 5H), 0.43 (dd, 6H); LC/MS *m/z* 564 $(M + H)^+$



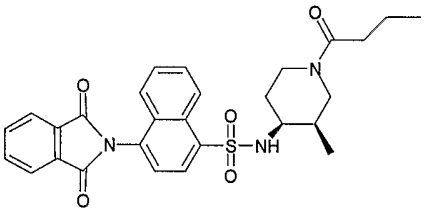
(±)-(*cis*,*cis*)-*N*-[4-(1-Acetyl-3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-73)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis*, *cis*)-*N*-[4-(3,5-dimethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-68**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting acetyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H), 8.28 (m, 3H), 7.76 (d, 1H), 7.64 (m, 3H), 7.35 (m, 3H), 5.26 (d, 1H), 4.16 (dd, 1H), 3.51 (dd, 1H), 3.32 (dd, 1H), 3.32 (dd, 1H), 2.74 (t, 1H), 2.56 (s, 3H), 2.18 (t, 1H), 1.99 (s, 3H), 1.70 (m, 2H), 0.60 (d, 3H), 0.38 (d, 3H); LC/MS *m/z* 495 $(M + H)^+$



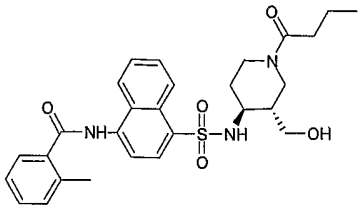
(±)-(*cis*)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (3-methyl-piperidin-4-yl)-amide (C-74)

The title compound was made as its formate salt following general procedure in Scheme 4-2, substituting (±)-1-benzyl-3-methyl-piperidin-4-ylamine (**1**) for (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**6**) and substituting 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonyl chloride for 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.88 (d, 1H), 8.45 (s, 1H), 8.39 (d, 1H), 8.02 (m, 2H), 7.93 (m, 2H), 7.80 (m, 2H), 7.67 (d, 2H), 3.50 (m, 1H), 3.05 (m, 3H), 2.80 (t, 1H), 1.95 (m, 1H), 1.65 (m, 2H), 0.60 (d, 3H); LC/MS *m/z* 451 $(M + H)^+$



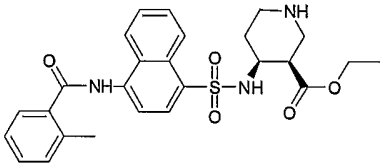
(±)-(*cis*)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (C-75)

The title compound was made following general procedure in Scheme 5, substituting (±)-(*cis*)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (3-methyl-piperidin-4-yl)-amide (**C-74**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting butyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (dd, 1H), 8.41 (dd, 1H), 8.03 (dd, 2H), 7.88 (m, 2H), 7.74 (m, 2H), 7.58 (m, 2H), 5.25 (dd, 1H), 3.30 (m, 4H), 2.22 (m, 2H), 1.65 (m, 6H), 0.90 (t, 3H), 0.70 (dd, 3H); LC/MS *m/z* 521 $(M + H)^+$



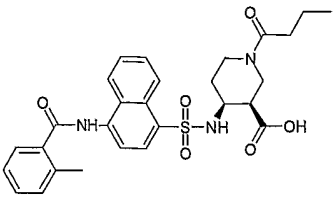
(±)-(*trans*)-*N*-[4-(1-butyryl-3-hydroxymethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-76)

(±)-(*trans*)-1-Butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting butyl chloride for 2-isocyanato-propane. To the solution of (±)-(*trans*)-1-butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (121 mg, 0.21 mmol) in THF (5 mL), was added lithium borohydride in THF solution (1.07 mL, 2.1 mmol) and the resultant solution was stired at 0 °C for 2h. The solvent was removed *in vacuo* and the crude material was purified by HPLC to give the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.32 (dd, 1H), 8.24 (d, 1H), 7.93 (d, 1H), 7.70 (m, 3H), 7.38 (m, 3H), 4.00 (m, 3H), 3.20 (m, 2H), 2.88 (m, 1H), 2.55 (s, 3H), 2.46 (m, 1H), 2.28 (m, 2H), 1.50 (m, 3H), 1.24 (m, 2H), 0.90 (dd, 3H); LC/MS *m/z* 525 $(M + H)^+$



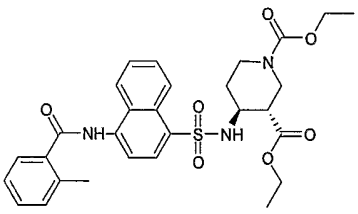
(±)-(*cis*)-4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (C-77)

The title compound was prepared as its formate salt following general procedure in Scheme 4-2. ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, 1H), 8.52 (s, 1H), 8.34 (d, 1H), 8.25 (d, 3H), 7.97 (d, 1H), 7.71 (m, 3H), 7.40 (m, 3H), 3.93 (m, 1H), 3.70 (m, 2H), 3.28 (m, 2H), 3.07 (m, 2H), 2.90 (m, 1H), 2.56 (s, 3H), 1.82 (m, 2H), 0.98 (t, 3H); LC/MS *m/z* 497 $(M + H)^+$



(±)-(*cis*)-1-Butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid (C-78)

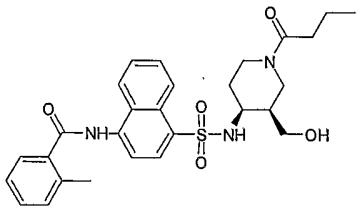
(±)-(*cis*)-1-Butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting butyl chloride for 2-isocyanato-propane. To the solution of (±)-(*cis*)-1-butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (70 mg, 0.12 mmol) in THF (5 mL), was added lithium hydroxide in water solution (6 mg, 0.25 mmol) and the resultant solution was stired at 25 °C for 2h. The reaction mixture was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide the crude product. HPLC purification of the residue gave the title compound. ^{1}H NMR (300 MHz, DMSO) δ 10.62 (s, 1H), 8.77 (t, 1H), 8.24 (m, 3H), 7.95 (d, 1H), 7.70 (m, 3H), 7.38 (m, 3H), 3.72 (m, 2H), 3.35 (m, 6H), 3.12 (m, 1H), 2.60 (m, 1H), 2.15 (m, 2H), 1.32 (m, 4H), 0.80 (dd, 3H); LC/MS *m/z* 539 $(M + H)^+$



(±)-(*trans*)-4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1,3-dicarboxylic acid diethyl ester (C-79)

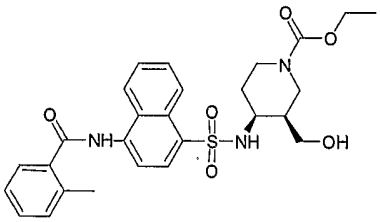
The title compound was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.68 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.70 (m, 3H), 7.38 (m, 3H), 4.00 (m, 4H), 3.48 (m, 3H),

2.85 (m, 2H), 2.55 (s, 3H), 2.36 (dt, 1H), 1.75 (d, 1H), 1.32 (d, 1H), 1.21 (t, 3H), 0.96 (t, 3H); LC/MS *m/z* 568 $(M + H)^+$



(±)-(*cis*)-*N*-[4-(1-Butyryl-3-hydroxymethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-80)

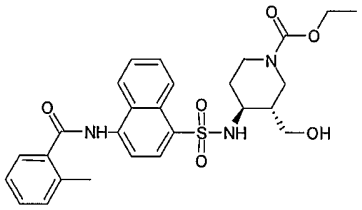
(±)-(*cis*)-1-Butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting butyl chloride for 2-isocyanato-propane. To the solution of (±)-(*cis*)-1-butyryl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (48 mg, 0.085 mmol) in THF (5 mL), was added lithium borohydride in THF solution (0.5 mL, 0.25 mmol) and the resultant solution was stired at 0 °C for 2h. The solvent was removed *in vacuo* and the crude material was purified by HPLC to give the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.81 (d, 1H), 8.34 (d, 1H), 8.25 (d, 1H), 7.95 (d, 1H), 7.72 (m, 3H), 7.40 (m, 3H), 3.46 (m, 7H), 2.56 (s, 3H), 2.32 (m, 2H), 2.55 (s, 3H), 1.52 (m, 5H), 0.92 (m, 3H); LC/MS *m/z* 525 $(M + H)^+$



(±)-(*cis*)-3-Hydroxymethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-81)

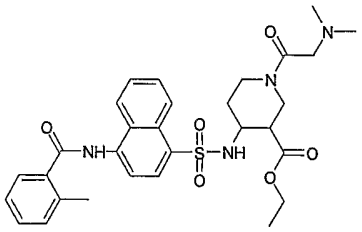
(±)-(*cis*)-4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1,3-dicarboxylic acid diethyl ester was made following general procedure in Scheme

5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and substituting ethyl chloroformate for 2-isocyanato-propane. To the solution of (±)-(*cis*)- 4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1,3-dicarboxylic acid diethyl ester (57 mg, 0.1 mmol) in THF (5 mL), was added lithium borohydride in THF solution (0.5 mL, 0.25 mmol) and the resultant solution was stired at 0 °C for 2h. The solvent was removed *in vacuo* and the crude material was purified by HPLC to give the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.81 (d, 1H), 8.33 (d, 1H), 8.24 (d, 1H), 7.94 (d, 1H), 7.72 (m, 3H), 7.40 (m, 3H), 4.06 (q, 2H), 3.55 (m, 2H), 3.32 (m, 5H), 2.56 (s, 3H), 1.75 (m, 1H), 1.30 (m, 2H), 1.20 (t, 3H); LC/MS *m/z* 526 $(M + H)^+$



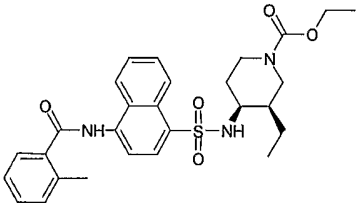
(±)-(*trans*)-3-Hydroxymethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-82)

(±)-(*trans*)-4-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1,3-dicarboxylic acid diethyl ester was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and substituting ethyl chloroformate for 2-isocyanato-propane. To the solution of (±)-(*trans*)- 4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1,3-dicarboxylic acid diethyl ester (57 mg, 0.1 mmol) in THF (5 mL), was added lithium borohydride in THF solution (0.5 mL, 0.25 mmol) and the resultant solution was stired at 0 °C for 2h. The solvent was removed *in vacuo* and the crude material was purified by HPLC to give the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.73 (d, 1H), 8.30 (d, 1H), 8.22 (d, 1H), 7.93 (d, 1H), 7.68 (m, 3H), 7.36 (m, 3H), 4.15 (d, 1H), 4.05 (q, 2H), 3.85 (d, 1H), 3.55 (d, 1H), 3.25 (m, 1H), 3.10 (m, 1H), 2.60 (m, 2H), 2.56 (s, 3H), 1.40 (m, 3H), 1.20 (t, 3H); LC/MS *m/z* 526 $(M + H)^+$



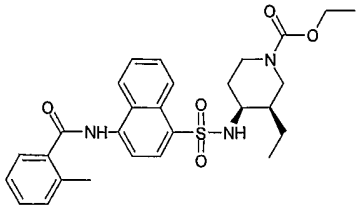
1-(2-Dimethylamino-acetyl)-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-3-carboxylic acid ethyl ester (C-83)

The title compound was made following general procedure in Scheme 5, substituting (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**5**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and substituting dimethylamino-acetyl chloride hydrochloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (m, 1H), 8.32 (m, 3H), 7.94 (d, 1H), 7.64 (m, 3H), 7.36 (m, 3H), 5.95 (m, 1H), 4.10 (m, 4H), 3.50 (s, br, 1H), 3.05 (m, 6H), 2.56 (m, 3H), 2.25 (dd, 6H), 1.84 (m, 1H), 1.10 (m, 3H); LC/MS *m/z* 581 $(M + H)^+$



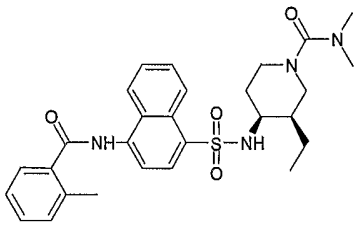
(±)-(*cis*)-3-Ethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-84)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, 1H), 8.37 (m, 2H), 8.13 (s, 1H), 7.93 (d, 1H), 7.66 (m, 3H), 7.43 (m, 1H), 7.33 (m, 2H), 4.78 (d, 1H), 4.05 (m, 2H), 3.42 (m, 1H), 3.22 (m, 4H), 2.58 (s, 3H), 1.35 (s, br, 2H), 1.17 (t, 3H), 1.00 (s, br, 2H), 0.55 (s, br, 3H); LC/MS *m/z* 524 $(M + H)^+$



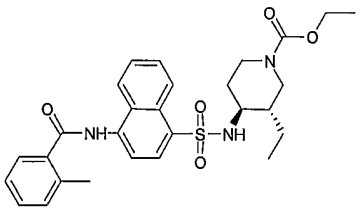
(±)-(*cis*)-*N*-[4-(1-Butyryl-3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-85)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and substituting butyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, 1H), 8.37 (m, 2H), 8.16 (s, 1H), 7.94 (d, 1H), 7.66 (m, 3H), 7.43 (m, 1H), 7.33 (m, 2H), 4.90 (m, 1H), 3.32 (m, 5H), 2.58 (s, 3H), 2.18 (m, 2H), 1.45 (m, 6H), 0.87 (t, 3H), 0.50 (m, 3H); LC/MS *m/z* 522 $(M + H)^+$



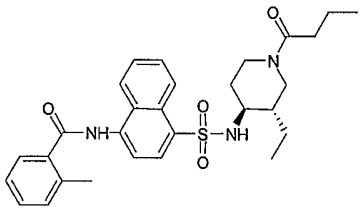
(±)-(*cis*)-3-Ethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (C-86)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and substituting dimethylamino-acetyl chloride hydrochloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, 1H), 8.36 (m, 2H), 8.16 (s, 1H), 7.93 (d, 1H), 7.65 (m, 3H), 7.42 (m, 1H), 7.32 (m, 2H), 4.88 (d, 1H), 3.45 (m, 1H), 3.20 (m, 1H), 3.00 (m, 2H), 2.80 (m, 1H), 2.70 (s, 6H), 2.50 (s, 3H), 1.40 (m, 3H), 1.00 (m, 2H), 0.52 (t, 3H); LC/MS *m/z* 523 $(M + H)^+$



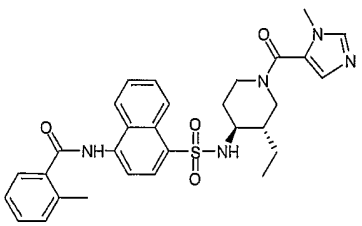
(±)-(*trans*)-3-Ethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-87)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and substituting ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, 1H), 8.36 (m, 2H), 8.12 (s, 1H), 7.93 (d, 1H), 7.66 (m, 3H), 7.43 (m, 1H), 7.33 (m, 2H), 4.50 (d, 1H), 4.05 (m, 2H), 3.55 (d, 1H), 2.95 (m, 1H), 2.70 (t, 1H), 2.57 (s, 3H), 2.49 (m, 1H), 1.50 (m, 3H), 1.17 (m, 5H), 0.85 (m, 1H), 0.65 (s, br, 3H); LC/MS *m/z* 524 $(M + H)^+$



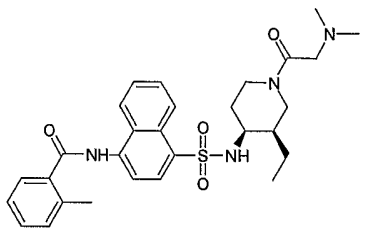
(±)-(*trans*)-*N*-[4-(1-Butyryl-3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-88)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and substituting butyl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (m, 1H), 8.35 (m, 2H), 8.18 (s, 1H), 7.94 (d, 1H), 7.66 (m, 3H), 7.42 (m, 1H), 7.32 (m, 2H), 4.65 (d, 1H), 4.30 (m, 1H), 3.68 (m, 1H), 2.95 (m, 2H), 2.57 (s, 3H), 2.50 (m, 1H), 2.20 (m, 2H), 1.55 (m, 5H), 1.15 (m, 2H), 0.85 (t, 3H), 0.60 (m, 3H); LC/MS *m/z* 522 $(M + H)^+$



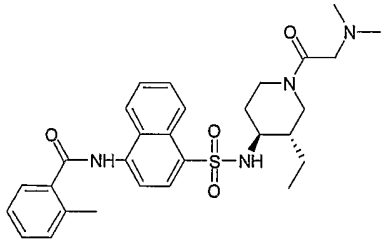
(±)-(*trans*)-*N*-{4-[3-Ethyl-1-(3-methyl-3H-imidazole-4-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-89)

The title compound was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and substituting 3-methyl-3H-imidazole-4-carbonyl chloride hydrochloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.79 (d, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 8.15 (s, 1H), 7.94 (d, 1H), 7.70 (m, 4H), 7.43 (m, 1H), 7.36 (m, 2H), 7.14 (s, 1H), 4.20 (m, 2H), 3.75 (s, 3H), 3.05 (m, 2H), 2.70 (m, 1H), 2.55 (s, 3H), 1.55 (m, 3H), 1.30 (m, 1H), 0.85 (m, 1H), 0.62 (m, 3H); LC/MS *m/z* 560 $(M + H)^+$



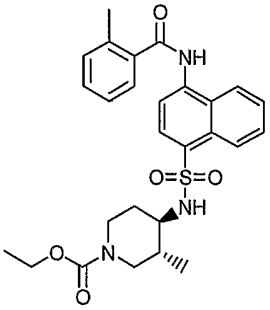
(±)-(*cis*)-*N*-{4-[1-(2-Dimethylamino-acetyl)-3-ethyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-90)

The title compound (formic acid salt) was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester, and substituting dimethylamino-acetyl chloride hydrochloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.85 (d, 1H), 8.55 (s, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.35 (m, 2H), 3.47 (m, 4H), 3.25 (m, 2H), 2.55 (s, 3H), 2.33 (d, 6H), 1.38 (m, 3H), 1.15 (m, 3H), 0.50 (m, 3H); LC/MS *m/z* 537 $(M + H)^+$



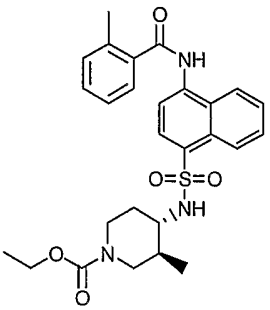
(±)-(*trans*)-*N*-{4-[1-(2-Dimethylamino-acetyl)-3-ethyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-91)

The title compound (formic acid salt) was made following general procedure in Scheme 5, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for 4-amino-piperidine-1-carboxylic acid tert-butyl ester and substituting dimethylamino-acetyl chloride hydrochloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.55 (s, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.35 (m, 2H), 4.05 (m, 2H), 3.10 (m, 3H), 2.60 (m, 1H), 2.55 (s, 3H), 2.30 (s, 6H), 1.25 (m, 2H), 1.10 (m, 3H), 0.90 (m, 1H), 0.85 (m, 3H); LC/MS *m/z* 537 $(M + H)^+$



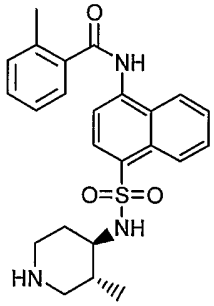
(*3R, 4R*)-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-92)

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3R, 4R*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.92 (d, 1H), 7.73 (m, 3H), 7.35 (m, 3H), 4.03 (q, 2H), 3.94 (t, 2H), 2.85 (dt, 1H), 2.64 (m, 1H), 2.55 (s, 3H), 2.40 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.20 (t, 3H), 0.59 (d, 3H); LC/MS *m/z* 510 $(M + H)^+$.



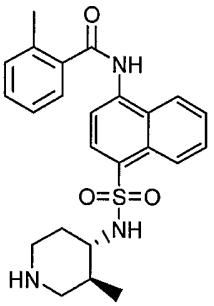
(*3S, 4S*)-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-93)

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3S, 4S*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and ethyl chloroformate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H), 8.30 (d, 1H), 8.23 (d, 1H), 7.92 (d, 1H), 7.73 (m, 3H), 7.35 (m, 3H), 4.03 (q, 2H), 3.94 (t, 2H), 2.85 (dt, 1H), 2.64 (m, 1H), 2.55 (s, 3H), 2.40 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.20 (t, 3H), 0.59 (d, 3H); LC/MS *m/z* 510 $(M + H)^+$.



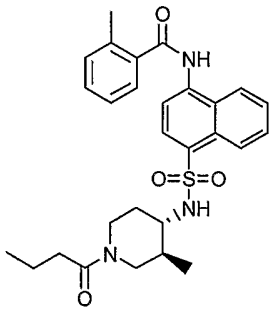
(*3R, 4R*)-2-Methyl-*N*-[4-(3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-94)

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3R, 4R*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (dd, 1H), 8.34 (d, 1H), 8.24 (dd, 1H), 7.94 (d, 1H), 7.78 (m, 1H), 7.74 (m, 1H), 7.69 (m, 1H), 7.44 (m, 1H), 7.37 (m, 2H), 3.23 (m, 2H), 3.00 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.55 (s, 3H), 1.76 (m, 2H), 1.58 (m, 1H), 0.66 (d, 3H); LC/MS *m/z* 438 $(M + H)^+$.



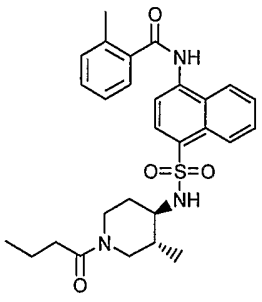
(*3S, 4S*)-2-Methyl-*N*-[4-(3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-95)

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3S, 4S*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (dd, 1H), 8.34 (d, 1H), 8.24 (dd, 1H), 7.94 (d, 1H), 7.78 (m, 1H), 7.74 (m, 1H), 7.69 (m, 1H), 7.44 (m, 1H), 7.37 (m, 2H), 3.23 (m, 2H), 3.00 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.55 (s, 3H), 1.76 (m, 2H), 1.58 (m, 1H), 0.66 (d, 3H); LC/MS *m/z* 438 $(M + H)^+$.



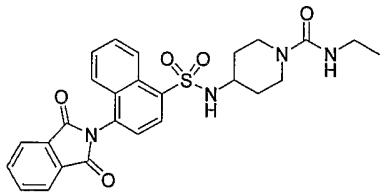
***(3S, 4S)-N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-96)**

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3S, 4S*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (t, 1H), 8.33 (m, 3H), 7.95 (d, 1H), 7.62 (m, 3H), 7.40 (m, 1H), 7.34 (m, 2H), 5.00 (d, 1H), 4.30 (dd, 1H), 3.63 (m, 1H), 2.85 (m, 1.5H), 2.57 (s, 3H), 2.40 (t, 0.5H), 2.15 (m, 1.5H), 2.09 (m, 0.5H), 1.83 (m, 0.5H), 1.50 (m, 1.5H); LC/MS *m/z* 508 $(M + H)^+$.



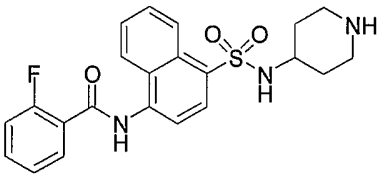
***(3R, 4R)-N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-97)**

The title compound was prepared according to the general procedure in Scheme 5, substituting (*3R, 4R*)-4-amino-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (t, 1H), 8.33 (m, 3H), 7.95 (d, 1H), 7.62 (m, 3H), 7.40 (m, 1H), 7.34 (m, 2H), 5.00 (d, 1H), 4.30 (dd, 1H), 3.63 (m, 1H), 2.85 (m, 1.5H), 2.57 (s, 3H), 2.40 (t, 0.5H), 2.15 (m, 1.5H), 2.09 (m, 0.5H), 1.83 (m, 0.5H), 1.50 (m, 1.5H); LC/MS *m/z* 508 $(M + H)^+$.



4-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-98)

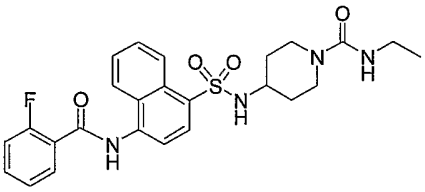
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonyl chloride, and substituting ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 8.75 (d, 1H), 8.29 (d, 1H), 8.23 (d, 1H), 8.03 (m, 5H), 7.83 (d, 1H), 7.80 (t, 1H), 7.67 (t, 1H), 6.36 (t, 1H), 3.69 (d, 2H), 3.27 (m, 1H), 2.97 (p, 2H), 2.64 (t, 2H), 1.47 (d, 2H), 1.23 (m, 2H), 0.95 (t, 3H); LC/MS *m/z* 505 $(M - H)^-$.



2-Fluoro-*N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-99)

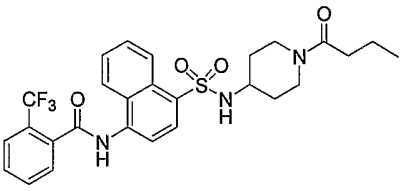
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-fluoro-benzoylamino)-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.72 (s, 1H), 8.67 (d, 1H), 8.30 (d, 1H), 8.20 (d, 1H), 8.10 (d, 1H), 8.01 (d, 1H), 7.83 (t, 1H), 7.74 (t, 2H), 7.65 (m, 1H), 7.41 (q, 2H), 3.67

(d, 2H), 3.18 (m, 1H), 2.70 (m, 2H), 1.43 (m, 2H), 1.18(m, 2H); LC/MS *m/z* 426 (M - H)$^-$, 428 (M + H)$^+$



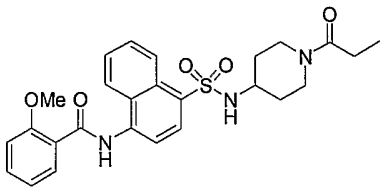
4-[4-(2-Fluoro-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-100)

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-fluoro-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting ethyl isocyanate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.74 (s, 1H), 8.67 (d, 1H), 8.29 (d, 1H), 8.19 (d, 1H), 8.05 (d, 1H), 7.99 (d, 1H), 7.82 (t, 1H), 7.73 (t, 2H), 7.65 (t, 2H), 7.41 (q, 2H), 6.32 (t, 1H), 3.67 (d, 2H), 3.17 (m, 1H), 2.94 (m, 2H), 2.59 (t, 2H), 1.36 (d, 2H), 1.14 (m, 2H), 0.95 (t, 3H); /MS *m/z* 498 (M - H)$^-$, 500 (M + H)$^+$



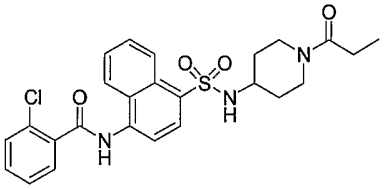
***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-trifluoromethyl-benzamide (C-101)**

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-trifluoromethyl-benzoylamino)-naphthalene-1-sulfonyl chloride and substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.91(s, 1H), 8.68 (d, 1H), 8.25 (m, 2H), 8.11 (d, 1H), 7.85 (m, 4H), 7.76 (m, 3H), 4.06 (m, 1H), 4.01(m, 1H), 3.62 (d, 1H), 2.94 (t, 1H), 2.59 (t, 2H), 1.48 (m, 2H), 1.41 (m, 2H), 1.19 (m, 2H), 0.82 (t, 3H); LC/MS *m/z* 546 (M - H)$^-$, 548 (M + H)$^+$



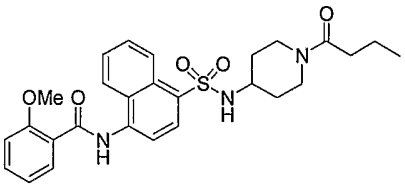
2-Methoxy-*N*-[4-(1-propionyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-102)

The title compound was prepared following the general procedure in Scheme 5 beginning with 4-(2-methoxy-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting propionyl chloride and triethylamine for 2-isocyanato-propane. LC/MS *m/z* 495 $(M - H)^-$, 497 $(M + H)^+$



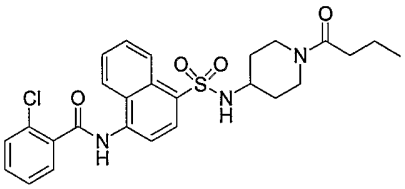
2-Chloro-*N*-[4-(1-propionyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-103)

The title compound was prepared following the general procedure in Scheme 5 beginning with 4-(2-chloro-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting propionyl chloride and triethylamine for 2-isocyanato-propane. ^1H NMR (300 MHz, DMSO) δ 10.86 (s, 1H), 8.68 (d, 1H), 8.33 (d, 1H), 8.22 (d, 1H), 8.12 (d, 1H), 7.98 (d, 1H), 7.74 (m, 3H), 7.64 (t, 1H), 7.54 (m, 2H), 4.01 (m, 1H), 3.59 (d, 1H), 3.24 (m, 1H), 3.16 (d, 1H), 2.96 (t, 1H), 2.20 (q, 2H), 1.51 (d, 2H), 1.20 (m, 2H), 0.81 (t, 3H); LC/MS *m/z* 498 $(M - H)^-$, 500 $(M + H)^+$



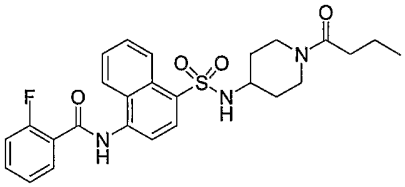
N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methoxy-benzamide (C-104)

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-methoxy-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting butyric chloride and triethylamine for 2-isocyanato-propane. LC/MS *m/z* 508 $(M - H)^-$, 510 $(M + H)^+$



***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-chloro-benzamide (C-105)**

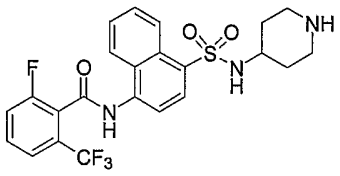
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-chloro-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.86 (s, 1H), 8.68 (d, 1H), 8.35 (d,1H), □□□(d,1H), 8.13 (d, 1H), 8.0 (m, 1H), 7.74 (m, 3H), 7.64 (m, 3H), 4.00 (d, 1H), 3.60 (d, 1H), 3.26 (m, 1H), 2.93 (t, 1H), 2.59 (m, 2H), 2.17 (t, 2H), 1.46 (m, 2H), 1.43 (q, 2H), 1.17 (m, 1H), 0.82 (t, 3H); LC/MS *m/z* 512 $(M - H)^-$, 514 $(M + H)^+$



***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-fluoro-benzamide (C-106)**

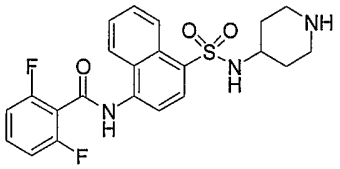
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-fluoro-benzoylamino)-naphthalene-1-sulfonyl chloride and substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.73 (s, 1H), 8.69 (d, 1H), 8.28 (d, 1H), 8.21 (d, 1H), 8.11 (d, 1H), 7.99 (d, 1H), 7.83 (t, 1H), 7.76 (m, 2H), 7.64 (m, 1H), 7.40 (q, 2H), 4.00 (d, 1H), □.60 (d, 1H), 3.26 (m, 1H), 2.93 (t, 1H), 2.59 (m, 2H), 2.17 (t, 2H), 1.46 (m,

2H), 1.43 (q, 2H), 1.17 (m, 1H), 0.82 (t, 3H); LC/MS *m/z* 496 (M - H)$^-$, 498 (M + H)$^+$



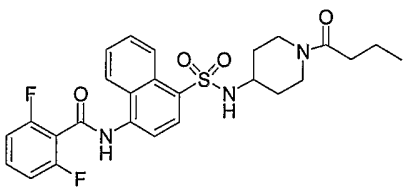
2-Fluoro-*N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-6-trifluoromethyl-benzamide (C-107)

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-fluoro-6-trifluoromethyl-benzoylamino)-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 11.15 (s, 1H), 8.70 (d, 1H), 8.32 (d, 1H), 8.29 (m, 1H), 8.01 (d, 1H), 7.77 (m, 1H), 7.65 (m, 1H), 7.32 (m, 1H), 6.94 (m, 1H), 3.08 (d, 1H), 2.85 (m, 1H), 2.54 (m, 5H), 1.64 (m, 1H), 1.51 (m, 1H). LC/MS *m/z* 494 (M - H)$^-$, 496 (M + H)$^+$



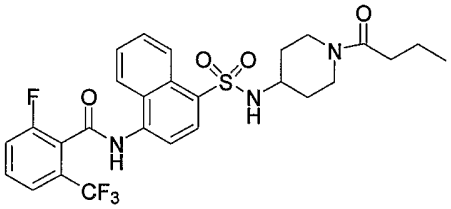
2,6-Difluoro-*N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-108)

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2,6-difluoro-benzoylamino)-naphthalene-1-sulfonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 11.15 (s, 1H), 8.70 (d, 1H), 8.32 (d, 1H), 8.29 (m, 1H), 8.01 (d, 1H), 7.77 (m, 1H), 7.65 (m, 1H), 7.32 (m, 1H), 6.94 (m, 1H), 3.08 (d, 1H), 2.85 (m, 1H), 2.54 (m, 5H), 1.64 (m, 1H), 1.51 (m, 1H). LC/MS *m/z* 444 (M - H)$^-$, 446 (M + H)$^+$



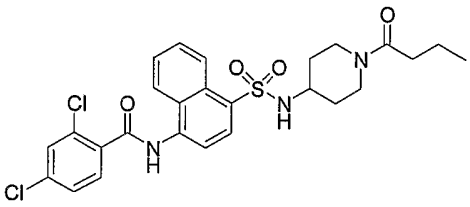
N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2,6-difluoro-benzamide (C-109)

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2,6-difluoro-benzoylamino)-naphthalene-1-sulfonyl chloride, and substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 11.12(s, 1H), 8.71 (m, 1H), 8.26 (m, 2H), 8.13 (d, 1H), 7.98 (d, 1H), 7.75 (m, 2H), 7.62 (m, 1H), 7.31 (t, 2H), 4.01 (d, 1H), 3.60 (d, 1H), 2.93 (t, 1H), 2.59 (m, 2H), 2.15 (t, 2H), 1.45 (m, 2H), 1.43 (q, 2H), 1.17 (m, 2H), 0.81 (t, 3H); LC/MS *m/z* 514 $(M - H)^-$, 516 $(M + H)^+$



N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-fluoro-6-trifluoromethyl-benzamide (C-110)

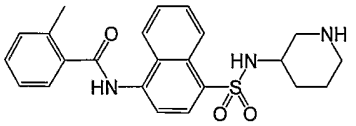
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2-fluoro-6-trifluoromethyl-benzoylamino)-naphthalene-1-sulfonyl chloride and substituting butyric chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 11.12 (s, 1H), 8.71 (m, 1H), 8.26 (m, 2H), 8.13 (m, 1H), 7.98 (d, 1H), 7.79 (m, 6H), 4.01 (d, 1H), 3.60 (d, 1H), 2.93 (t, 1H), 2.59 (m, 2H), 2.15 (t, 2H), 1.45 (m, 2H), 1.43 (q, 2H), 1.17 (m, 2H), 0.81 (t, 3H). LC/MS *m/z* 514 $(M - H)^-$, 516 $(M + H)^+$



N-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2,4-dichloro-benzamide (C-111)

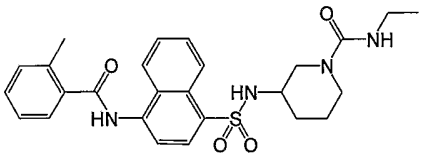
The title compound was prepared following the general procedure in Scheme 5, beginning with 4-(2,4-dichloro-benzoylamino)-naphthalene-1-sulfonyl chloride and

substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.87 (s, 1H), 8.70 (dd, 1H), 8.34 (dd, 1H), 8.21 (d, 1H), 8.13 (d, 1H), 8.01 (d, 1H), 7.82 (m, 2H), 7.73 (m, 1H), 7.63 (d, 1H), 4.00 (d, 1H), 3.6 (d, 1H), 3.24 (m, 1H), 2.92 (t, 1H), 2.59 (m, 1H), 2.17 (t, 2H), 1.47 (m, 2H), 1.43 (m, 2H), 1.18 (m, 2H), 0.82 (t, 3H). LC/MS *m/z* 548 $(M - H)^-$, 560 $(M + H)^+$



(±)-2-Methyl-*N*-[4-(piperidin-3-ylsulfamoyl)-naphthalen-1-yl]-benzamide (C-112)

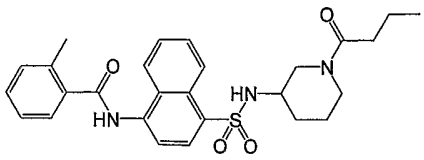
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and 3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 2H), 8.25 (d, 1H), 7.96 (d, 1H), 7.71 (m, 3H), 7.45 (m, 1H), 7.38 (m, 2H), 3.33 (m, 1H), 3.19 (m, 2H), 2.70 (m, 2H), 2.57 (s, 3H), 1.83 (m, 1H), 1.55 (m, 3H); LC/MS $(M + H)^+$ *m/z* 424.



(±)-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (C-113)

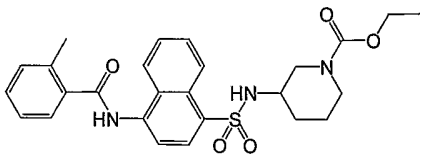
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.79 (m,

1H), 3.55 (m, 1H), 3.12 (q, 2H), 3.10 (m, 1H), 2.85 (m, 1H), 2.72 (m, 1H), 2.55 (s, 3H), 1.58 (m, 2H), 1.30 (m, 2H), 1.19 (m, 3H); LC/MS $(M + H)^+$ *m/z* 495.



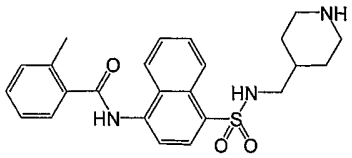
(±)-*N*-[4-(1-Butyryl-piperidin-3-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-114)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (m, 1H), 8.33 (m, 2H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 3.79 (m, 1H), 3.91 (m, 1H), 3.55 (q, 1H), 3.08 (m, 1H), 2.95 (m, 1H), 2.82 (m, 1H), 2.55 (s, 3H), 2.01 (m, 2H), 1.50 (m, 6H), 0.90 (m, 3H); LC/MS $(M + H)^+$ *m/z* 494.



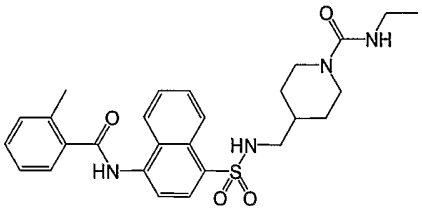
(±)-3-[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-115)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl chlorofomate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (m, 1H), 8.33 (m, 2H), 8.23 (m, 1H), 7.94 (m, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.02 (m, 2H), 3.70 (m, 2H), 3.06 (m, 1H), 2.69 (m, 1H), 2.38 (m, 1H), 2.55 (s, 3H), 1.71 (m, 2H), 1.30 (m, 2H), 1.18 (m, 3H); LC/MS $(M + H)^+$ *m/z* 496.



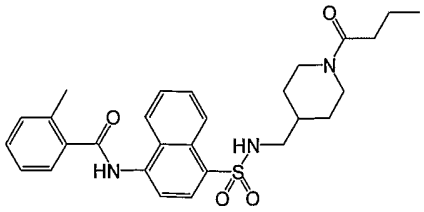
2-Methyl-*N*-{4-[(piperidin-4-ylmethyl)-sulfamoyl]-naphthalen-1-yl}-benzamide (C-116)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, and 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.29 (m, 2H), 7.93 (m, 1H), 7.74 (m, 3H), 7.41 (m, 3H), 3.30 (m, 2H), 2.82 (m, 2H), 2.80 (d, 2H), 2.55 (s, 3H), 1.84 (m, 2H), 1.65 (m, 1H), 1.28 (m, 2H); LC/MS $(M + H)^+$ *m/z* 438.



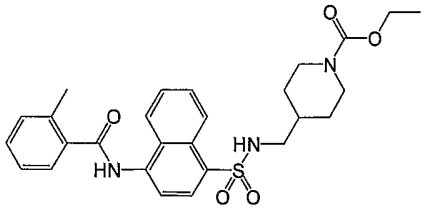
4-{[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-methyl}-piperidine-1-carboxylic acid ethylamide (C-117)

The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and isocyanato-ethane for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.29 (m, 2H), 7.93 (m, 1H), 7.74 (m, 3H), 7.41 (m, 3H), 3.79 (m, 2H), 3.25 (q, 2H), 2.78 (d, 2H), 2.61 (m, 2H), 2.57 (s, 3H), 1.56 (m, 3H), 1.09 (t, 3H), 0.92 (m, 2H); LC/MS $(M + H)^+$ *m/z* 509.



N-{4-[(1-Butyryl-piperidin-4-ylmethyl)-sulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-118)

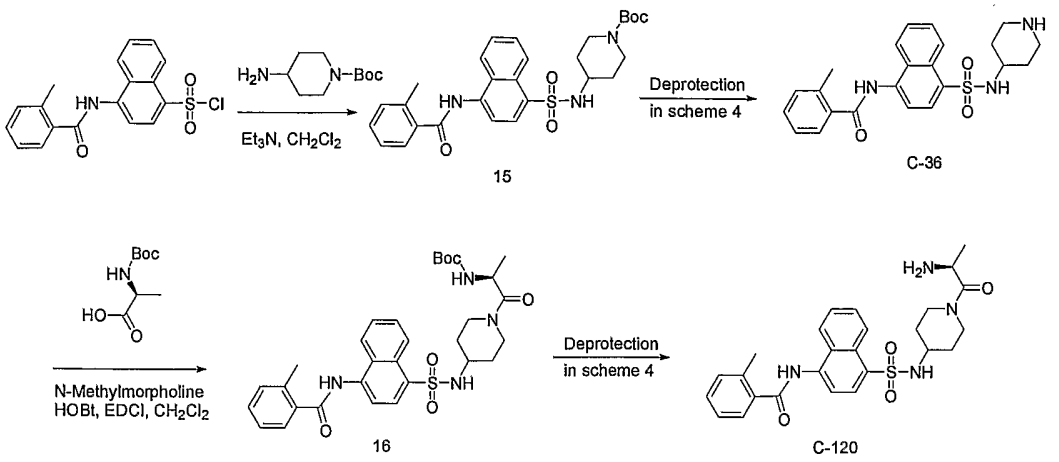
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and butyryl chloride for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.29 (m, 2H), 7.93 (m, 1H), 7.74 (m, 3H), 7.41 (m, 3H), 4.49 (m, 1H), 3.85 (m, 1H), 2.89 (m, 1H), 2.78 (d, 2H), 2.57 (s, 3H), 2.41 (m, 1H), 2.30 (t, 2H), 1.61 (m, 5H), 0.96 (t, 3H), 0.93 (m, 2H); LC/MS $(M + H)^+$ *m/z* 508.



4-{[4-(2-Methyl-benzoylamino)-naphthalene-1-sulfonylamino]-methyl}-piperidine-1-carboxylic acid ethyl ester (C-119)

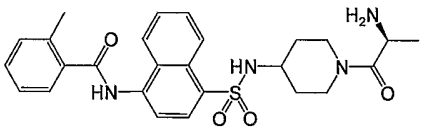
The title compound was made following general procedure in Scheme 5, substituting 4-(2-methyl-benzoylamino)-naphthalene-1-sulfonyl chloride for 4-benzoylamino-naphthalene-1-sulfonyl chloride, 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and ethyl chlorofomate for 2-isocyanato-propane. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.29 (m, 2H), 7.93 (m, 1H), 7.74 (m, 3H), 7.41 (m, 3H), 4.09 (q, 2H), 4.00 (m, 2H), 2.78 (d, 2H), 2.59 (m, 2H), 2.57 (s, 3H), 1.59 (m, 3H), 1.22 (t, 3H), 0.90 (m, 2H); LC/MS $(M + H)^+$ *m/z* 510.

Scheme 6



4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (15)

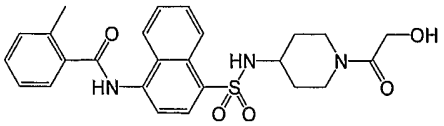
The title compound was prepared following the general procedure in Scheme 2, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine and 2-methylbenzoyl chloride for benzoyl chloride. LC/MS $(M + H)^+$ *m/z* 524.



(*S*)-*N*-{4-[1-(2-Amino-propionyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-120)

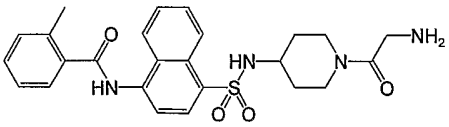
2-Methyl-*N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide **(C-36)** was prepared from 4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester **15** via coupling and deprotection as shown in Scheme 4-1. To a 25 °C mixture of 2-methyl-*N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide **(C-36)** hydrochloride (368 mg, 0.8 mmol) in CH_2Cl_2 (12 mL), was added 1-hydroxybenzotriazole hydrate (108 mg, 0.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.96 mmol), *N*-methylmorpholine (243 mg, 2.4 mmol) and (*S*)-2-tert-butoxycarbonylamino-propionic acid. After stirring at 25 °C for 20 hours, the reaction mixture was filtered and the filtrate was concentrated to dryness *in vacuo* to afford **16**. A solution of 4N HCl/Dioxane (5 mL) was added and the mixture was

stirred for 2 hours. After removing the solvent, the crude product was purified *via* chromatography. ^{1}H NMR (300 MHz, MeOD) δ 8.71 (d, 1H), 8.28 (m, 3H), 7.96 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.00 (m, 2H), 3.60 (m, 2H), 3.01 (m, 1H), 2.71 (m, 1H), 2.49 (s, 3H), 1.57 (m, 2H), 1.22 (m, 2H), 1.09 (m, 3H); LC/MS $(M + H)^+$ *m/z* 495.



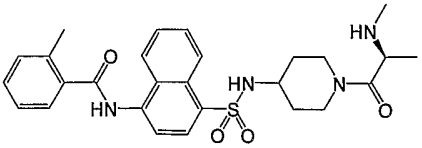
***N*-{4-[1-(2-Hydroxy-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-121)**

The title compound was made following general procedure in Scheme 6, substituting hydroxy-acetic acid for (*S*)-2-*tert*-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.16 (m, 1H), 4.13 (s, 2H), 3.55 (m, 1H), 3.34 (m, 1H), 2.95 (m, 1H), 2.74 (m, 1H), 2.55 (s, 3H), 1.63 (m, 2H), 1.41 (m, 2H); LC/MS $(M + H)^+$ *m/z* 483.



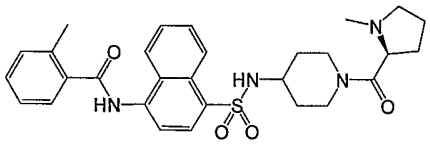
***N*-{4-[1-(2-Amino-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-122)**

The title compound was made following general procedure in Scheme 6, substituting *tert*-butoxycarbonylamino-acetic acid for (*S*)-2-*tert*-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.25 (m, 3H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.05 (m, 1H), 3.60 (m, 4H), 2.95 (m, 1H), 2.74 (m, 1H), 2.49 (s, 3H), 1.55 (m, 2H), 1.31 (m, 2H); LC/MS $(M + H)^+$ *m/z* 481.



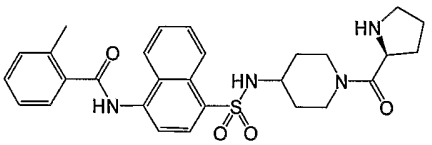
(*S*)-2-Methyl-*N*-{4-[1-(2-methylamino-propionyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-123)

The title compound was made following general procedure in Scheme 6, substituting (*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-propionic acid for (*S*)-2-tert-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.25 (m, 3H), 7.96 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.10 (m, 1H), 3.60 (m, 2H), 3.01 (m, 1H), 2.71 (m, 1H), 2.49 (s, 3H), 2.19 (d, 3H), 1.57 (m, 2H), 1.22 (m, 2H), 1.05 (m, 3H); LC/MS $(M + H)^+$ *m/z* 509.



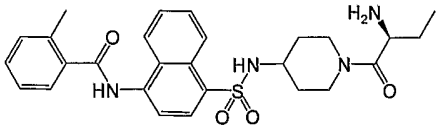
(*S*)-2-Methyl-*N*-{4-[1-(1-methyl-pyrrolidine-2-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-124)

The title compound was made following general procedure in Scheme 6, substituting (*S*)-1-methyl-pyrrolidine-2-carboxylic acid for (*S*)-2-*tert*-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.25 (m, 3H), 7.96 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.03 (m, 2H), 3.40 (m, 5H), 2.99 (m, 1H), 2.68 (m, 1H), 2.49 (s, 3H), 2.21 (d, 3H), 2.02 (m, 1H), 1.71 (m, 2H), 1.55 (m, 2H), 1.20 (m, 2H); LC/MS $(M + H)^+$ *m/z* 535.



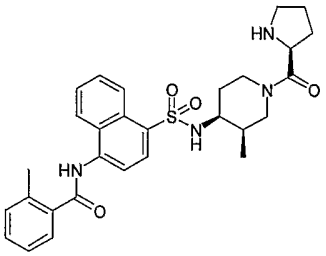
(*S*)-2-Methyl-*N*-{4-[1-(pyrrolidine-2-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-125)

The title compound was made following general procedure in Scheme 6, substituting (*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester for (*S*)-2-*tert*-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.25 (m, 3H), 7.96 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.03 (m, 2H), 3.40 (m, 2H), 3.02 (m, 2H), 2.78 (m, 2H), 2.49 (s, 3H), 2.06 (m, 1H), 1.62 (m, 5H), 1.25 (m, 2H); LC/MS $(M + H)^+$ *m/z* 521.



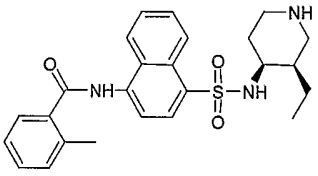
(*S*)-*N*-{4-[1-(2-Amino-butyryl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-126)

The title compound was made following general procedure in Scheme 6, substituting (*S*)-2-*tert*-butoxycarbonylamino-butyric acid for (*S*)-2-*tert*-butoxycarbonylamino-propionic acid. ^{1}H NMR (300 MHz, MeOD) δ 8.71 (d, 1H), 8.28 (m, 3H), 7.96 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.38 (m, 2H), 4.09 (m, 1H), 3.78 (m, 2H), 3.01 (m, 2H), 2.71 (m, 1H), 2.49 (s, 3H), 1.57 (m, 2H), 1.25 (m, 4H), 0.82 (m, 3H); LC/MS $(M + H)^+$ *m/z* 509.



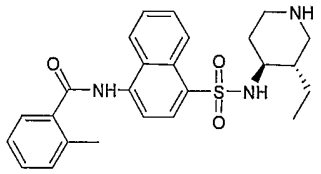
(±)-cis-2-Methyl-*N*-{4-[3-methyl-1-((s)-pyrrolidine-2-carbonyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-127) (mixture of two diastereomers)

The title compound (mixture of disatereomers) was made following general procedure in scheme 6, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid tert-butyl ester, and substituting (s)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester for (s)-2-tert-butoxycarbonylamino-propionic acid. LC/MS $(M + H)^+$ *m/z* 535.



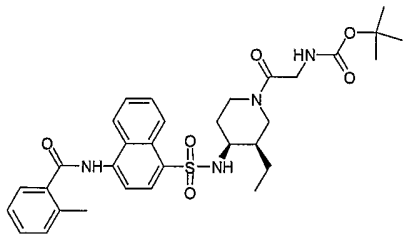
(±)-(*cis*)-*N*-[4-(3-Ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-128)

The title compound was prepared as its formate salt following general procedure in scheme 4-2, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**6**). ^{1}H NMR (300 MHz, MeOD) δ 8.84 (d, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 8.26 (d, 1H), 7.96 (d, 1H), 7.73 (m, 3H), 7.38 (m, 3H), 3.55 (m, 1H), 3.05 (m, 3H), 2.92 (m, 1H), 2.55 (s, 3H), 1.68 (m, 3H), 1.00 (m, 2H), 0.42 (t, 3H); LC/MS *m/z* 452 $(M + H)^+$



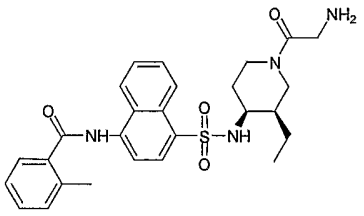
(±)-(*trans*)-*N*-[4-(3-Ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-129)

The title compound was prepared as its formate salt following general procedure in scheme 4-2, substituting (±)-1-benzyl-3-ethyl-piperidin-4-ylamine (**3**) for (±)-4-amino-1-benzyl-piperidine-3-carboxylic acid ethyl ester (**6**). ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.53 (s, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.72 (m, 3H), 7.40 (m, 3H), 3.35 (m, 1H), 3.20 (m, 2H), 2.85 (m, 1H), 2.60 (m, 1H), 2.56 (s, 3H), 1.75 (m, 1H), 1.52 (m, 3H), 0.90 (m, 1H), 0.58 (t, 3H); LC/MS *m/z* 452 $(M + H)^+$



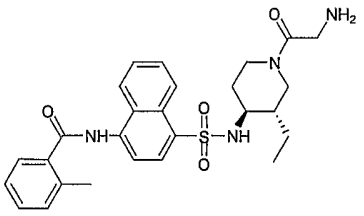
(±)-(*cis*)-(2-{3-Ethyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidin-1-yl}-2-oxo-ethyl)-carbamic acid tert-butyl ester (C-130)

The title compound was made following general procedure in Scheme 6, substituting (±)-(*cis*)-*N*-[4-(3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-128**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting *tert*-butoxycarbonylamino-acetic acid for 3-*tert*-butoxycarbonylamino-butyric acid. ^{1}H NMR (300 MHz, MeOD) δ 8.85 (d, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.95 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.36 (m, 2H), 3.80 (s, 2H), 3.45 (m, 3H), 3.25 (m, 2H), 2.56 (s, 3H), 1.40 (m, 12H), 1.04 (m, 2H), 0.50 (m, 3H); LC/MS *m/z* 609 $(M + H)^+$



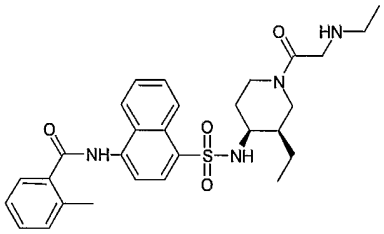
(±)-(*cis*)-*N*-{4-[1-(2-Amino-acetyl)-3-ethyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-131)

The title compound was prepared as its formate salt following general procedure in Scheme 6, substituting (±)-(*cis*)-*N*-[4-(3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-128**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**), and substituting *tert*-butoxycarbonylamino-acetic acid for 3-*tert*-butoxycarbonylamino-butyric acid. ^{1}H NMR (300 MHz, MeOD) δ 8.85 (d, 1H), 8.52 (s, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.95 (d, 1H), 7.72 (m, 3H), 7.43 (m, 1H), 7.36 (m, 2H), 3.78 (m, 2H), 3.45 (m, 3H), 3.20 (m, 2H), 2.56 (s, 3H), 1.45 (m, 3H), 1.05 (m, 2H), 0.50 (m, 3H); LC/MS *m/z* 509 $(M + H)^+$



(±)-(*trans*)-*N*-{4-[1-(2-Amino-acetyl)-3-ethyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-132)

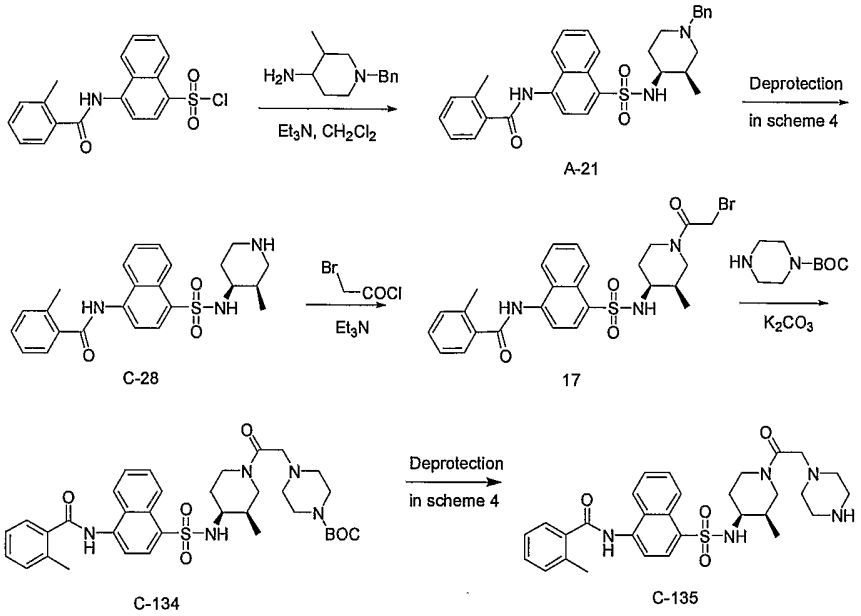
The title compound was prepared as its formate salt following general procedure in Scheme 6, substituting (±)-(*trans*)-*N*-[4-(3-ethyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**C-129**) for *N*-[4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-1**) and substituting *tert*-butoxycarbonylamino-acetic acid for 3-*tert*-butoxycarbonylamino-butyric acid. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.52 (s, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.95 (d, 1H), 7.72 (m, 3H), 7.43 (m, 1H), 7.36 (m, 2H), 4.25 (m, 1H), 3.75 (m, 2H), 3.55 (m, 1H), 3.05 (m, 2H), 2.56 (s, 3H), 2.50 (m, 1H), 1.40 (m, 4H), 0.85 (m, 1H), 0.65 (m, 3H); LC/MS *m/z* 509 $(M + H)^+$



(±)-(*cis*)-*N*-{4-[3-Ethyl-1-(2-ethylamino-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-133)

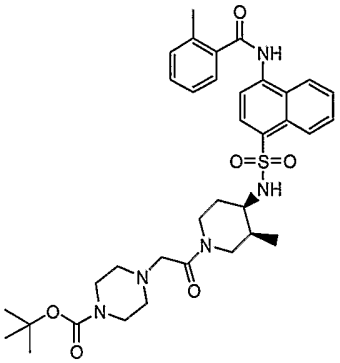
To a 25 °C solution of (±)-(*cis*)-*N*-{4-[1-(2-amino-acetyl)-3-ethyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (**C-131**) (65 mg, 0.128 mmol) in MeOH (4 mL) was added acetyl aldehyde (5.62 mg, 0.128 mmol) and sodium cyanoborohydride (40 mg, 0.64 mmol). After stirring for 2h at 25 °C, the solution was concentrated *in vacuo to* give a solid. The resultant solid was purified by reverse phase HPLC to provide the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.85 (d, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.43 (m, 1H), 7.35 (m, 2H), 3.55 (m, 5H), 3.20 (m, 2H), 2.85 (m, 2H), 2.56 (s, 3H), 1.25 (m, 7H), 0.50 (m, 3H); LC/MS *m/z* 537 $(M + H)^+$

Scheme 7



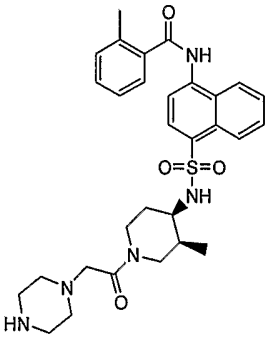
N-{4-[1-(2-bromo-acetyl)-3-*cis*-methyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (17)

(±)-*cis*-*N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**A-21**) was prepared as described previously according to the general procedure in Scheme 2. Deprotection of **A-21** to afford 2-Methyl-*N*-[4-(3-*cis*-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-28**) was achieved according to the general procedure described in Scheme 4-2. 2-Methyl-*N*-[4-(3-*cis*-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-benzamide (**C-28**) (700 mg, 1.6 mmol) was dissolved in dichloromethane (8 mL). Triethylamine (192 mg, 0.26 mL, 1.9 mmol) was added followed by bromoacetyl chloride (378 mg, 0.20 mL, 2.4 mmol). The reaction was stirred for 1 hour at room temperature and then passed through a plug of silica gel. Elution with ethyl acetate followed by evaporation *in vacuo* afforded the title product (644 mg, 72%) as a white solid. This material was used without further purification. LC/MS *m/z* 556 $(M - H)^-$.



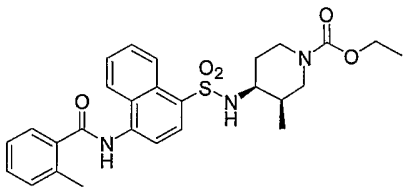
(±)-4-(2-{3-*cis*-methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidin-1-yl}-2-oxo-ethyl)-piperazine-1-carboxylic acid tert-butyl ester (C-134)

N-{4-[1-(2-Bromo-acetyl)-3-*cis*-methyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (100 mg, 0.18 mM) was dissolved in a mixture of acetonitrile (1 mL) and water (0.25 mL). Potassium carbonate (37 mg, 0.27 mmol) was added followed by piperazine-1-carboxylic acid tert-butyl ester (37 mg, 0.2 mM). The reaction was stirred for 1 hour at room temperature before being passed through a plug of silica gel. Elution with ethyl acetate:methanol (90:10) afforded the titled compound (43 mg, 34%) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.85 (d, 1H), 8.30 (d, 1H), 8.22 (d, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.38 (m, 4H), 3.57 (m, 5H), 3.40 (m, 6H), 3.18 (m, 4H), 2.58 (s, 3H), 1.78 (m, 1H), 1.52 (m, 2H), 1.42 (s, 9H), 0.70 (d, 1.5H), 0.65 (d, 1.5H); LC/MS *m/z* 664 $(M+H)^+$.



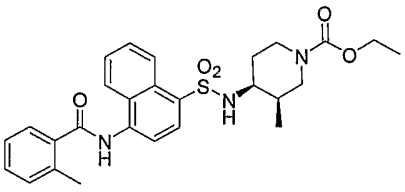
(±)-2-methyl-*N*-{4-[3-*cis*-methyl-1-(2-piperazin-1-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-135)

(±)-4-(2-{3-*cis*-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidin-1-yl}-2-oxo-ethyl)-piperazine-1-carboxylic acid tert-butyl ester (43 mg, 0.07 mmol) was dissolved in a solution of 4N HCl/dioxane (3 mL). The reaction was left standing for 3 hours at room temperature; concentration *in vacuo* afforded the titled compound (14 mg, 40%) as its bis-hydrochloride salt. ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.85 (d, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.96 (d, 1H), 7.72 (m, 3H), 7.40 (m, 4H), 4.30 (m, 2H), 3.52 (m, 12H), 3.22 (m, 2H), 2.58 (s, 3H), 1.83 (m, 1H), 1.58 (m, 2H), 0.74 (d, 1.5H), 0.68 (d, 1.5H); LC/MS *m/z* 564 $(M + H)^+$.



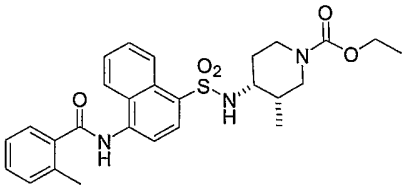
(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (C-136)

The title compound was prepared from **A-21** according to the general procedure in Scheme 7. To a solution of **A-21** in ethyl acetate was added $Pd(OH)_2$ and diethyl pyrocarbonate (1.0 eq). The vessel was evacuated and pressurized to 50 psi H_2 and allowed to agitate on a Parr apparatus overnight. The solution was filtered through a celite plug, washed with hot ethyl acetate and concentrated at 40°C at reduced pressure. The residue was purified using flash chromatography to provide the title compound. ^{1}H NMR (300 MHz, DMSO) δ 10.63 (s, 1H), 8.77 (d, 1H), 8.28 (d, 1H), 8.21 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H), 7.74 (m, 3H), 7.45 (d, 1H), 7.38 (m, 2H), 3.98 (q, 2H), 3.38(m, 1H), 3.29 (m, 1H), 3.21 (m, 3H), 2.52 (s, 3H), 1.67 (m,1H), 1.30 (m, 2H), 1.13 (t, 3H), 0.57 (d, 3H); LC/MS *m/z* 508 $(M - H)^-$, 510 $(M + H)^+$



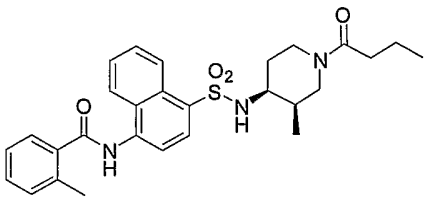
***cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (single enantiomer, absolute stereochemistry not determined) (C-137)**

Compound **C-136** was subjected to reverse phase chiral HPLC separation, and the title compound was the first enantiomer to elute from the column. ^{1}H NMR (300 MHz, DMSO) δ 8.70 (d, 1H), 8.42 (d, 1H), 8.34 (d, 1H), 8.11 (s, 1H), 7.93 (d, 1H), 7.63 (m, 3H), 7.42 (d, 1H), 7.34 (d, 2H), 4.64 (d, 1H), 4.05 (m, 2H), 3.48 (m, 0.5H), 3.38 (m, 1H), 3.21 (m, 2.5H), 2.59 (s, 3H), 1.74 (m, 1H), 1.48 (s, 1H), 1.43 (m, 2H), 1.19 (t, 3H), 0.66 (s, 3H. LC/MS *m/z* 508 $(M - H)^-$, 510 $(M + H)^+$



cis-3-Methyl-4-[4-(2-methyl-benzoylamino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (single enantiomer, absolute stereochemistry not determined) (C-138)

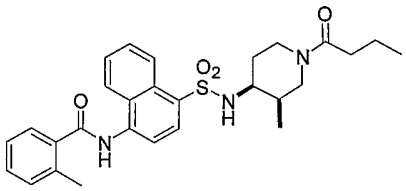
Compound **C-136** was subjected to reverse phase chiral HPLC separation, and the title compound was the second enantiomer to elute from the column. ^{1}H NMR (300 MHz, DMSO) δ 8.70 (d, 1H), 8.42 (d, 1H), 8.34 (d, 1H), 8.11 (s, 1H), 7.93 (d, 1H), 7.63 (m, 3H), 7.42 (d, 1H), 7.34 (d, 2H), 4.64 (d, 1H), 4.05 (m, 2H), 3.48 (m, 0.5H), 3.38 (m, 1H), 3.21 (m, 2.5H), 2.59 (s, 3H), 1.74 (m, 1H), 1.48 (s, 1H), 1.43(m, 2H), 1.19 (t, 3H), 0.66 (s, 3H). LC/MS *m/z* 508 $(M - H)^-$, 510 $(M + H)^+$



(±)-*cis*-*N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-139)

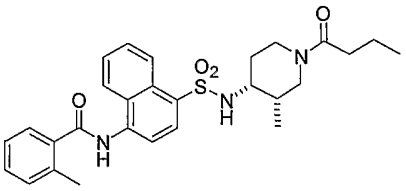
The title compound was prepared from **A-21** according to the general procedure in Scheme 7. To a solution of **A-21** in ethyl acetate was added $Pd(OH)_2$ and butyric

anhydride (1.0 eq). The vessel was evacuated and pressurized to 50 psi H_2 and allowed to agitate on a Parr apparatus overnight. The solution was filtered through a celite plug, washed with hot ethyl acetate and concentrated at 40°C at reduced pressure. The residue was purified using flash chromatography to provide the title compound. ^{1}H NMR (300 MHz, DMSO) δ (m, 1H), 8.32 (m, 3H), 7.95 (d, 1H), 7.63 (m, 3H), 7.43 (m, 1H), 7.33 (m, 2H), 5.20 (d, 1H), 3.63 (m, 0.5H), 3.40 (m, 2H), 3.20 (m, 2H), 3.01 (m, 0.5H), 2.57 (s, 3H), 2.19 (m, 2H), 1.82 (m, 0.5H), 1.67 (m, 0.5H), 1.56 (m, 3H), 1.30 (m 1H), 0.95 (dt, 3H), 0.73 (d, 0.5H), 0.59 (d, 0.5H). LC/MS *m/z* 506 $(M - H)^-$, 508 $(M + H)^+$.



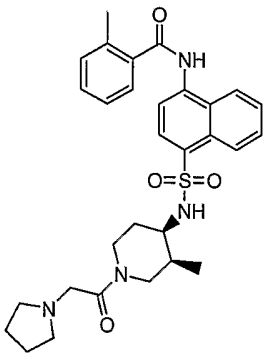
***cis*-*N*-[4-(1-butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-140) (single enantiomer, absolute stereochemistry not determined)**

Compound **C-139** was subjected to reverse phase chiral HPLC separation, and the title compound was the first enantiomer to elute from the column. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (m, 1H), 8.42 (d, 1H), 8.37 (d, 1H), 8.12 (s, 1H), 7.94 (d, 1H), 7.73 (m, 1H), 7.63 (m, 2H), 7.43 (m, 1H), 7.34 (d, 2H), 4.68 (m, 1H), 3.42-3.20 (m, 3H), 2.59 (s, 3H), 2.20 (m, 2H), 1.57 (m, 4H), 1.35 (m, 1H), 1.25 (m, 2H), 0.89 (m, 3H), 0.74 (d, 1.5H), 0.55 (d, 1.5H). LC/MS *m/z* 506 $(M - H)^-$, 508 $(M + H)^+$.



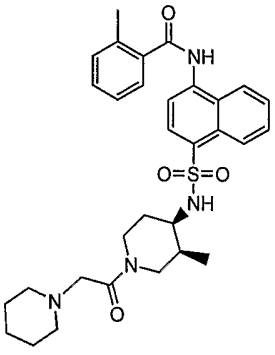
***cis*-*N*-[4-(1-butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (C-141) (single enantiomer, absolute stereochemistry not determined)**

Compound **C-139** was subjected to reverse phase chiral HPLC separation, and the title compound was the second enantiomer to elute from the column. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (m, 1H), 8.42 (d, 1H), 8.37 (d, 1H), 8.12 (s, 1H), 7.94 (d, 1H), 7.73 (m, 1H), 7.63 (m, 2H), 7.43 (m, 1H), 7.34 (d, 2H), 4.68 (m, 1H), 3.42-3.20 (m, 3H), 2.59 (s, 3H), 2.20 (m, 2H), 1.57 (m, 4H), 1.35 (m, 1H), 1.25 (m, 2H), 0.89 (m, 3H), 0.74 (d, 1.5H), 0.55 (d, 1.5H). LC/MS *m/z* 506 $(M - H)^-$, 508 $(M + H)^+$.



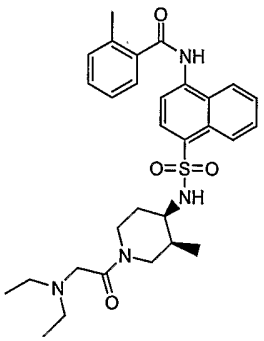
(±)-2-Methyl-*N*-{4-[*cis*-3-methyl-1-(2-pyrrolidin-1-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-142)

The title compound was prepared as shown in Scheme 7 for the preparation of **C-134** except substituting pyrrolidine for piperazine-1-carboxylic acid *tert*-butyl ester. Reverse phase HPLC purification afforded the title compound as its formate salt. Wt.: 37 mg (38%). ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.85 (d, 1H), 8.47 (s, 1H), 8.36 (d, 1H), 8.27 (d, 1H), 7.96 (d, 1H), 7.70 (m, 3H), 7.40 (m, 3H), 4.22 (m, 2H), 3.68 (m, 1H), 3.45 (m, 4H), 3.24 (m, 4H), 2.58 (s, 3H), 2.04 (m, 4H), 1.80 (m, 1H), 1.47 (m, 2H), 0.70 (d, 1.5H), 0.65 (d, 1.5H); LC/MS *m/z* 549 $(M + H)^+$.



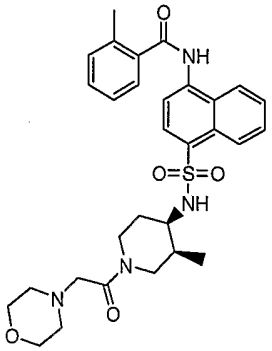
(±)-2-Methyl-*N*-{4-[*cis*-3-methyl-1-(2-piperidin-1-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-143)

The title compound was prepared as shown in Scheme 7 for the preparation of **C-134** except substituting piperidine for piperazine-1-carboxylic acid *tert*-butyl ester. Reverse phase HPLC purification afforded the title compound as its formate salt. Wt.: 43 mg (43 %). ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.85 (d, 1H), 8.33 (d, 2H), 8.25 (d, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.40 (m, 3H), 4.04 (m, 2H), 3.63 (m, 1H), 3.45 (m, 4H), 3.20 (m, 4H), 2.56 (s, 3H), 1.88 (m, 6H), 1.67 (m, 2H), 1.45 (m, 1H), 0.70 (d, 1.5H), 0.64 (d, 1.5H); LC/MS *m/z* 563 $(M+H)^+$.



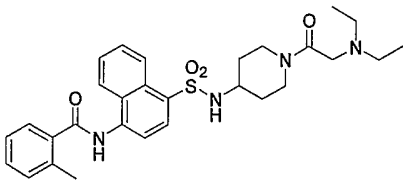
(±)-*N*-{4-[1-(2-diethylamino-acetyl)-3-*cis*-methyl-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-144)

The title compound was prepared as shown in Scheme 7 for the preparation of **C-134** except substituting diethylamine for piperazine-1-carboxylic acid *tert*-butyl ester. Reverse phase HPLC purification afforded the title compound as its formate salt. Wt.: 49 mg (50%). ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.85 (d, 1H), 8.46 (s, 1H), 8.38 (d, 1H), 8.28 (d, 1H), 7.95 (d, 1H), 7.70 (m, 3H), 7.40 (m, 3H), 4.16 (m, 2H), 3.65 (m, 1H), 3.44 (m, 4H), 3.19 (m, 4H), 2.56 (s, 3H), 1.80 (m, 1H), 1.52 (m, 2H), 1.25 (t, 6H), 0.70 (d, 1.5H), 0.64 (d, 1.5H); LC/MS *m/z* 551 $(M+H)^+$.



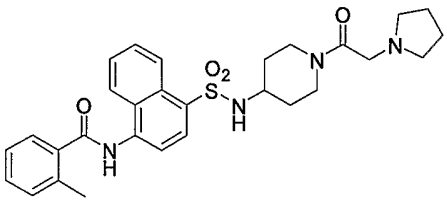
(±)-2-Methyl-*N*-{4-[3-*cis*-methyl-1-(2-morpholin-4-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-145)

The title compound was prepared as shown in Scheme 7 for the preparation of **C-134** except substituting morpholine for piperazine-1-carboxylic acid *tert*-butyl ester. Wt.: 60 mg (58%). ^{1}H NMR (300 MHz, CD_3OD) (1:1 mixture of rotamers) δ 8.88 (d, 1H), 8.38 (d, 1H), 8.32 (d, 1H), 8.00 (d, 1H), 7.80 (m, 3H), 7.45 (m, 3H), 4.26 (m, 2H), 4.06 (m, 2H), 3.86 (m, 3H), 3.50 (m, 4H), 3.24 (m, 3H), 2.60 (s, 3H), 1.85 (m, 1H), 1.55 (m, 2H), 0.76 (d, 1.5H), 0.69 (d, 1.5H); LC/MS *m/z* 565 $(M + H)^+$.



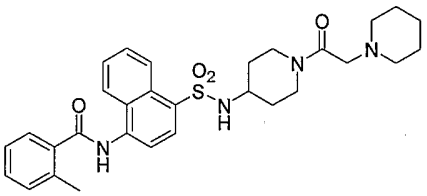
***N*-{4-[1-(2-Diethylamino-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-2-methyl-benzamide (C-146)**

The title compound was prepared following the general procedure for preparing **C-134** in Scheme 7, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 1-benzyl-3-methyl-piperidin-4-ylamine, and diethyl amine for piperazine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 10.66 (s, 1H), 9.08 (m, 1H), 8.69 (d, 1H), 8.27 (d, 1H), 8.22 (t, 2H), 7.94 (d, 1H), 7.70 (m, 3H), 7.42 (m, 1H), 7.35 (m, 2H), 4.27-4.02 (m, 2H), 4.03 (d, 1H), 3.40 (m, 3H), 2.98 (m, 3H), 2.83 (m, 1H), 2.56 (s, 3H), 1.92 (m,5 H), 1.58 (m, 2H), 1.30 (m, 2H), 1.11 (t, 2H). LC/MS *m/z* 536 $(M - H)^-$, 538 $(M + H)^+$



2-Methyl-*N*-{4-[1-(2-pyrrolidin-1-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-147)

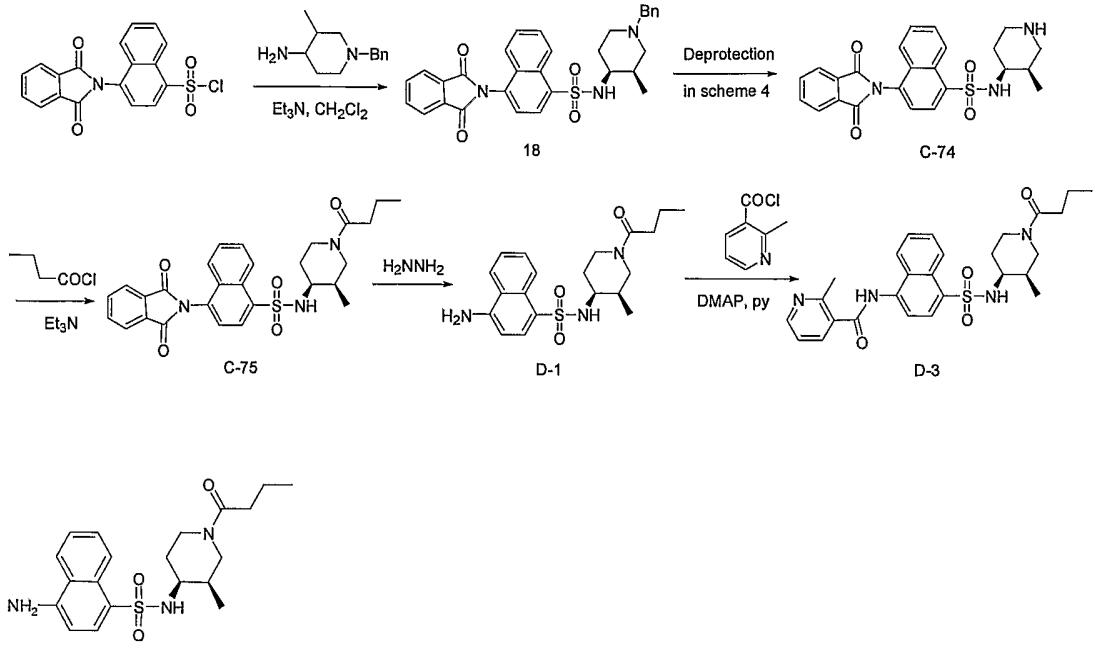
The title compound was prepared following the general procedure for preparing **C-134** in Scheme 7, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 1-benzyl-3-methyl-piperidin-4-ylamine, and pyrrole for piperazine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 10.56 (s, 1H), 9.28 (m, 1H), 8.68 (d, 1H), 8.27 (d, 1H), 8.21 (m, 2H), 7.94 (d, 1H), 7.72 (m, 3H), 7.43 (d, 1H), 7.38 (m, 2H), 4.31 (m, 2H), 4.03 (d, 1H), 3.27 (m, 2H), 2.98 (m, 3H), 2.83 (m, 1H), 2.56 (s, 3H), 1.92 (m, 5H), 1.58 (m, 2H), 1.3 (m, 2H). LC/MS *m/z* 534 $(M - H)^-$, 535 $(M + H)^+$



2-Methyl-*N*-{4-[1-(2-piperidin-1-yl-acetyl)-piperidin-4-ylsulfamoyl]-naphthalen-1-yl}-benzamide (C-148)

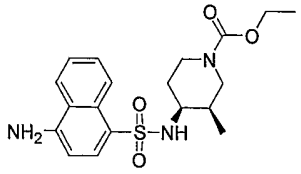
The title compound was prepared following the general procedure for preparing **C-134** in Scheme 7, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 1-benzyl-3-methyl-piperidin-4-ylamine, and substituting piperidine for piperazine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, DMSO) δ 10.56 (s, 1H), 9.28 (m, 1H), 8.68 (d, 1H), 8.27 (d, 1H), 8.21 (m, 2H), 7.94 (d, 1H), 7.72 (m, 3H), 7.43 (d, 1H), 7.38 (m, 2H), 4.15 (m, 3H), 3.36 (m, 3H), 2.99 (m, 1H), 2.80 (m, 3H), 2.56 (s, 3H), 1.74 (m, 3H), 1.58 (m, 4H), 1.27 (m, 3H). LC/MS *m/z* 548 $(M - H)^-$, 549 $(M + H)^+$

Scheme 8



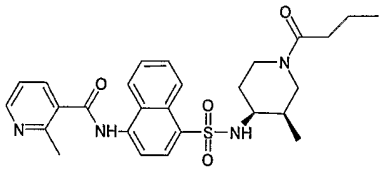
(±)-(*cis*)-4-Amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (D-1)

(±)-*cis*-*N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-benzamide (**18**) was prepared as described previously according to the general procedure in Scheme 3, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for *p*-anisidine. (±)-(*cis*)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (3-methyl-piperidin-4-yl)-amide (**C-74**) and (±)-(*cis*)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (**C-75**) were prepared as described previously according to the general procedure in Scheme 5. The title compound was made following general procedure in Scheme 3, substituting (±)-(*cis*)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (**C-75**) for 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (4-methoxy-phenyl)-amide (**A-2**). ^{1}H NMR (300 MHz, MeOD) δ 8.62 (d, 1H), 8.30 (d, 1H), 7.98 (d, 1H), 7.60 (dt, 1H), 7.48 (dt, 1H), 6.70 (d, 1H), 3.66 (m, 1H), 3.42 (m, 1H), 3.28 (m, 5H), 2.25 (m, 2H), 1.67 (m, 1H), 1.50 (m, 2H), 1.30 (m, 2H), 0.88 (t, 3H), 0.64 (m, 3H); LC/MS *m/z* 391 $(M + H)^+$



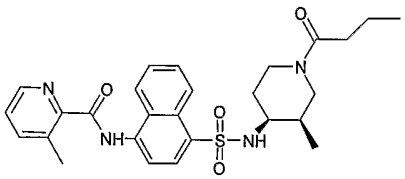
(±)-(*cis*)-4-(4-Amino-naphthalene-1-sulfonylamino)-3-methyl-piperidine-1-carboxylic acid ethyl ester (D-2)

The title compound was made following general procedure in Scheme 8, substituting ethyl chloroformate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.61 (d, 1H), 8.10 (d, 1H), 7.97 (d, 1H), 7.60 (t, 1H), 7.48 (t, 1H), 6.70 (d, 1H), 4.02 (q, 2H), 3.47 (m, 1H), 3.24 (m, 4H), 1.64 (m, 1H), 1.38 (m, 1H), 1.25 (m, 1H), 1.17 (t, 3H), 0.64 (d, 3H); LC/MS *m/z* 393 $(M + H)^+$



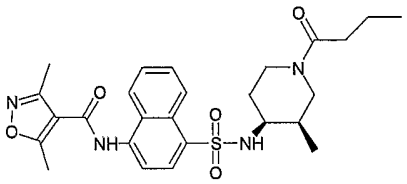
(±)-(*cis*)-*N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-nicotinamide (D-3)

To a solution of naphthalenyl amine (**D-1**) (78 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was added acetyl chloride (20 uL, 0.24 mmol) and Et_3N (60 uL, 0.4 mmol). The resultant solution was stirred at 25 °C overnight. The solvent was removed *in vacuo* and the residue was purified using HPLC to give the title compound. ^{1}H NMR (300 MHz, MeOD) δ 8.84 (d, 1H), 8.57 (dd, 1H), 8.31 (d, 1H), 8.24 (d, 1H), 8.11 (m, 1H), 7.98 (m, 1H), 7.72 (m, 2H), 7.43 (dd, 1H), 3.40 (m, 5H), 2.75 (s, 3H), 2.25 (m, 2H), 1.50 (m, 5H), 0.90 (t, 3H), 0.65 (dd, 3H); LC/MS *m/z* 510 $(M + H)^+$



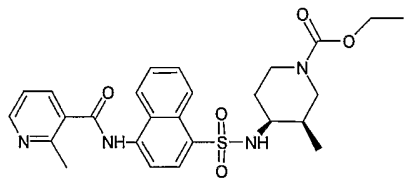
(±)-(*cis*)-3-Methyl-pyridine-2-carboxylic acid [4-(1-butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-4)

The title compound was made following general procedure in Scheme 8, substituting 3-methyl-pyridine-2-carbonyl chloride for 2-methyl-nicotinoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.83 (m, 1H), 8.59 (d, 1H), 8.28 (m, 3H), 7.74 (m, 3H), 7.53 (dd, 1H), 3.40 (m, 5H), 2.75 (s, 3H), 2.25 (m, 2H), 1.50 (m, 5H), 0.95 (t, 3H), 0.80 (dd, 3H); LC/MS *m/z* 510 $(M + H)^+$



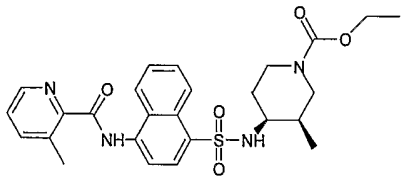
(±)-(*cis*)-3,5-Dimethyl-isoxazole-4-carboxylic acid [4-(1-butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-5)

The title compound was made following general procedure in Scheme 8, substituting 3,5-dimethyl-isoxazole-4-carbonyl chloride for 2-methyl-nicotinoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.82 (d, 1H), 8.28 (d, 1H), 8.18 (d, 1H), 7.93 (d, 1H), 7.71 (m, 2H), 3.34 (m, 5H), 2.70 (s, 3H), 2.47 (s, 3H), 2.25 (m, 2H), 1.50 (m, 5H), 0.89 (t, 3H), 0.63 (dd, 3H); LC/MS *m/z* 514 $(M + H)^+$



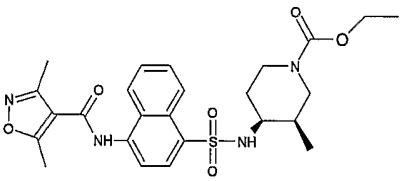
(±)-(*cis*)-3-Methyl-4-{4-[(2-methyl-pyridine-3-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (D-6)

The title compound was made following general procedure in Scheme 8, substituting (±)-(*cis*)-4-(4-amino-naphthalene-1-sulfonylamino)-3-methyl-piperidine-1-carboxylic acid ethyl ester (**D-2**) for (±)-(*cis*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (**D-1**). ^{1}H NMR (300 MHz, MeOD) δ 8.83 (d, 1H), 8.56 (dd, 1H), 8.31 (d, 1H), 8.23 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H),7.71 (m, 2H), 7.43 (dd, 1H), 4.03 (q, 2H), 3.48 (m, 1H), 3.28 (m, 4H), 2.75 (s, 3H), 1.68 (m, 1H), 1.40 (m, 1H), 1.29 (m, 1H), 1.18 (t, 3H), 0.64 (d, 3H); LC/MS *m/z* 512 $(M + H)^+$



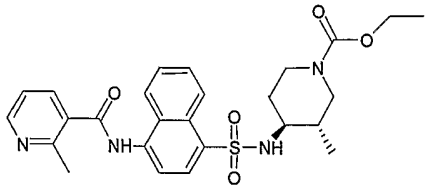
(±)-(*cis*)-3-Methyl-4-{4-[(3-methyl-pyridine-2-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (D-7)

The title compound was made following general procedure in Scheme 8, substituting (±)-(*cis*)-4-(4-amino-naphthalene-1-sulfonylamino)-3-methyl-piperidine-1-carboxylic acid ethyl ester (**D-2**) for (±)-(*cis*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (**D-1**), and substituting 3-methyl-pyridine-2-carbonyl chloride for 2-methyl-nicotinoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.82 (m, 1H), 8.56 (d, 1H), 8.28 (m, 1H), 8.18 (m, 1H), 7.74 (m, 3H), 7.59 (dd, 1H), 4.02 (q, 2H), 3.48 (m, 1H), 3.28 (m, 4H), 2.73 (s, 3H), 1.68 (m, 1H), 1.40 (m, 1H), 1.28 (m, 1H), 1.17 (t, 3H), 0.63 (d, 3H); LC/MS *m/z* 512 $(M + H)^+$



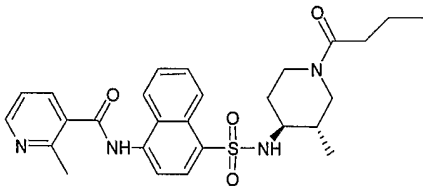
(±)-(*cis*)-4-{4-[(3,5-Dimethyl-isoxazole-4-carbonyl)-amino]-naphthalene-1-sulfonylamino}-3-methyl-piperidine-1-carboxylic acid ethyl ester (D-8)

The title compound was made following general procedure in Scheme 8, substituting (±)-(*cis*)-4-(4-amino-naphthalene-1-sulfonylamino)-3-methyl-piperidine-1-carboxylic acid ethyl ester (**D-2**) for (±)-(*cis*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide (**D-1**) and substituting 3,5-dimethyl-isoxazole-4-carbonyl chloride for 2-methyl-nicotinoyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.82 (d, 1H), 8.27 (d, 1H), 8.18 (d, 1H), 7.93 (d, 1H), 7.71 (m, 2H), 4.03 (q, 2H), 3.30 (m, 5H), 2.70 (s, 3H), 2.47 (s, 3H), 1.68 (m, 1H), 1.40 (m, 1H), 1.28 (m, 1H), 1.18 (t, 3H), 0.64 (d, 3H); LC/MS *m/z* 516 $(M + H)^+$



(±)-(*trans*)-3-Methyl-4-{4-[(2-methyl-pyridine-3-carbonyl)-amino]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (D-9)

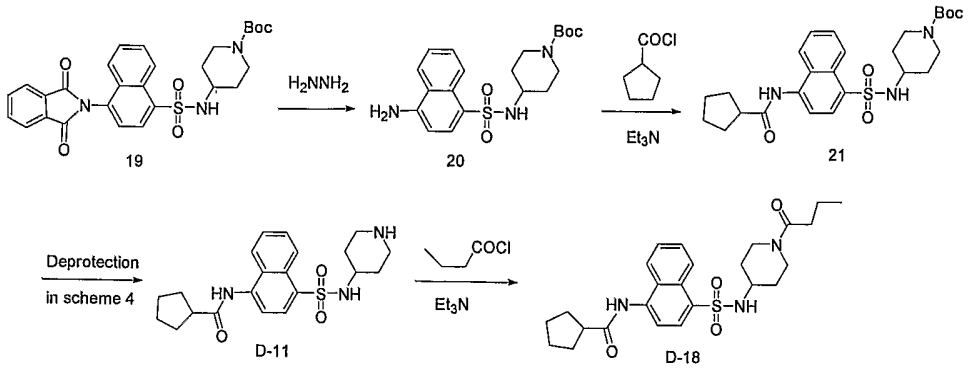
The title compound was made following general procedure in Scheme 8, substituting (±)-(*trans*)-4-(4-amino-naphthalene-1-sulfonylamino)-3-methyl-piperidine-1-carboxylic acid ethyl ester for (±)-(*cis*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide **(D-1)**. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.58 (dd, 1H), 8.32 (d, 1H), 8.23 (d, 1H), 8.12 (d, 1H), 7.98 (d, 1H), 7.72 (m, 2H), 7.44 (dd, 1H), 4.04 (q, 2H), 3.88 (m, 2H), 3.28 (m, 1H), 2.82 (m, 1H), 2.75 (s, 3H), 2.65 (m, 1H), 2.38 (s, br, 1H), 1.40 (m, 2H), 1.18 (t, 3H), 0.57 (d, 3H); LC/MS *m/z* 512 $(M + H)^+$

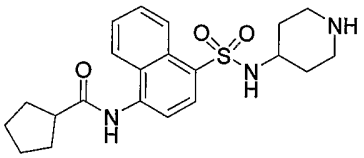


(±)-(*trans*)-*N*-[4-(1-Butyryl-3-methyl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-nicotinamide (D-10)

The title compound was made following general procedure in Scheme 8, substituting (±)-(*trans*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide for (±)-(*cis*)-4-amino-naphthalene-1-sulfonic acid (1-butyryl-3-methyl-piperidin-4-yl)-amide **(D-1)**. ^{1}H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.57 (dd, 1H), 8.31 (d, 1H), 8.23 (d, 1H), 8.12 (d, 1H), 7.98 (d, 1H), 7.72 (m, 2H), 7.42 (dd, 1H), 4.28 (t, 1H), 3.72 (m, 1H), 2.90 (m, 1H), 2.74 (s, 3H), 2.56 (m, 1H), 2.23 (m, 3H), 1.53 (m, 3H), 1.28 (m, 2H), 0.89 (m, 3H), 0.61 (dd, 3H); LC/MS *m/z* 510 $(M + H)^+$

Scheme 9





Cyclopentanecarboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-11)

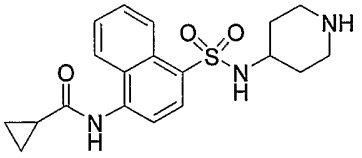
4-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester (**19**) was prepared according to the general procedure in Scheme 3, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for *p*-anisidine.

4-(4-Amino-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**20**) was prepared according to the general procedure in Scheme 3 substituting 4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-naphthalene-1-sulfonic acid (4-methoxyphenyl)-amide.

4-[4-(Cyclopentanecarbonyl-amino)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (**21**) was prepared according to the general procedure in Scheme 3, substituting cyclopentanecarbonyl chloride for acetyl chloride.

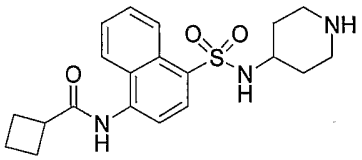
The title compound (**D-11**) was prepared according to Scheme 9 by following the general deprotection strategy in Scheme 4-1. ^{1}H NMR (300 MHz, DMSO) δ 10.15

(s, 1H), 8.66 (m, 1H), 8.58 (m, 1H), 8.41 (m, 1H), 8.26 (m, 2H), 8.12 (d, 1H), 7.94 (d, 1H), 7.71 (m, 2H), 3.11 (m, 3H), 2.82 (m, 2H), 1.94 (m, 2H), 1.86-1.40 (m, 10H). LC/MS *m/z* 400 $(M - H)^-$, 402 $(M + H)^+$



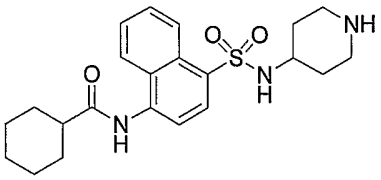
Cyclopropanecarboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-12)

The title compound was made following the general procedure in Scheme 9, substituting cyclopropanecarbonyl chloride for cyclopentanecarbonyl chloride. ^1H NMR (300 MHz, DMSO) δ 10.49 (s, 1H), 8.67 (m, 1H), 8.54 (m, 1H), 8.39 (m, 1H), 8.26 (d, 1H), 8.11 (d, 1H), 8.01 (d, 1H), 7.73 (m, 2H), 3.56 (s, 1H), 3.05 (m, 2H), 2.79 (m, 2H), 2.19 (m, 1H), 1.60 (m, 2H), 1.50 (m, 2H), 0.87 (d, 4H). LC/MS *m/z* 372 $(M - H)^-$, 374 $(M + H)^+$



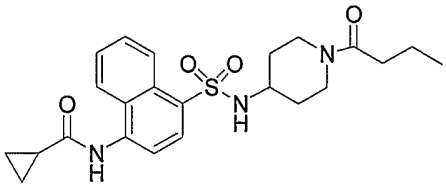
Cyclobutanecarboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-13)

The title compound was made following the general procedure in Scheme 9, substituting cyclobutanecarbonyl chloride for cyclopentanecarbonyl chloride. ^1H NMR (300 MHz, DMSO) δ 9.98 (s, 1H), 8.62 (d, 1H), 8.21 (d, 1H), 8.12 (d, 1H), 7.99 (d, 1H), 7.95 (d, 1H), 7.70 (m, 2H), 3.59 (d, 2H), 3.51 (t, 1H), 3.13 (m, 1H), 2.67 (m, 2H), 2.32-2.16 (m, 4H), 1.99 (m, 1H), 1.84 (m, 1H), 1.37 (d, 2H), 1.10 (m, 2H). LC/MS *m/z* 386 $(M - H)^-$, 388 $(M + H)^+$



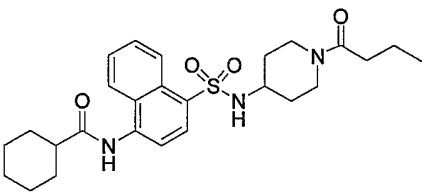
Cyclohexanecarboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-14)

The title compound was made following the general procedure in Scheme 9, substituting cyclohexanecarbonyl chloride for cyclopentanecarbonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.07 (s, 1H), 8.64 (dd, 1H), 8.25 (m,4 H), 8.12 (d, 1H), 7.96 (d, 1H), 7.72 (m, 2H), 3.06 (m, 2H), 2.81 (m, 2H), 2.66 (m, 2H), 1.91 (d, 2H), 1.78 (d, 2H), 1.61 (m, 3H), 1.49 (m, 4H), 1.31 (m, 2H). LC/MS *m/z* 415 $(M-H)^-$, 417 $(M+H)^+$



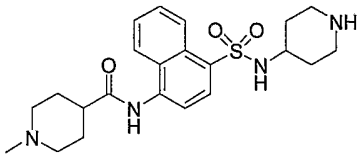
Cyclopropanecarboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-15)

The title compound was made following the general procedure in Scheme 9, substituting cyclopropanecarbonyl chloride for cyclopentanecarbonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.43 (s, 1H), 8.64 (m, 1H), 8.33 (m, 1H), 8.13 (m, 1H), 8.02 (d, 1H), 7.97 (m, 2H), 3.98 (d, 1H), 3.59 (m, 1H), 3.19 (m, 1H), 2.90 (t, 1H), 2.61 (m, 1H), 2.13 (m, 3H), 1.40 (m, 4H), 1.16 (m, 2H), 0.84 (d, 4H), 0.80 (t, 3H). LC/MS *m/z* 442 $(M-H)^-$, 444 $(M+H)^+$



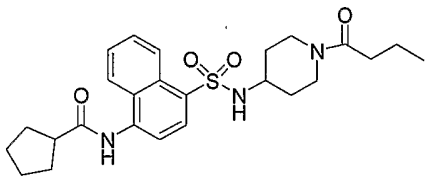
Cyclohexanecarboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-16)

The title compound was made following the general procedure in Scheme 9, substituting cyclohexanecarbonyl chloride for cyclopentanecarbonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.05 (s, 1H), 8.64 (dd, 1H), 8.25 (dd, 1H), 8.13 (d, 1H), 8.03 (d, 1H), 7.91 (d, 1H), 7.71 (m, 2H), 3.98 (d, 1H), 3.59 (d, 1H), 3.18 (m, 1H), 2.91 (t, 1H), 2.61 (t, 1H), 2.16 (t, 2H), 1.90 (d, 2H), 1.77 (m, 2H), 1.67 (m, 2H), 1.49-1.20 (m, 9H), 0.81 (t, 3H). LC/MS *m/z* 529 $(M - H)^-$, 531 $(M + H)^+$



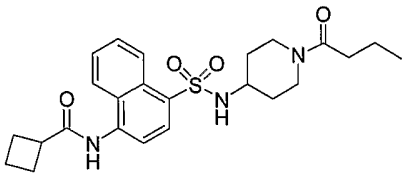
1-Methyl-piperidine-4-carboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-17)

The title compound was made following general procedure in Scheme 9, substituting 1-methyl-piperidine-4-carbonyl chloride (prepared *in situ* from the corresponding acid using oxalyl chloride) for cyclopentanecarbonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 10.39 (s, 1H), 8.64 (dd, 1H), 8.29 (dd, 1H), 8.14 (d, 1H), 8.05 (d, 1H), 7.89 (d, 1H), 7.72 (m, 2H), 3.62 (d, 2H), 3.40 (m, 2H), 3.15 (m, 1H), 2.95 (m, 2H), 2.78-2.67 (m, 6H), 2.09 (m, 2H), 2.00 (m, 2H), 1.84 (m, 1H), 1.39 (m, 1H), 1.18 (m, 2H). LC/MS *m/z* 384 $(M - H)^-$, 386 $(M + H)^+$



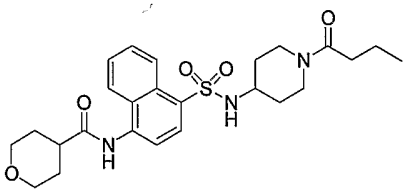
Cyclopentanecarboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-18)

The title compound was made following the general procedure in Scheme 9. ^{1}H NMR (300 MHz, DMSO) δ 10.12 (s, 1H), 8.66 (m, 1H), 8.28 (m, 1H), 8.13 (d, 1H), 7.95 (d, 1H), 7.71 (m, 2H), 3.98 (d, 1H), 3.59 (d, 1H), 3.19 (m, 1H), 3.09 (m, 1H), 2.90 (m, 1H), 2.57 (m, 1H), 2.16 (t, 2H), 1.94 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H), 1.62 (m, 2H), 1.42 (m, 4H), 1.16 (m, 2H), 0.81 (t, 3H). LC/MS *m/z* 471 $(M - H)^-$, 473 $(M + H)^+$



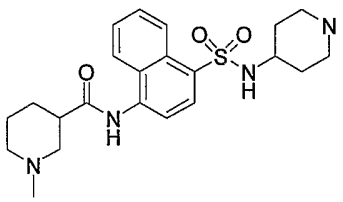
Cyclobutanecarboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-19)

The title compound was made following the general procedure in Scheme 9, substituting cyclobutanecarbonyl chloride for cyclopentanecarbonyl chloride. ^{1}H NMR (300 MHz, DMSO) δ 9.98 (s, 1H), 8.62 (d, 1H), 8.21 (d, 1H), 8.12 (d, 1H), 7.99 (d, 1H), 7.95 (d, 1H), 7.70 (m, 2H), 3.59 (d, 2H), 3.51 (t, 1H), 3.13 (m, 1H), 2.67 (m, 2H), 2.32-2.16 (m, 4H), 2.16 (t, 2H), 1.99 (m, 1H), 1.84 (m, 1H), 1.42 (m, 2H), 1.37 (d, 2H), 1.10 (m, 2H), 0.81 (t, 3H). LC/MS *m/z* 457 $(M - H)^-$, 459 $(M + H)^+$



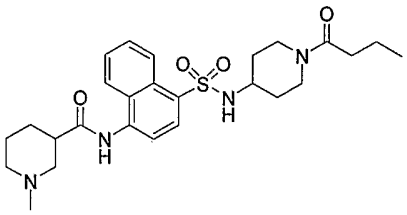
Tetrahydro-pyran-4-carboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-20)

The title compound was made following the general procedure in Scheme 9, substituting tetrahydro-pyran-4-carbonyl chloride (prepared *in situ* from the corresponding acid using oxalyl chloride) for cyclopentanecarbonyl chloride. LC/MS *m/z* 488 $(M + H)^+$



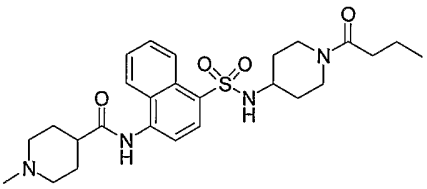
1-Methyl-piperidine-3-carboxylic acid [4-(piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-22)

The title compound was made following the general procedure in Scheme 9, substituting 1-methyl-piperidine-3-carbonyl chloride (prepared *in situ* from the corresponding acid using oxalyl chloride) for cyclopentanecarbonyl chloride. LC/MS *m/z* 431 $(M + H)^+$.



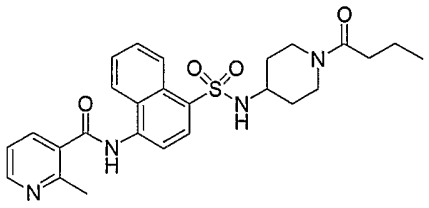
1-Methyl-piperidine-3-carboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-23)

The title compound was made following the general procedure in Scheme 9, substituting 1-methyl-piperidine-3-carbonyl chloride (prepared *in situ* from the corresponding acid using oxalyl chloride) for cyclopentanecarbonyl chloride. LC/MS *m/z* 501 $(M + H)^+$.



1-Methyl-piperidine-4-carboxylic acid [4-(1-butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-amide (D-24)

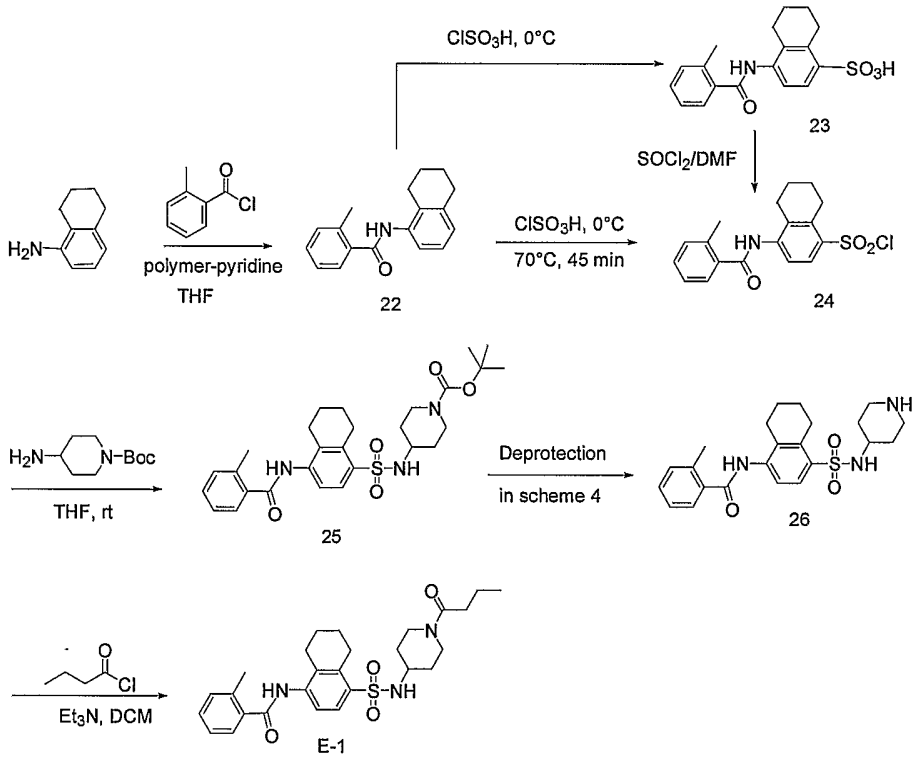
The title compound was made following the general procedure in Scheme 9, substituting 1-methyl-piperidine-4-carbonyl chloride (prepared *in situ* from the corresponding acid using oxalyl chloride) for cyclopentanecarbonyl chloride. ^1H NMR (300 MHz, DMSO) δ 10.39 (s, 1H), 8.64 (dd, 1H), 8.29 (dd, 1H), 8.14 (d, 1H), 8.05 (d, 1H), 7.891 (d, 1H), 7.72 (m, 2H), 3.62 (d, 2H), 3.40 (m, 2H), 3.15 (m, 1H), 2.95 (m, 2H), 2.78-2.67 (m, 6H), 2.17 (t, 2H), 2.09 (m, 2H), 2.0 (m, 2H), 1.84 (m, 1H), 1.43 (m, 2H), 1.39 (m, 1H), 1.18 (m, 2H), 0.82 (t, 3H). LC/MS *m/z* 501 $(M + H)^+$

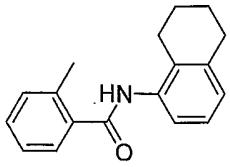


***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalen-1-yl]-2-methyl-nicotinamide (D-25)**

The title compound was prepared following the general procedure in Scheme 5, beginning with 4-[(2-methyl-pyridine-3-carbonyl)-amino]-naphthalene-1-sulfonyl chloride, and substituting butyryl chloride and triethylamine for 2-isocyanato-propane. ^{1}H NMR (300 MHz, DMSO) δ 10.76 (s, 1H), 8.68 (d, 1H), 8.59 (d, 1H), 8.31 (d, 1H), 8.24 (d, 1H), 8.10 (d, 1H), 8.04 (d, 1H), 7.98 (d, 1H), 7.73 (m, 2H), 7.41 (m, 1H), 4.00 (d, 1H), 3.61 (d, 1H), 3.23 (m, 1H), 2.93 (t, 1H), 2.66 (s, 3H), 2.59 (m, 1H), 2.17 (t, 2H), 1.48 (m, 2H), 1.43 (m, 2H), 1.19 (m, 2H), 0.82 (m, 2H). LC/MS *m/z* 494 $(M - H)^-$, 496 $(M + H)^+$

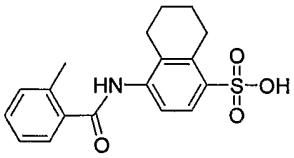
Scheme 10





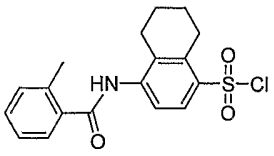
2-Methyl-*N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-benzamide (22)

To a 25 ^{0}C solution of aniline (1 eq) in anhydrous THF (2 mL per mmol aniline), was added polymer bound pyridine (1.5 eq) followed by acid chloride (1 eq). The mixture was stirred at 25 ^{0}C for 12 - 24 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. Hexane or MeOH was added to the residue and the resulting precipitate was collected by filtration, resulting in a white solid (yield 65%). LC/MS $(M + H)^+$ *m/z* 266. The crude material was used without further purification.



4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonic acid (23)

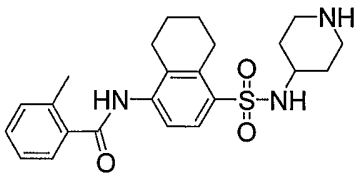
To a 0°C solution of amide **(22)** in TFA (1 mL per mmol amide), was added chlorosulfonic acid (2 eq) dropwise under nitrogen atmosphere. The temperature was allowed to warm to 25°C and stirred for 72 hours. The reaction mixture was quenched by pouring into ice water. The desired product was collected via precipitation from either water/methanol, or ethyl acetate/methanol solution, resulting in a white solid (yield 68%). LC/MS $(M + H)^+$ *m/z* 346, $(M - H)^-$ *m/z* 344. The crude material was used without further purification.



4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonyl chloride (24)

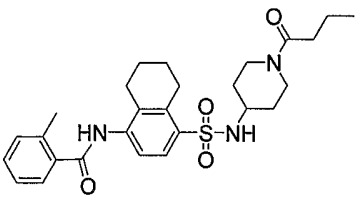
Method A: To a 0°C solution of sulfonic acid **(23)** in DMF (1 mL per mmol acid), was added thionyl chloride (1.1 eq.) dropwise under nitrogen atmosphere. The temperature was allowed to warm to 25°C and stirred for 18 hours. The reaction mixture was quenched by pouring into ice water and filtered to give the title compound as a white solid.

Method B: To neat amide **(22),** at 0°C, was added chlorosulfonic acid (5 eq) dropwise. The temperature was allowed to warm to 25 °C and then heated at 70°C for 45 minutes. After cooling to 25°C, the reaction mixture was poured into ice water, and the resultant precipitate was collected by filtration to give the title sulfonyl chloride as a white solid. The product was used without further purification.



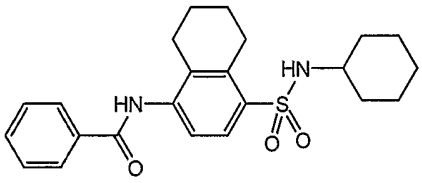
2-Methyl-*N*-[4-(piperidin-4-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (26)

To a 25°C solution of sulfonyl chloride **(24)** (1.61 g, 4 mmol) in THF (60 mL) was added 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester (880 mg, 4.4 mmol), and followed by triethyl amine (668 mg, 6.6 mmol). The resultant solution was stirred at 25 °C for 18 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford **25**. 4 N HCl/Dioxane was added and this mixture was stirred for 2 hours, followed by filtration to collect a light gray solid (1.7 g, yield 75%) as the HCl salt of the title compound. LC/MS $(M + H)^+$ *m/z* 527.



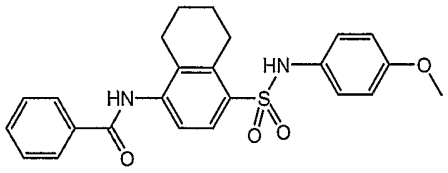
***N*-[4-(1-Butyryl-piperidin-4-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-2-methyl-benzamide (E-1)**

To a 25°C mixture of sulfonamide (**26**) (134 mg, 0.29 mmol) in THF (10 mL) was added butyryl chloride (77 mg, 0.725 mmol) and triethylamine (367 mg, 3.625 mmol). The mixture was stirred for 18 hours, followed by filtration to remove the precipitate. The filtrate was concentrated *in vacuo* and purified *via* chromatography, resulting in the title compound as white solid (50 mg). ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.55 (m, 2H), 7.41 (m, 1H), 7.31 (m, 2H), 4.30 (m, 1H), 3.89 (m, 1H), 3.21 (m, 2H), 3.09 (m, 1H), 2.85 (m, 2H), 2.61 (m, 1H), 2.55 (s, 3H), 2.34 (t, 2H), 1.88 (m, 7H), 1.62 (m, 2H), 1.39 (m, 2H), 0.95 (t, 3H)); LC/MS $(M + H)^+$ *m/z* 498.



***N*-(4-Cyclohexylsulfamoyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-benzamide (E-2)**

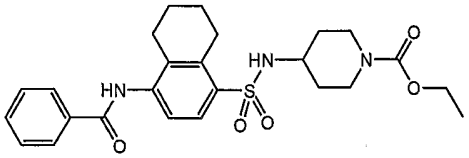
The title compound was made following general procedure in Scheme 10, substituting benzoyl chloride for 2-methyl-benzoyl chloride, and cyclohexylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, 1H), 7.95 (d, 1H), 7.89 (m, 2H), 7.82 (br s, 1H, NH), 7.53 (m, 3H), 3.90 (m, 1H), 3.20 (t, 2H), 2.72 (t, 2H), 1.52 (m, 14H); LC/MS $(M + H)^+$ *m/z* 413.



***N*-[4-(4-Methoxy-phenylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (E-3)**

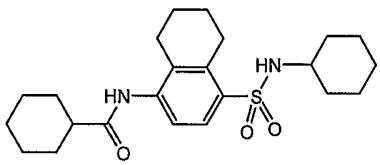
The title compound was made following general procedure in Scheme 10, substituting benzoyl chloride for 2-methyl-benzoyl chloride, and 4-methoxy-phenylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H), 7.84 (m, 4H), 7.55 (m, 3H), 6.96 (dd, 2H), 6.74

(dd, 2H), 6.64 (br s, 1H, *N*-H), 3.73 (s, 3H), 3.19 (t, 2H), 2.70 (t, 2H), 1.82 (m, 4H); LC/MS $(M + H)^+$ *m/z* 437.



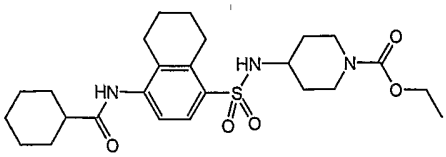
4-(4-Benzoylamino-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (E-4)

The title compound was made following general procedure in Scheme 10, substituting benzoyl chloride for 2-methyl-benzoyl chloride, and ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1H), 7.94 (d, 1H), 7.89 (m, 2H), 7.53 (m, 3H), 4.70 (m, 1H), 4.08 (q, 2H), 3.92 (m, 2H), 3.32 (m, 1H), 3.15 (m, 2H), 2.76 (m, 4H), 1.80 (m, 4H), 1.36 (m, 3H), 1.22 (t, 3H); LC/MS $(M + H)^+$ *m/z* 486.



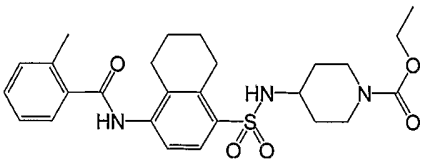
Cyclohexanecarboxylic acid (4-cyclohexylsulfamoyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-amide (E-5)

The title compound was made following general procedure in Scheme 10, substituting cyclohexanecarbonyl chloride for 2-methyl-benzoyl chloride, and cyclohexylamine for 4-amino-piperidine-1-carboxylic acid tert-butyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 1H), 7.84(d, 1H), 4.24 (m, 1H), 3.11 (m, 3H), 2.57 (m, 2H), 2.22 (m, 1H), 2.02 (m, 2H), 1.79 (m, 9H), 1.66 (m, 3H), 1.17 (t, 9H); LC/MS $(M + H)^+$ *m/z* 419.



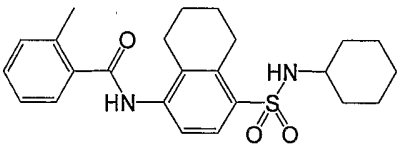
4-(4-(Cyclohexanecarbonyl-amino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (E-6)

The title compound was made following general procedure in Scheme 10, substituting cyclohexanecarbonyl chloride for 2-methyl-benzoyl chloride, and ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.93 (d, 1H), 7.51 (d, 1H), 4.19 (q, 2H), 4.08 (m, 2H), 3.32 (m, 2H), 3.05 (m, 2H), 2.96 (m, 2H), 2.60 (m, 1H), 1.66 (m, 19H), 1.22 (t, 3H); LC/MS $(M + H)^+$ *m/z* 492.



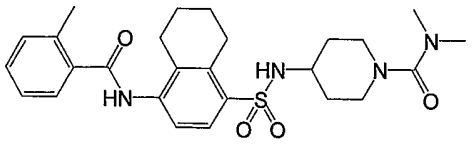
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (E-8)

The title compound was made following general procedure in Scheme 10, substituting ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.89 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.29 (m, 2H), 4.22 (q, 2H), 3.92 (m, 2H), 3.21 (m, 3H), 2.81 (m, 4H), 2.49(s, 3H), 1.81 (m, 4H), 1.70(m, 2H), 1.39 (m, 2H), 1.21 (t, 3H); LC/MS $(M + H)^+$ *m/z* 500.



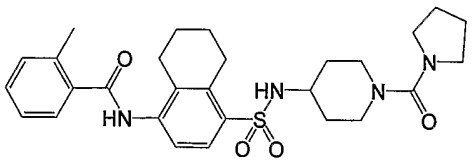
***N*-(4-Cyclohexylsulfamoyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-2-methyl-benzamide (E-9)**

The title compound was made following general procedure in Scheme 10, substituting cyclohexylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.92 (d, 1H), 7.57 (m, 2H), 7.43 (m, 1H), 7.34 (m, 2H), 3.25 (m, 2H), 3.03 (m, 1H), 2.88 (m, 2H), 2.45 (s, 3H), 1.88 (m, 4H), 1.78 (m, 5H), 1.22 (m, 5H); LC/MS $(M + H)^+$ *m/z* 427.



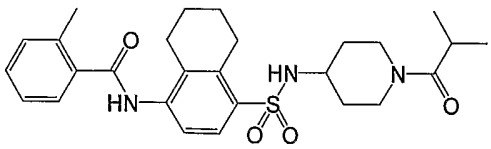
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-10)

The title compound was made following general procedure in Scheme 10, substituting dimethylcarbamyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.54 (m, 2H), 3.21 (m, 4H), 2.81 (m, 4H), 2.79 (s, 6H), 2.50 (s, 3H), 1.77(m, 3H), 1.71 (m, 2H), 1.45 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 499.



2-Methyl-*N*-{4-[1-(pyrrolidine-1-carbonyl)-piperidin-4-ylsulfamoyl]-5,6,7,8-tetrahydro-naphthalen-1-yl}-benzamide (E-11)

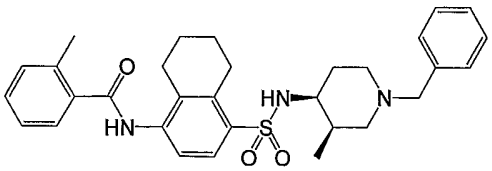
The title compound was made following general procedure in Scheme 10, substituting pyrrolidine-1-carbonyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.07 (d, 1H), 7.69 (m, 2H), 7.55 (m, 1H), 7.48 (m, 2H), 3.79 (m, 2H), 3.46 (m, 4H), 2.91 (m, 4H), 2.61 (s, 3H), 1.98 (m, 10H), 1.85 (m, 2H), 1.61 (m, 3H)); LC/MS $(M + H)^+$ *m/z* 525.



N-[4-(1-Isobutyryl-piperidin-4-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-2-methyl-benzamide (E-12)

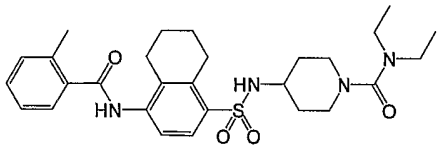
The title compound was made following general procedure in Scheme 10, substituting isobutyryl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.95 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.29 (m, 2H), 4.29 (m, 1H), 3.89 (m, 1H),

3.19 (m, 3H), 2.85 (m, 3H), 2.47 (s, 3H), 1.82 (m, 7H), 1.38 (m, 3H), 1.09 (m, 6H); LC/MS $(M + H)^+$ *m/z* 498.



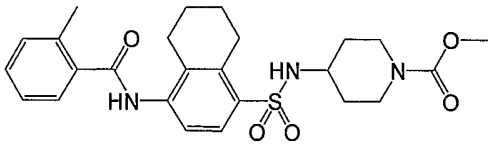
(±)-*cis*-*N*-[4-(1-Benzyl-3-methyl-piperidin-4-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-2-methyl-benzamide (E-13)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.88 (d, 1H), 7.50 (m, 2H), 7.35 (m, 1H), 7.25 (m, 7H), 3.71 (m, 2H), 3.44 (m, 2H), 3.21 (m, 3H), 2.82 (s, 2H), 2.47 (s, 3H), 2.30 (m, 2H), 1.81 (m, 5H), 1.60 (m, 2H), 0.83 (d, 3H)); LC/MS $(M + H)^+$ *m/z* 532.



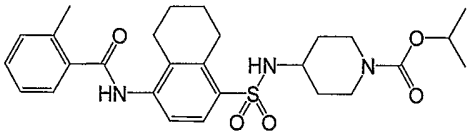
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid diethylamide (E-14)

The title compound was made following general procedure in Scheme 10, substituting diethylcarbamyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.51 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.50 (m, 2H), 3.20 (m, 4H), 3.18 (q, 4H), 2.80 (m, 4H), 2.50 (s, 3H), 1.85 (m, 3H), 1.73 (m, 2H), 1.49 (m, 2H), 1.11 (t, 6H)); LC/MS $(M + H)^+$ *m/z* 527.



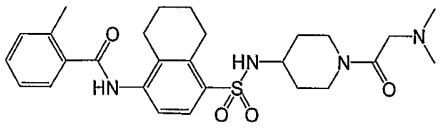
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid methyl ester (E-15)

The title compound was made following general procedure in Scheme 10, substituting methyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.92 (m, 2H), 3.63 (s, 3H), 3.20 (m, 4H), 2.85 (m, 4H), 2.50 (s, 3H), 1.85 (m, 3H), 1.72 (m, 2H), 1.41 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 486.



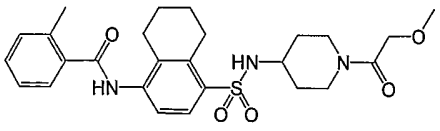
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid isopropyl ester (E-16)

The title compound was made following general procedure in Scheme 10, substituting isopropyl chlorofomate chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.56 (m, 2H), 7.40 (m, 1H), 7.31 (m, 2H), 3.92 (m, 2H), 3.26 (m, 1H), 3.21 (m, 4H), 2.83 (m, 4H), 2.50 (s, 3H), 1.85 (m, 3H), 1.72 (m, 2H), 1.39 (m, 2H), 1.20 (d, 6H)); LC/MS $(M + H)^+$ *m/z* 514.



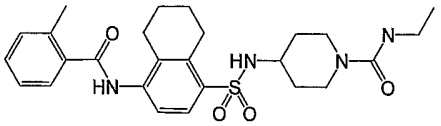
***N*-{4-[1-(2-Dimethylamino-acetyl)-piperidin-4-ylsulfamoyl]-5,6,7,8-tetrahydro-naphthalen-1-yl}-2-methyl-benzamide (E-17)**

The title compound was made following general procedure in Scheme 10, substituting dimethylamino-acetyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.56 (m, 2H), 7.40 (m, 1H), 7.31 (m, 2H), 4.28 (m, 1H), 3.93 (d, 2H), 3.66 (m, 1H), 3.25 (m, 4H), 2.80 (m, 4H), 2.72 (s, 6H), 2.51 (s, 3H), 1.85 (m, 5H), 1.45 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 513.



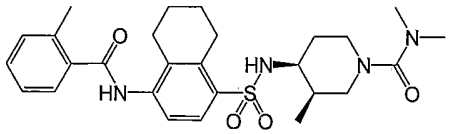
***N*-{4-[1-(2-Methoxy-acetyl)-piperidin-4-ylsulfamoyl]-5,6,7,8-tetrahydro-naphthalen-1-yl}-2-methyl-benzamide (E-18)**

The title compound was made following general procedure in Scheme 10, substituting methoxy-acetyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.92 (d, 1H), 7.56 (m, 2H), 7.41 (m, 1H), 7.35 (m, 2H), 4.25 (m, 1H), 4.12 (d, 2H), 3.73 (m, 1H), 3.36 (s, 3H), 3.26 (m, 4H), 3.02 (m, 1H), 2.80 (m, 3H), 2.49 (s, 3H), 1.84 (m, 5H), 1.40 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 500.



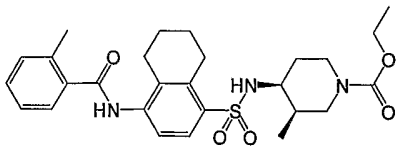
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethylamide (E-19)

The title compound was made following general procedure in Scheme 10, substituting isocyanato-ethane for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.55 (m, 2H), 7.41 (m, 1H), 7.31 (m, 2H), 3.83 (m, 2H), 3.24 (m, 4H), 3.14 (q, 2H), 2.79 (m, 4H), 2.50 (s, 3H), 1.84 (m, 3H), 1.70 (m, 2H), 1.38 (m, 2H), 1.07 (t, 3H)); LC/MS $(M + H)^+$ *m/z* 499.



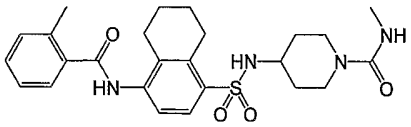
(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-20)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.36 (m, 2H), 3.22 (m, 2H), 3.10 (m, 3H), 2.82 (m, 2H), 2.80 (s, 6H), 2.49 (s, 3H), 1.85 (m, 5H), 1.65 (m, 1H), 1.51 (m, 1H), 0.82 (d, 3H)); LC/MS $(M + H)^+$ *m/z* 513.



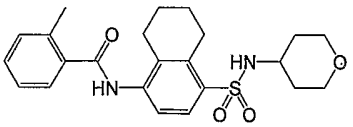
(±)-*cis*-3-Methyl-4-[4-(2-methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (E-21)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.92 (d, 1H), 7.58 (m, 2H), 7.41 (m, 1H), 7.35 (m, 2H), 4.12 (q, 2H), 3.71 (m, 1H), 3.29 (m, 6H), 2.88 (m, 2H), 2.52 (s, 3H), 1.88 (m, 5H), 1.62 (m, 1H), 1.51 (m, 1H), 1.25 (t, 3H), 0.89 (d, 3H)); LC/MS $(M + H)^+$ *m/z* 514.



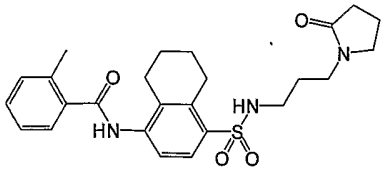
4-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid methylamide (E-22)

The title compound was made following general procedure in Scheme 10, substituting isocyanato-methane for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.93 (d, 1H), 7.59 (m, 2H), 7.43 (m, 1H), 7.36 (m, 2H), 3.88 (m, 2H), 3.29 (m, 4H), 2.83 (m, 4H), 2.71 (s, 3H), 2.54 (s, 3H), 1.88 (m, 3H), 1.73 (m, 2H), 1.41 (m, 2H)); LC/MS $(M + H)^+$.*m/z* 486.



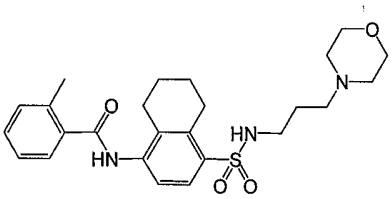
2-Methyl-*N*-[4-(tetrahydro-pyran-4-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (E-23)

The title compound was made following general procedure in Scheme 10, substituting tetrahydro-pyran-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.54 (m, 2H), 7.39 (m, 1H), 7.32 (m, 2H), 3.84 (m, 2H), 3.29 (m, 6H), 2.83 (m, 2H), 2.51 (s, 3H), 1.88 (m, 3H), 1.69 (m, 2H), 1.54 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 429.



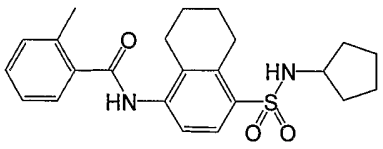
2-Methyl-*N*-{4-[3-(2-oxo-pyrrolidin-1-yl)-propylsulfamoyl]-5,6,7,8-tetrahydro-naphthalen-1-yl}-benzamide (E-24)

The title compound was made following general procedure in Scheme 10, substituting 1-(3-amino-propyl)-pyrrolidin-2-one for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.80 (d, 1H), 7.50 (t, 2H), 7.37 (m, 1H), 7.29 (m, 2H), 3.34(t, 2H), 3.21 (t, 2H), 3.17 (m, 2H), 2.86 (t, 2H), 2.79 (m, 2H), 2.46 (s, 3H), 2.31 (t, 2H), 1.98 (m, 2H), 1.82 (m, 4H), 1.65 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 470.



2-Methyl-*N*-[4-(3-morpholin-4-yl-propylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (E-25)

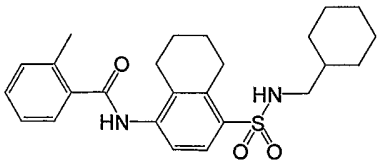
The title compound was made following general procedure in Scheme 10, substituting 3-morpholin-4-yl-propylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.83 (d, 1H), 7.54 (t, 2H), 7.41 (m, 1H), 7.31 (m, 2H), 3.74(m, 4H), 3.19 (m, 2H), 2.98 (t, 2H), 2.75 (m, 8H), 2.49 (s, 3H), 1.81 (m, 6H)); LC/MS $(M + H)^+$ *m/z* 472.



N-(4-Cyclopentylsulfamoyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-2-methyl-benzamide (E-26)

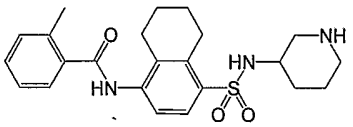
The title compound was made following general procedure in Scheme 10, substituting cyclopentylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.88 (d, 1H), 7.54 (m, 2H), 7.39 (m, 1H), 7.31

(m, 2H), 3.49 (m, 1H), 3.21 (m, 2H), 2.72 (m, 2H), 2.50 (s, 3H), 1.83 (m, 4H), 1.69 (m, 4H), 1.48 (m, 4H); LC/MS $(M + H)^+$ *m/z* 413.



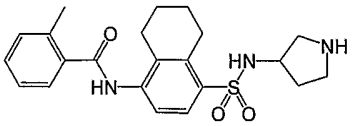
N-[4-(Cyclohexylmethyl-sulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-2-methyl-benzamide (E-27)

The title compound was made following general procedure in Scheme 10, substituting C-cyclohexyl-methylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.82 (d, 1H), 7.54 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.21 (m, 2H), 2.83 (m, 2H), 2.69 (d, 2H), 2.49 (s, 3H), 1.83 (m, 3H), 1.69 (m, 6H), 1.39 (m, 1H), 1.19 (m, 3H), 0.85 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 441.



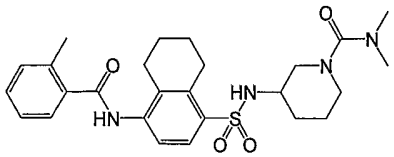
(±)-2-Methyl-N-[4-(piperidin-3-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (E-28)

The title compound was made following general procedure in Scheme 10, substituting (*R, S*)-3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.91 (d, 1H), 7.57 (m, 2H), 7.41 (m, 1H), 7.33 (m, 2H), 3.23 (m, 4H), 3.11 (m, 1H), 2.85 (m, 2H), 2.70(m, 2H), 2.50 (s, 3H), 1.73 (m, 6H), 1.54 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 428.



(±)-2-Methyl-N-[4-(pyrrolidin-3-ylsulfamoyl)-5,6,7,8-tetrahydro-naphthalen-1-yl]-benzamide (E-29)

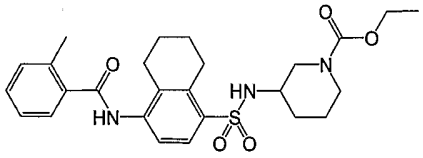
The title compound was made following general procedure in Scheme 10, substituting (*R, S*)-3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, MeOD) δ 7.89 (d, 1H), 7.57 (m, 2H), 7.41 (m, 1H), 7.33 (m, 2H), 3.81 (m, 1H), 3.22 (m, 7H), 2.84 (m, 2H), 2.50 (s, 3H), 2.09 (m, 1H), 1.83 (m, 4H)); LC/MS $(M + H)^+$ *m/z* 414.



(±)-3-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-30)

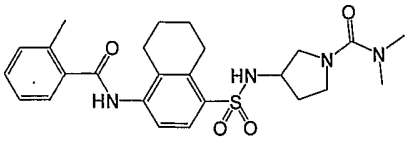
The title compound was made following general procedure in Scheme 10, substituting (*R, S*)-3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride.

^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.56 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.40 (m, 3H), 3.15 (m, 3H), 2.85 (m, 2H), 2.74 (s, 6H), 2.69(m, 2H), 2.50 (s, 3H), 1.73 (m, 4H), 1.69 (m, 1H), 1.44 (m, 2H)); LC/MS $(M + H)^+$ *m/z* 499.



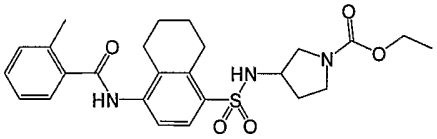
(±)-3-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (E-31)

The title compound was made following general procedure in Scheme 10, substituting (*R, S*)-3-amino-piperidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.92 (d, 1H), 7.59 (m, 2H), 7.42 (m, 1H), 7.34 (m, 2H), 4.09 (q, 2H), 3.91 (m, 1H), 3.79 (m, 1H), 3.24 (m, 2H), 3.09 (m, 2H), 2.85 (m, 4H), 2.51 (s, 3H), 1.86 (m, 4H), 1.71 (m, 1H), 1.42 (m, 2H), 1.23 (t, 3H)); LC/MS $(M + H)^+$ *m/z* 500.



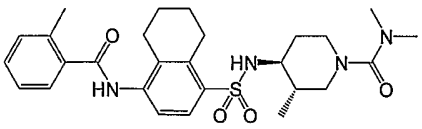
(±)-3-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-pyrrolidine-1-carboxylic acid dimethylamide (E-32)

The title compound was made following general procedure in Scheme 10, substituting (R,S)-3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.57 (m, 2H), 7.41 (m, 1H), 7.32 (m, 2H), 3.78 (m, 1H), 3.48 (m, 1H), 3.28 (m, 2H), 3.18 (m, 3H), 2.84 (m, 3H), 2.78 (s, 6H), 2.50 (s, 3H), 1.96 (m, 1H), 1.82 (m, 4H)); LC/MS $(M + H)^+$ *m/z* 485.



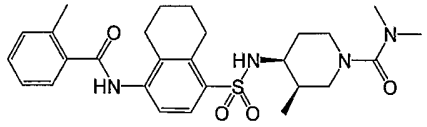
(±)-3-[4-(2-Methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-pyrrolidine-1-carboxylic acid ethyl ester (E-33)

The title compound was made following general procedure in Scheme 10, substituting (*R, S*)-3-amino-pyrrolidine-1-carboxylic acid *tert*-butyl ester for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and ethyl chlorofomate for butyryl chloride. ^{1}H NMR (300 MHz, MeOD) δ 7.89 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.30 (m, 2H), 4.09 (m, 2H), 3.79 (m, 1H), 3.41 (m, 3H), 3.18 (m, 4H), 2.82 (m, 2H), 2.50 (s, 3H), 1.99 (m, 1H), 1.89 (m, 4H), 1.22 (m, 3H)); LC/MS $(M + H)^+$ *m/z* 486.



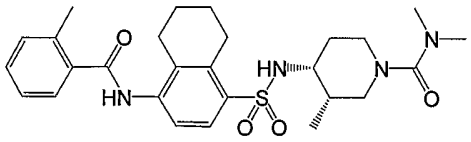
(±)-*trans*-3-Methyl-4-[4-(2-methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-34)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride. LC/MS $(M + H)^+$ *m/z* 513.



(*3R, 4S*)-3-Methyl-4-[4-(2-methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-35)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride. Compound **E-20** was prepared as described previously, and the enantiomers were separated *via* chiral HPLC chromatography of **E-35**; the title compound eluted as peak 1. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 3.36 (m, 2H), 3.22 (m, 2H), 3.10 (m, 3H), 2.82 (m, 2H), 2.80 (s, 6H), 2.49 (s, 3H), 1.85 (m, 4H), 1.65 (m, 1H), 1.49 (m, 1H), 0.83 (d, 3H)); LC/MS $(M + H)^+$ *m/z* 537.

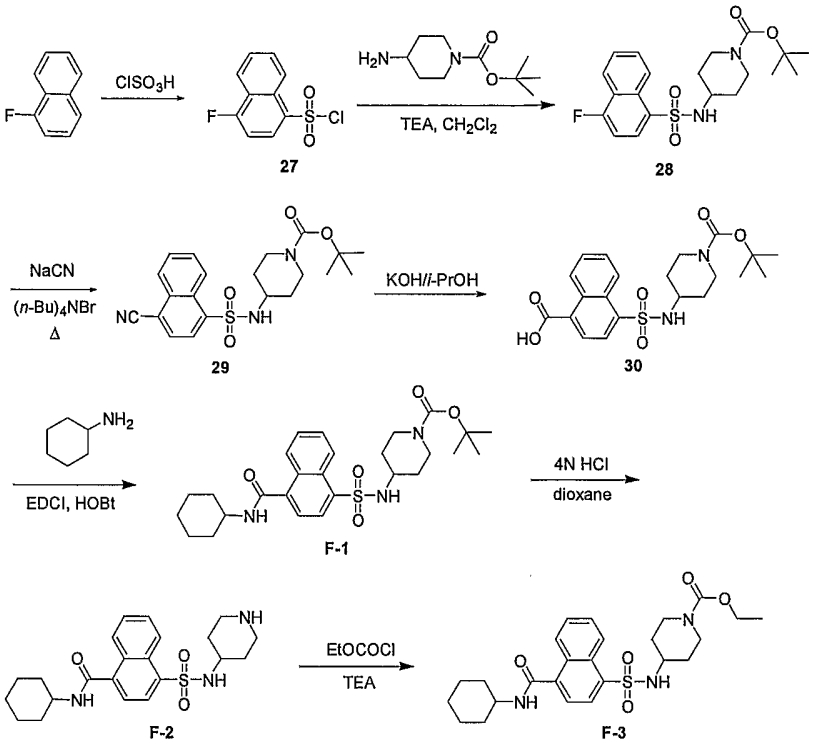


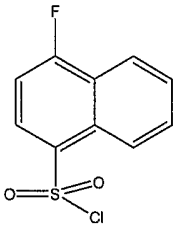
(*3S, 4R*) - 3-Methyl-4-[4-(2-methyl-benzoylamino)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (E-36)

The title compound was made following general procedure in Scheme 10, substituting 1-benzyl-3-methyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester, and dimethylcarbamyl chloride for butyryl chloride. Compound **E-20** was prepared as described previously, and the enantiomers were separated *via* chiral HPLC chromatography of **E-35**; the title compound eluted as peak 2. ^{1}H NMR (300 MHz, MeOD) δ 7.90 (d, 1H), 7.55 (m, 2H), 7.39 (m, 1H),

7.31 (m, 2H), 3.36 (m, 2H), 3.22 (m, 2H), 3.10 (m, 3H), 2.82 (m, 2H), 2.80 (s, 6H), 2.49 (s, 3H), 1.85 (m, 4H), 1.65 (m, 1H), 1.49 (m, 1H), 0.83 (d, 3H)); LC/MS (M + H)$^+$ *m/z* 513.

Scheme 11

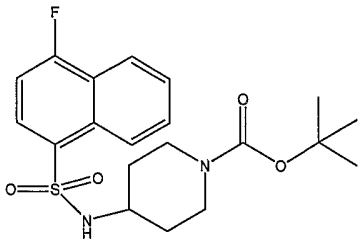




4-Fluoro-naphthalene-1-sulfonyl chloride (27)

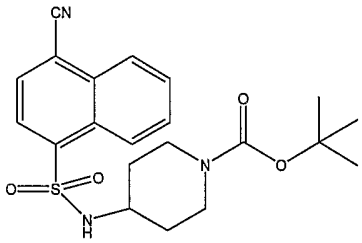
1-Fluoronaphthalene (20.0 g, 0.14 mol) was added in small portions to a stirred solution of chlrosulfonic acid (79 g, 45 mL, 0.68 mol) at room temperature. The reaction was stirred for 30 minutes until gas evolution ceased. The reaction mixture was poured carefully over a mixture of ice (300 g) and dichloromethane (300 mL) and charged to a separatory funnel. The organic layer was separated, washed twice with water and brine and dried over $MgSO_4$. Filtration and concentration *in vacuo*

afforded **27** as a tan solid. Wt.: 27.6 g (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, 1H), 8.38 (dd, 1H), 8.28 (d, 1H), 7.88 (m, 1H), 7.77 (m, 1H), 7.26 (dd, 1H).



4-(4-Fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (28)

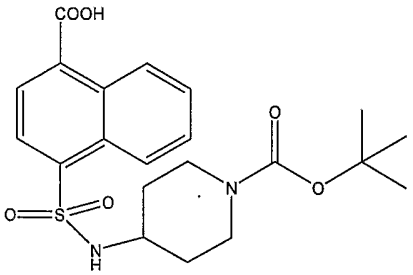
4-Fluoro-naphthalene-1-sulfonyl chloride **27** (10.0 g, 40.9 mmol) was dissolved in THF (100 mL) and stirred at room temperature. 4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester (8.19 g, 40.9 mmol) and triethylamine (4.14 g, 5.75 mL, 40.9 mmol) were added and the reaction was stirred overnight at room temperature. The solvent was removed *in vacuo*. Dichloromethane (250 mL) was added and the solution was charged to a separatory funnel. The organic layer was washed twice with water and brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded **28** as a yellow foam. Wt.: 15.1 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 1H), 8.26 (m, 2H), 7.69 (m, 2H), 7.20 (m, 1H), 4.92 (d, 1H), 3.82 (m, 2H), 3.26 (m, 1H), 2.70 (m, 2H), 1.61 (m, 2H), 1.40 (s, 9H), 1.24 (m, 2H); LC/MS *m/z* 409 $(M + H)^+$.



4-(4-Cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (29)

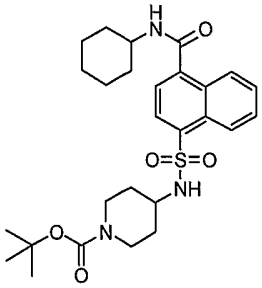
4-(4-Fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester **28** (2.00 g, 4.9 mmol) was dissolved in DMF (20 mL). Sodium cyanide (1.2 g, 24.5 mmol) and tetra-*n*-butylammonium bromide (7.9 g, 24.5 mmol) were added and

the reaction was heated to 100°C overnight. The reaction was diluted with dichloromethane (100 mL) and charged to a separatory funnel. The organic layer was washed three times with water, brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a dark colored oil. Flash column chromatography (98:2 dichloromethane:methanol) afforded an oil that was rechromatographed (99:1 dichloromethane:methanol) to afford **29** as an orange solid. Wt.: 640 mg (31%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (m, 1H), 8.40 (m, 1H), 8.34 (d, 1H), 8.00 (d, 1H), 7.83 (m, 2H), 4.80 (d, 1H), 3.87 (m, 2H), 3.32 (m, 1H), 2.61 (m, 2H), 1.63 (m, 2H), 1.38 (s, 9H), 1.27 (m, 2H); LC/MS *m/z* 414 $(M - H)^-$



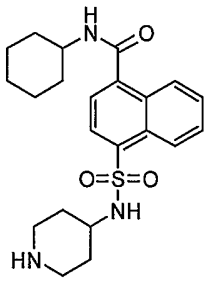
4-(4-Carboxy-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (30)

4-(4-Cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester **29** (0.48 g, 1.15 mmol) was dissolved in a mixture of aqueous potassium hydroxide (20 mL, 1.8N, 36 mmol) and isopropanol (25 mL). The mixture was heated to 75°C for two days. LC/MS analysis showed a mixture of starting material, carboxylic acid and amide. The isopropanol was removed *in vacuo* and the aqueous layer was extracted with ethyl acetate and the organic layer discarded. The aqueous layer was acidified to pH 3 and extracted with ethyl acetate. The organic layer washed with water, then brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded **30** as a tan colored foam. Wt.: 360 mg (72%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (m, 1H), 8.70 (m, 1H), 8.33 (dd, 2H), 7.74 (m, 2H), 4.78 (d, 1H), 3.85 (m, 2H), 3.31 (m, 1H), 2.71 (m, 2H), 1.62 (m, 2H), 1.40 (s, 9H), 1.27 (m, 2H); LC/MS *m/z* 433 $(M - H)^-$.



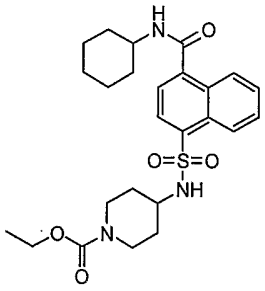
4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (F-1)

4-(4-Carboxy-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester **5** (400 mg, 0.92 mmol) was dissolved in dichloromethane (5 mL). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (350 mg, 1.84 mmol), 1-hydroxybenzotriazole (186 mg, 1.38 mmol), triethylamine (280 mg, 0.38 mL, 2.76 mmol) and cyclohexylamine (0.14 g, 0.16 mL, 1.38 mmol) were added and the reaction was stirred overnight at room temperature. The reaction was diluted with dichloromethane (30 mL) and charged to a separatory funnel. The organic layer was washed twice with water and brine and dried over Na_2SO_4. Filtration and concentration *in vacuo* afforded a foam that was purified via flash column chromatography (98:2 dichloromethane:methanol) to give the title compound. Wt.: 320 mg (68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (m, 1H), 8.31 (m, 1H), 8.26 (d, 1H), 7.68 (m, 2H), 7.59 (d, 1H), 5.91 (d, 1H), 4.64 (d, 1H), 4.12 (m, 1H), 3.82 (m, 2H), 3.22 (m, 1H), 2.68 (m, 2H), 2.13 (m, 2H), 1.79 (m, 2H), 1.57 (m, 6H), 1.38 (s, 9H), 1.27 (m, 4H); LC/MS *m/z* 516 $(M + H)^+$.



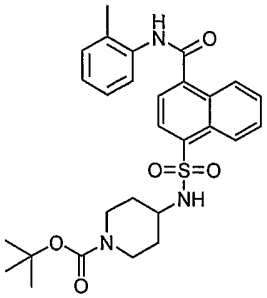
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide (F-2)

4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester **F-1** (320 mg, 0.62 mmol) was dissolved in 4N HCl/dioxane (10 mL). The reaction was stirred for 2 hours at room temperature and concentrated *in vacuo* to afford the title compound as its hydrochloride salt. Wt.: 271 mg (97%) ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.68 (d, 1H), 8.59 (d, 1H), 8.40 (d, 1H), 8.15 (m, 2H), 7.72 (m, 2H), 7.60 (d, 1H), 3.75 (m, 1H), 3.67 (m, 1H), 3.08 (m, 2H), 2.80 (m, 2H), 2.54 (m, 1H), 1.92 (m, 2H), 1.74 (m, 2H), 1.62 (m, 4H), 1.48 (m, 1H), 1.32 (m, 4H), 1.25 (m, 1H); LC/MS *m/z* 416 $(M + H)^+$.



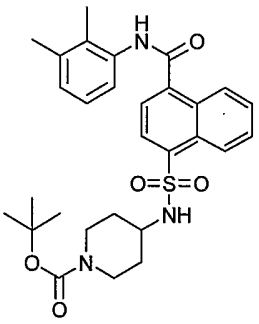
4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (F-3)

4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide hydrochloride **F-2** (87 mg, 0.19 mmol) was dissolved and stirred in dichloromethane (2 mL). Triethylamine (58 mg, 0.08 mL, 0.57 mmol) was added followed by ethyl chloroformate (41 mg, 0.037 mL, 0.39 mmol). The reaction was stirred overnight at room temperature, then charged directly to a flash column. Elution with 99:1 dichloromethane:methanol afforded the titled compound the title compound as a white solid. Wt.: 60 mg (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (m, 1H), 8.28 (m, 1H), 8.19 (d, 1H), 7.64 (m, 2H), 7.54 (d, 1H), 4.10 (m, 1H), 4.03 (q, 2H), 3.80 (m, 2H), 3.64 (m, 1H), 3.18 (m, 1H), 2.68 (m, 2H), 2.12 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.58 (m, 2H), 1.47 (m, 2H), 1.24 (m, 6H), 1.18 (t, 3H); LC/MS *m/z* 488 $(M + H)^+$.



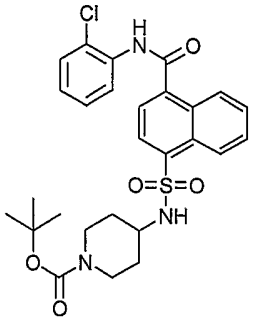
4-(4-*o*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (F-4)

The titled compound was prepared according to the general procedure in Scheme 11, substituting 2-methylphenylamine for cyclohexylamine. Wt.: 337 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H), 8.46 (d, 1H), 8.35 (d, 1H), 8.04 (d, 1H), 7.80 (m, 1H), 7.72 (m, 2H), 7.54 (s, 1H), 7.34 (m, 1H), 7.21 (m, 1H), 4.16 (d, 1H), 3.85 (m, 2H), 3.27 (m, 1H), 2.70 (m, 2H), 2.34 (s, 3H), 2.23 (m, 1H), 1.66 (m, 2H), 1.56 (m, 4H), 1.40 (s, 9H), 1.27 (m, 4H); LC/MS *m/z* 524 $(M + H)^+$.



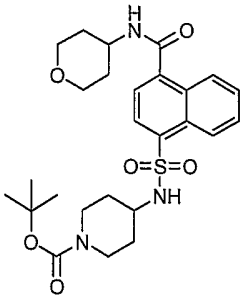
4-[4-(2,3-Dimethyl-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (F-13)

The titled compound was prepared according to the general procedure in Scheme 11, substituting 2,3-dimethyl-phenylamine for cyclohexylamine. Wt.: 353 mg (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (m, 1H), 8.47 (d, 1H), 8.35 (d, 1H), 7.81 (d, 1H), 7.72 (m, 2H), 7.54 (s, 1H), 7.22 (m, 1H), 7.13 (m, 1H), 4.63 (d, 1H), 3.86 (m, 2H), 3.27 (m, 1H), 2.70 (m, 2H), 2.35 (s, 3H), 2.24 (s, 3H), 1.64 (m, 2H), 1.34 (m, 2H); LC/MS *m/z* 537 $(M - H)^-$.



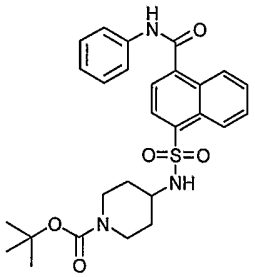
4-[4-(2-Chloro-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (F-14)

The titled compound was prepared according to the general procedure in Scheme 11, substituting 2-chloro-phenylamine for cyclohexylamine. Wt.: 329 mg (66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (m, 1H), 8.62 (m, 1H), 8.46 (d, 1H), 8.37 (m, 1H), 8.20 (s, 1H), 7.83 (d, 1H), 7.73 (m, 2H), 7.46 (m, 1H), 7.40 (m, 1H), 7.17 (m, 1H), 4.68 (d, 1H), 3.87 (m, 2H), 3.30 (m, 1H), 2.62 (m, 2H), 1.68 (m, 2H), 1.40 (s, 9H), 1.26 (m, 2H); LC/MS *m/z* 543 $(M - H)^-$.



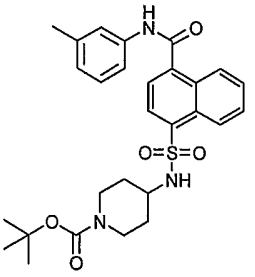
4-[4-(Tetrahydro-pyran-4-ylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester (F-15)

The title compound was prepared according to the general procedure in Scheme 11, substituting tetrahydro-pyran-4-ylamine for cyclohexylamine. Wt.: 368 mg (77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (m, 1H), 8.29 (m, 1H), 8.24 (d, 1H), 7.68 (m, 2H), 7.59 (d, 1H), 6.12 (d, 1H), 4.73 (d, 1H), 4.34 (m, 1H), 4.04 (m, 2H), 3.82 (m, 2H), 3.57 (m, 2H), 3.21 (m, 1H), 2.67 (m, 2H), 2.11 (m, 1H), 1.62 (m, 3H), 1.36 (s, 9H), 1.20 (m, 4H); LC/MS *m/z* 516 $(M - H)^-$.



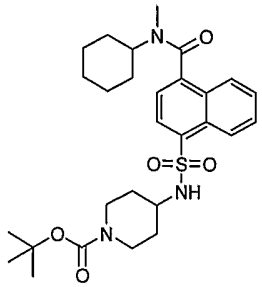
4-(4-Phenylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

The titled compound was prepared according to the general procedure in Scheme 11, substituting phenylamine for cyclohexylamine. Wt.: 66 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 1H), 8.37 (m, 2H), 8.26 (d, 1H), 7.93 (s, 1H), 7.70 (m, 4H), 7.43 (m, 3H), 4.76 (d, 1H), 3.80 (m, 2H), 3.24 (m, 1H), 2.67 (m, 2H), 1.60 (m, 2H), 1.39 (s, 9H), 1.22 (m, 2H); LC/MS *m/z* 510 $(M + H)^+$.



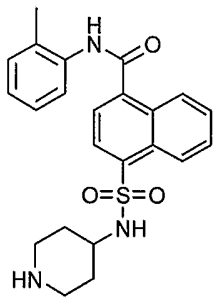
4-(4-*m*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared according to the general procedure in Scheme 11, substituting *m*-tolylamine for cyclohexylamine. Wt.: 61 mg (51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 1H), 8.35 (m, 2H), 8.18 (d, 1H), 7.65 (m, 4H), 7.28 (m, 2H), 7.03 (d, 1H), 5.13 (d, 1H), 3.73 (m, 2H), 3.18 (m, 1H), 2.62 (m, 2H), 2.40 (s, 3H), 1.55 (m, 2H), 1.38 (s, 9H), 1.12 (m, 2H); LC/MS *m/z* 524 $(M + H)^+$.



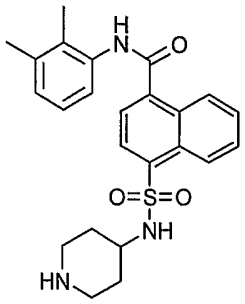
4-[4-(Cyclohexyl-methyl-carbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester

The title compound was prepared according to the general procedure in Scheme 11, substituting cyclohexyl-methyl-amine for cyclohexylamine, and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate for EDCI. Wt.: 440 mg (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, 1H), 8.31 (d, 1H), 7.89 (m, 1H), 7.67 (m, 2H), 7.42 (m, 1H), 4.77 (s, 1H), 3.87 (m, 2H), 3.22 (m, 1H), 2.79 (s, 3H), 2.60 (m, 2H), 1.88 (m, 4H), 1.55 (m, 8H), 1.38 (s, 9H), 1.15 (m, 2H); LC/MS *m/z* 530 $(M + H)^+$.



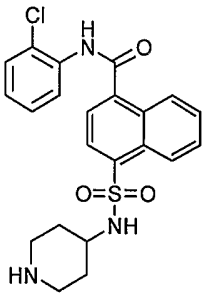
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid o-tolylamide (F-5)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(4-*o*-tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid tert-butyl ester. Wt.: 275 mg (97%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 10.22 (s, 1H), 8.73 (m, 1H), 8.44 (m, 2H), 8.30 (m, 1H), 8.24 (m, 1H), 7.88 (d, 1H), 7.77 (m, 2H), 7.52 (d, 1H), 7.28 (m, 1H), 7.22 (m, 1H), 3.11 (m, 2H), 2.83 (m, 2H), 2.53 (m, 1H), 2.32 (s, 3H), 1.67 (m, 2H), 1.51 (m, 2H); LC/MS *m/z* 424 $(M + H)^+$.



4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2,3-dimethyl-phenyl)-amide (F-16)

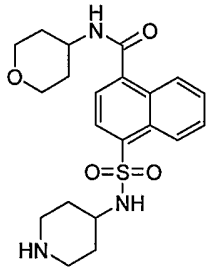
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-[4-(2,3-dimethyl-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt.: 312 mg (99%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 10.27 (s, 1H), 8.72 (d, 1H), 8.47 (d, 1H), 8.30 (m, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 7.75 (m, 2H), 7.31 (d, 1H), 7.12 (m, 2H), 3.68 (m, 1H), 3.10 (m, 2H), 2.80 (m, 2H), 2.30 (s, 3H), 2.20 (s, 3H), 2.02 (m, 1H), 1.67 (m, 2H), 1.53 (m, 2H); LC/MS *m/z* 436 (M - H)$^-$.



4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2-chloro-phenyl)-amide (F-17)

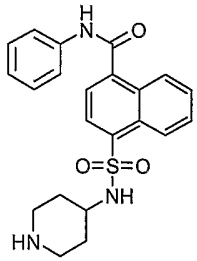
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-[4-(2-chloro-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt.: 219 mg (98%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 10.51 (s, 1H), 8.72 (d, 1H), 8.52 (m, 1H), 8.47 (d, 1H), 8.35 (m, 1H), 8.24 (d, 1H), 7.90 (d, 1H), 7.75 (m, 2H), 7.59

(d, 1H), 7.43 (m, 1H), 7.32 (m, 1H), 3.67 (m, 1H), 3.08 (m, 2H), 2.82 (m, 2H), 1.65 (m, 2H), 1.50 (m, 2H); LC/MS *m/z* 442 $(M - H)^-$.



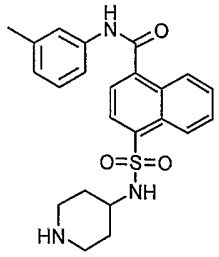
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide (F-18)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-[4-(tetrahydro-pyran-4-ylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt.: 321 mg (100%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.69 (m, 2H), 8.42 (m, 2H), 8.15 (m, 1H), 7.72 (m, 2H), 7.63 (d, 1H), 4.08 (m, 1H), 3.87 (m, 2H), 3.42 (m, 2H), 3.08 (m, 2H), 2.80 (m, 2H), 1.86 (m, 2H), 1.64 (m 4H), 1.51 (m, 4H); LC/MS *m/z* 416 $(M - H)^-$.



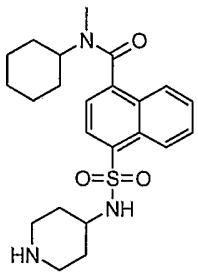
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid phenylamide

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(4-phenylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt.: 38 mg (67%). LC/MS *m/z* 410 $(M + H)^+$.



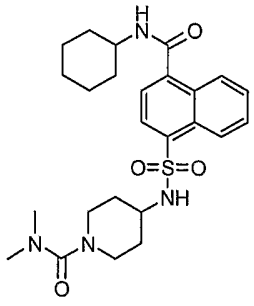
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid *m*-tolylamide

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(4-*m*-tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt. 39 mg (75%). LC/MS *m/z* 424 $(M + H)^+$.



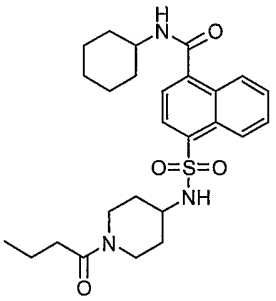
4-(Piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexyl-methyl-amide

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-[4-(cyclohexyl-methyl-carbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester for 4-(4-cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. Wt.: 440 mg (100%). LC/MS *m/z* 424 $(M + H)^+$.



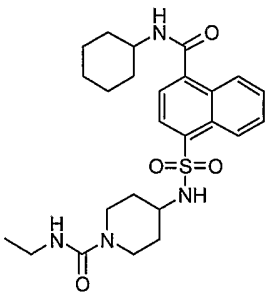
4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid dimethylamide (F-6)

The title compound was prepared according to the general procedure in Scheme 11, substituting dimethylcarbamyl chloride for ethyl chloroformate. Wt.: 56 mg (50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, 1H), 8.30 (d, 1H), 8.25 (d, 2H), 7.68 (m, 2H), 7.56 (d, 1H), 6.00 (d, 1H), 4.77 (d, 1H), 4.11 (m, 1H), 3.42 (m, 2H), 3.23 (m, 1H), 2.71 (s, 6H), 2.63 (m, 2H), 2.13 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.47 (m, 2H), 1.27 (m, 6H); LC/MS *m/z* 485 (M - H)$^-$.



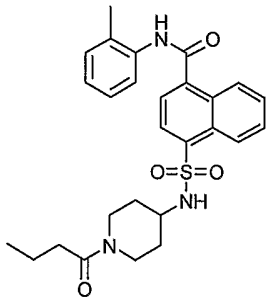
4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide (F-7)

The title compound was prepared according to the general procedure in Scheme 11, substituting butyryl chloride for ethyl chloroformate. Wt.: 50 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, 1H), 8.32 (d, 1H), 8.27 (d, 1H), 7.72 (m, 2H), 7.57 (d, 1H), 6.00 (d, 1H), 4.78 (d, 1H), 4.24 (m, 1H), 4.11 (m, 1H), 3.64 (m, 1H), 3.27 (m, 1H), 2.91 (m, 1H), 2.56 (m, 1H), 2.15 (m, 4H), 1.62 (m, 8H), 1.25 (m, 4H), 0.95 (m, 2H), 0.88 (t, 3H); LC/MS *m/z* 484 (M - H)$^-$.



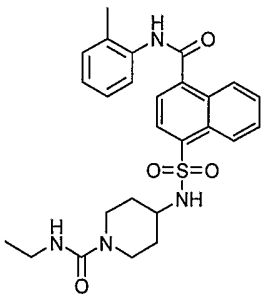
4-(4-Cyclohexylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethylamide (F-8)

The title compound was prepared according to the general procedure in Scheme 11, substituting ethyl isocyanate for ethyl chloroformate. Wt.: 56 mg (49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, 1H), 8.29 (d, 1H), 8.23 (d, 1H), 7.68 (m, 2H), 7.57 (d, 1H), 6.03 (d, 1H), 4.83 (d, 1H), 4.30 (m, 1H), 4.11 (m, 1H), 3.62 (m, 2H), 3.17 (m, 3H), 2.68 (m, 2H), 2.12 (m, 2H), 1.79 (m, 2H), 1.55 (m, 4H), 1.25 (m, 6H), 1.06 (t, 3H); LC/MS *m/z* 485 (M - H)$^-$.



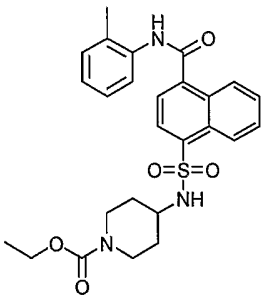
4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid o-tolylamide (F-9)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid *o*-tolylamide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chloroformate. Wt.: 29 mg (33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H), 8.45 (d, 1H), 8.34 (d, 1H), 8.04 (d, 1H), 7.78 (d, 1H), 7.71 (m, 2H), 7.60 (s, 1H), 7.30 (m, 2H), 7.20 (m, 2H), 4.75 (d, 1H), 4.29 (d, 1H), 3.66 (d, 1H), 3.31 (m, 1H), 2.95 (m, 1H), 2.60 (m, 1H)2.34 (s, 3H), 2.20 (m, 2H), 1.70 (m, 2H), 1.23 (m, 3H), 0.89 (t, 3H); LC/MS *m/z* 492 (M - H)$^-$.



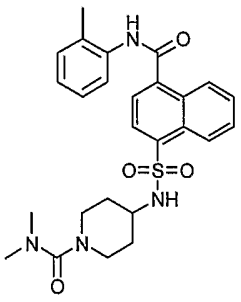
4-(4-*o*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethylamide (F-10)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid o-tolylamide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and ethyl isocyanate for ethyl chloroformate. Wt.: 26 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 1H), 8.46 (d, 1H), 8.32 (d, 1H), 8.03 (d, 1H), 7.77 (d, 1H), 7.70 (m, 2H), 7.64 (s, 1H), 7.30 (m, 2H), 7.20 (m, 2H), 4.81 (d, 1H), 4.28 (m, 1H), 3.66 (m, 2H), 3.27 (m, 1H), 3.17 (m, 2H), 2.71 (m, 2H), 2.32 (s, 3H), 1.65 (m, 1H), 1.25 (m, 2H), 1.07 (t, 3H); LC/MS *m/z* 493 $(M - H)^-$.



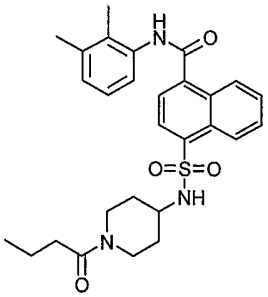
4-(4-*o*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (F-11)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid o-tolylamide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide. Wt.: 60 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H), 8.46 (d, 1H), 8.33 (d, 1H), 8.03 (d, 1H), 7.79 (d, 1H), 7.71 (m, 2H), 7.55 (s, 1H), 7.30 (m, 2H), 7.21 (m, 2H), 4.71 (d, 1H), 4.05 (q, 2H), 3.89 (m, 2H), 3.27 (m, 1H), 2.72 (m, 2H), 2.31 (s, 3H), 1.65 (m, 1H), 1.26 (m, 2H), 1.20 (t, 3H); LC/MS *m/z* 494 $(M - H)^-$.



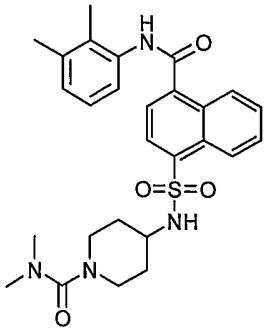
4-(4-*o*-Tolylcarbamoyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid dimethylamide (F-12)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid *o*-tolylamide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and dimethylcarbamyl chloride for ethyl chloroformate. Wt.: 35 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, 1H), 8.45 (d, 1H), 8.33 (d, 1H), 8.05 (d, 1H), 7.80 (d, 1H), 7.71 (m, 2H), 7.54 (s, 1H), 7.30 (m, 2H), 7.20 (m, 2H), 4.68 (d, 1H), 3.43 (m, 2H), 3.30 (m, 1H), 2.71 (s, 6H), 2.68 (m, 2H), 2.34 (s, 3H), 1.62 (m, 1H), 1.31 (m, 2H); LC/MS *m/z* 493 $(M - H)^-$.



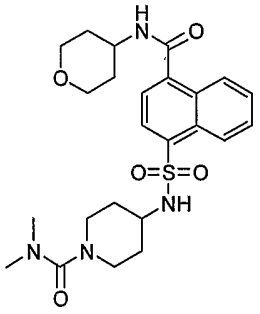
4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2,3-dimethyl-phenyl)-amide (F-19)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2,3-dimethyl-phenyl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chloroformate. Wt.: 64 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (m, 2H), 8.40 (m, 1H), 8.30 (s, 1H), 8.22 (d, 1H), 7.72 (d, 1H), 7.68 (m, 1H), 7.60 (d, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 5.57 (d, 1H), 4.02 (m, 1H), 3.55 (m, 1H), 3.28 (m, 1H), 2.85 (m, 1H), 2.49 (m, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 2.09 (2H), 1.63 (m, 2H), 1.50 (m, 2H), 1.20 (m, 1H), 1.03 (m, 1H), 0.84 (t, 3H); LC/MS *m/z* 508 $(M + H)^+$.



4-[4-(2,3-Dimethyl-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (F-20)

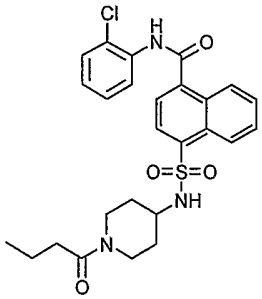
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2,3-dimethyl-phenyl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and dimethycarbamyl chloride for ethyl chloroformate. Wt.: 116 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (m, 1H), 8.40 (m, 1H), 8.20 (m, 2H), 7.72 (d, 1H), 7.63 (m, 2H), 7.35 (d, 1H), 7.16 (m, 1H), 7.09 (m, 1H), 5.42 (d, 1H), 3.32 (m, 2H), 3.15 (m, 1H), 2.67 (s, 6H), 2.55 (m, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 1.52 (m, 2H), 1.23 (m, 2H); LC/MS *m/z* 509 $(M + H)^+$.



4-[4-(Tetrahydro-pyran-4-ylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (F-21)

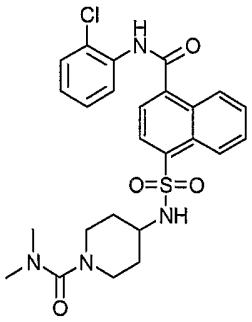
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and dimethylcarbamyl chloride for ethyl chloroformate. Wt.: 125 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.8.59 (m, 1H), 8.29 (m, 1H), 8.23 (d, 1H), 7.69 (m, 2H), 7.58 (d, 1H), 6.17 (d, 1H), 4.82 (d, 1H), 4.32 (m, 1H), 4.03 (m,

2H), 3.57 (m, 2H), 3.40 (m, 2H), 3.25 (m, 1H), 2.73 (s, 6H), 2.64 (m, 2H), 2.10 (m, 2H), 1.61 (m, 4H), 1.27 (m, 2H); LC/MS *m/z* 489 $(M + H)^+$.



4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2-chloro-phenyl)-amide (F-22)

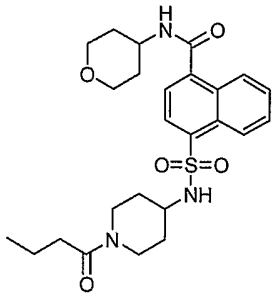
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2-chloro-phenyl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chlroformate. Wt.: 21 mg (27%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (m, 2H), 8.48 (d, 1H), 8.35 (d, 1H), 8.20 (s, 1H), 7.82 (d, 1H), 7.72 (m, 2H), 7.41 (m, 2H), 7.09 (m, 1H), 4.78 (d, 1H), 4.31 (m, 1H), 3.67 (m, 1H), 3.35 (m, 1H), 2.95 (m, 1H), 2.22 (m, 2H), 1.60 (4H), 1.27 (m, 2H), 0.92 (t, 3H); LC/MS *m/z* 515 $(M + H)^+$.



4-[4-(2-Chloro-phenylcarbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (F-23)

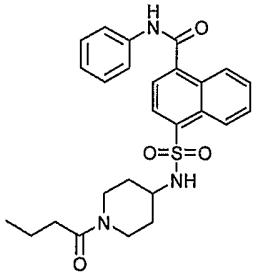
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (2-chloro-phenyl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and dimethylcarbamyl chloride for ethyl chloroformate. Wt.: 28

mg (36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, 1H), 8.60 (d, 1H), 8.47 (d, 1H), 8.35 (d, 1H), 8.20 (s, 1H), 7.82 (d, 1H), 7.72 (m, 2H), 7.43 (m, 2H), 7.17 (m, 1H), 4.83 (d, 1H), 3.46 (m, 2H), 3.31 (m, 1H), 2.71 (s, 6H), 2.70 (m, 2H), 1.67 (m, 2H), 1.35 (m, 2H); LC/MS *m/z* 516 $(M + H)^+$.



4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide (F-24)

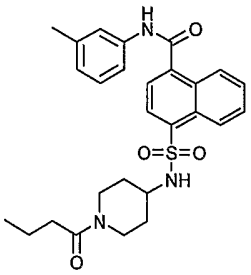
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chloroformate. Wt.: 30 mg (19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H), 8.26 (d, 1H), 8.13 (d, 1H), 7.67 (m, 2H), 7.52 (d, 1H), 6.68 (m, 1H), 5.28 (m, 1H), 4.32 (m, 1H), 4.05 (m, 3H), 3.15 (m, 1H), 2.46 (m, 1H), 2.10 (m, 4H), 1.65 (m, 4H), 1.49 (m, 2H), 1.18 (m, 1H), 9.95 (m, 1H), 0.88 (t, 3H); LC/MS *m/z* 488 $(M + H)^+$.



4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid phenylamide (F-25)

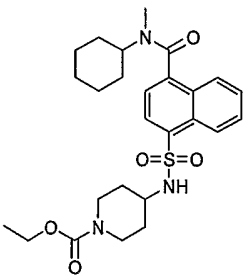
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid phenylamide

for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chloroformate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.67 (m, 1H), 8.36 (m, 2H), 8.25 (d, 1H), 8.08 (m, 2H), 7.87 (d, 1H), 7.78 (d, 1H), 7.70 (m, 1H), 7.63 (m, 1H), 5.50 (d, 1H), 3.95 (m, 1H), 3.55 (m, 1H), 3.26 (m, 1H), 2.88 (m, 1H), 2.48 (m, 1H), 2.13 (m, 2H), 1.66 (m, 2H), 1.48 (m, 3H), 1.19 (m, 1H), 0.88 (t, 3H); LC/MS *m/z* 480 $(M + H)^+$.



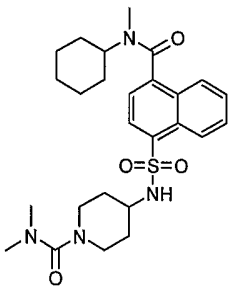
4-(1-Butyryl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid *m*-tolylamide (F-26)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid *m*-tolylamide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and butyryl chloride for ethyl chloroformate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 1H), 8.35 (d, 1H), 8.27 (m, 2H), 7.70 (m, 2H), 7.60 (s, 1H), 7.52 (m, 1H), 7.28 (m, 2H), 7.02 (d, 1H), 5.10 (d, 1H), 4.07 (m, 1H), 3.58 (m, 1H), 3.23 (m, 1H), 2.90 (m, 1H), 2.50 (m, 1H), 2.14 (m, 2H), 1.57 (m, 4H), 1.21 (m, 1H), 1.04 (m, 1H), 0.89 (t, 3H); LC/MS *m/z* 494 $(M + H)^+$.



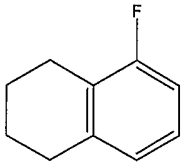
4-[4-(Cyclohexyl-methyl-carbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (F-27)

The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexyl-methyl-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, 1H), 8.29 (d, 1H), 7.88 (m, 1H), 7.65 (m, 2H), 7.42 (m, 1H), 4.83 (m, 1H), 4.72 (m, 1H), 4.05 (q, 2H), 3.88 (m, 2H), 3.25 (m, 1H), 3.05 (m, 1H), 2.80 (s, 3H), 2.74 (m, 1H), 1.90 (m, 4H), 1.54 (m, 8H), 1.20 (t, 3H), 0.85 (m, 2H); LC/MS *m/z* 502 $(M + H)^+$.



4-[4-(Cyclohexyl-methyl-carbamoyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid dimethylamide (F-28)

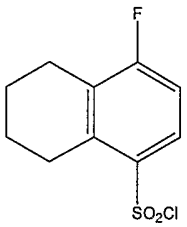
The title compound was prepared according to the general procedure in Scheme 11, substituting 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexyl-methyl-amide for 4-(piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid cyclohexylamide, and dimethylcarbamyl chloride for ethyl chloroformate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, 1H), 8.28 (d, 1H), 7.87 (m, 1H), 7.62 (m, 2H), 7.21 (m, 1H), 5.35 (m, 1H), 5.27 (d, 1H), 4.74 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 3.27 (m, 1H), 3.05 (m, 1H), 2.72 (s, 6H), 2.60 (s, 3H), 1.83 (m, 4H), 1.50 (m, 8H), 0.82 (m, 2H); LC/MS *m/z* 501 $(M + H)^+$.



Preparation of 5-fluoro-1,2,3,4-tetrahydro-naphthalene

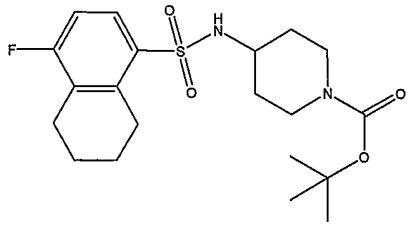
A modified procedure of Mirsadehgi et al. was used (*J. Org. Chem.* **1989**, 54, 3091). Boron trifluoride etherate (30.0 g, 26.8 mL, 0.21 mol) was dissolved and stirred in dimethoxyethane (50 mL) and cooled to 0°C. A solution of tetrahydro-1-

naphthylamine (25 g, 0.17 mol) in dimethoxyethane (75 mL) was added dropwise and the solution was allowed to warm slowly to room temperature over the period of 1 hour. The reaction was cooled to 0°C and a solution of *t*-butyl nitrite (18.0 g, 20.7 mL, 0.17 mol) in dimethoxyethane (75 mL) was added dropwise. The reaction was stirred for 2 hours at 0°C upon which a large quantity of material crystallized. The solvent was removed *in vacuo* and chlorobenzene (200 mL) was charged to the reaction flask. The flask was stirred vigorously and heated to 135°C (**Caution: N_2 evolution**) for 1 hour until gas evolution ceased. The flask was cooled to room temperature and the solvent removed *in vacuo*. Kughelrohr distillation of the residue (1 mm Hg) afforded a yellow liquid. Wt: 14.4 g (56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (dd, 1H), 6.83 (m, 2H), 2.75 (m, 4H), 1.80 (m, 4H)



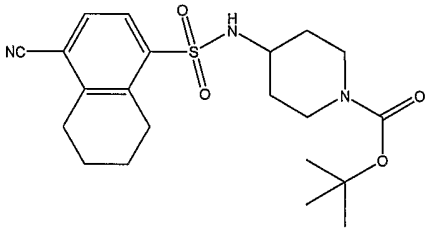
Preparation of 4-fluoro-5,6,7,8-tetrahydro-naphthalene-1-sulfonyl chloride

The compound was prepared according to Scheme 10 in a similar manner to the method for preparing 4-fluoro-naphthalene-1-sulfonyl chloride. Chlorosulfonic acid (2.65 g, 1.5 mL, 22.7 mmol) was stirred in a round-bottom flask cooled by a water bath at room temperature. 5-Fluoro-1,2,3,4-tetrahydro-naphthalene (0.62 g, 4.13 mmol) was added dropwise and the dark mixture was stirred for 30 minutes until gas evolution ceased. The reaction mixture was poured carefully over a mixture of ice (75 g) and dichloromethane (100 mL) and charged to a separatory funnel. The organic layer was separated, washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a tan solid. Wt.: 860 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H), 7.02 (t, 1H), 3.27 (m, 2H), 2.80 (m, 2H), 1.86 (m, 4H).



4-(4-Fluoro-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

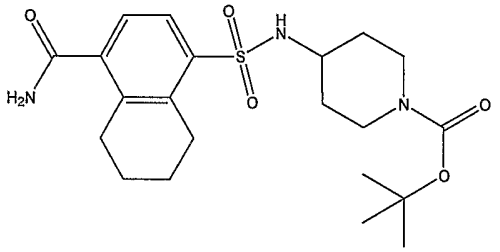
4-Fluoro-5,6,7,8-tetrahydro-naphthalene-1-sulfonyl chloride (860 mg, 3.46 mmol) was dissolved in THF (10 mL). Triethylamine (350 mg, 0.49 mg, 3.46 mmol) was added, followed by 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester (694 mg, 3.46 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was diluted with dichloromethane (50 mL) and charged to a separatory funnel. The organic layer was washed with water and brine, then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a yellow foam. Wt.: 1.35 g (95%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, 1H), 6.95 (t, 1H), 4.47 (d, 1H), 3.93 (m, 2H), 3.27 (m, 1H), 3.11 (m, 2H), 2.76 (m, 4H), 1.81 (m, 6H), 1.44 (s, 9H), 1.32 (m, 2H); LC/MS *m/z* 411 $(M - H)^-$.



Preparation of 4-(4-Cyano-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

4-(4-Fluoro-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (970 mg, 2.35 mmol) was dissolved in DMSO (10 mL) and sodium cyanide (577 mg, 11.77 mmol) was added. The mixture was heated overnight at 100 °C. An additional 5 equivalents of sodium cyanide (577 mg, 11.77 mmol) were added and the reaction was stirred overnight at 100 °C. The reaction was cooled to room temperature and diluted with dichloromethane (100 mL). The mixture was charged to a separatory funnel and extracted three times with water, brine and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a

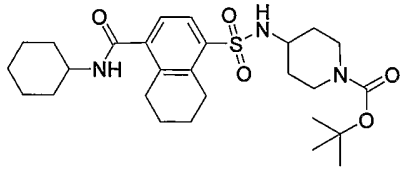
brown color foam that was triturated with EtOAc to afford a tan solid. Wt.: 550 mg (56%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1H), 7.48 (d, 1H), 4.52 (d, 1H), 3.93 (m, 2H), 3.30 (m, 1H), 3.07 (m, 4H), 2.73 (m, 2H), 1.80 (m, 6H), 1.37 (s, 9H), 1.30 (m, 2H); LC/MS *m/z* 418 (M - H)$^-$.



4-(4-Carbamoyl-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid tert-butyl ester (F-29) and 4-(4-carboxy-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester

4-(4-Cyano-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (545 mg, 1.30 mmol) was dissolved in a mixture of isopropanol (2 ml) and 2N KOH (4 mL). The reaction was stirred for 5 days at 80 °C. The isopropanol was removed *in vacuo* and the residue was diluted with H_2O (20 mL). The mixture was charged to a separatory funnel and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to a white solid that was triturated with dichloromethane to afford 4-(4-carbamoyl-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester **F-29** as a white solid. Wt.: 340 mg (60%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 7.81 (m, 2H), 7.72 (d, 1H), 7.52 (s, 1H), 7.23 (d, 1H), 3.72 (m, 2H), 3.09 (m, 3H), 2.81 (m, 2H), 2.71 (m, 2H), 1.70 (m, 4H), 1.55 (m, 2H), 1.36 (s, 9H), 1.25 (m, 2H); LC/MS *m/z* 436 (M - H)$^-$.)$^-$. The aqueous extract was acidified to pH 2 with 1N HCl and extracted twice with dichloromethane. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded 4-(4-carboxy-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid tert-butyl ester as a white solid. Wt.: 76 mg (13%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 7.72

(d, 1H), 7.33 (s, 1H), 7.23 (d, 1H), 3.72 (m, 2H), 3.09 (m, 3H), 2.81 (m, 2H), 2.71 (m, 2H), 1.70 (m, 4H), 1.55 (m, 2H), 1.36 (s, 9H), 1.25 (m, 2H); LC/MS *m/z* 437 (M - H)$^-$.

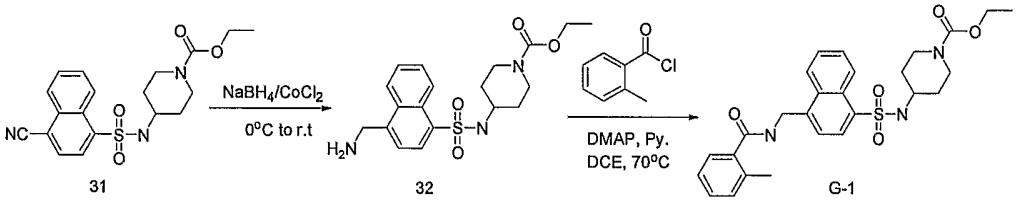


4-[4-(3-Dimethylamino-propylcarbamoyl)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid tert-butyl ester (F-30) and 4-(4-Cyclohexylcarbamoyl-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid tert-butyl ester (F-31)

4-(4-Carboxy-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid tert-butyl ester (76 mg, 0.17 mmol) was dissolved in dichloromethane (2 mL). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (32 mg, 0.17 mmol) was added followed by cyclohexylamine (21 mg, 24 ml, 0.21 mmol). The reaction was stirred overnight at room temperature. The reaction was diluted with dichloromethane (15 ml0 and charged to a separatory funnel. The organic layer was washed twice with water, brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a clear oil that was subjected to flash column chromatography (96:4 dichloromethane:methanol). Concentration of the more polar fractions afforded 4-[4-(3-dimethylamino-propylcarbamoyl)-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (**F-30**) as a yellow solid. Wt.: 40 mg, (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.98 (d, 1H), 7.31 (d, 1H), 5.02 (d, 1H), 3.96 (m, 3H), 3.37 (m, 2H), 3.20 (m, 2H), 2.83 (m, 4H), 2.70 (s, 6H), 2.13 (m, 2H), 1.97 (m, 2H), 1.83 (m, 4H), 1.42 (s, 9H), 1.32 (m, 4H); LC/MS *m/z* 523 (M + H)$^+$. Concentration of the less polar fractions afforded 4-(4-cyclohexylcarbamoyl-5,6,7,8-tetrahydro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (**F-31**) as a clear oil. Wt.: 28 mg (32%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1H), 7.20 (d, 1H), 5.73 (d, 1H), 4.38 (d, 1H), 3.91 (m, 3H), 3.22 (m, 1H), 3.12 (m, 2H), 2.89 (m,

2H), 2.73 (m, 2H), 2.03 (m, 2H), 1.78 (m, 8H), 1.74 (m, 2H), 1.43 (s, 9H), 1.27 (m, 6H); LC/MS *m/z* 518 $(M - H)^-$.

Scheme 12

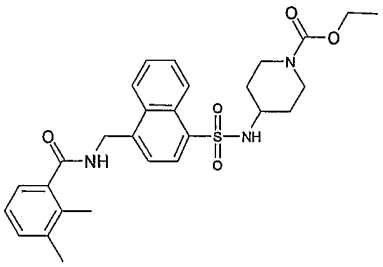


4-{4-[(2-Methyl-benzoylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-1)

4-(4-cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**31**) was prepared according to the procedure in Scheme 11, substituting for 4-(4-fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester for 4-(4-fluoro-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. To a 0 °C solution of 4-(4-cyano-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**31**) (615 mg, 1.59 mmol) in EtOH (10 mL) was added cobalt chloride (207 mg, 1.59 mmol). After stirring at 0 °C for 5 min under argon, sodium borohydride (181 mg, 4.77 mmol) was added into the reaction mixture. The resultant solution was stirred at 0°C for 30 minutes, and then warmed up to room temperature. After stirring for another 30 min., the resultant mixture was quenched with water. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product. The crude material was purified by Flash column chromatography (CH_2Cl_2: MeOH) to provide 268 mg (43.0% yield) of 4-(4-aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**32**). LCMS showed *m/z*: 392 $(M + H)^+$.

To a solution of 4-(4-aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**32**) (60 mg, 0.153 mmol) in DCE (5 mL), was added pyridine (62 ul, 0.765 mmol), 2-methyl-benzoyl chloride (22ul, 0.168 mmol) and dimethyl-pyridin-4-yl-amine (4 mg, 0.031 mmol). After stirring at 70 °C overnight,

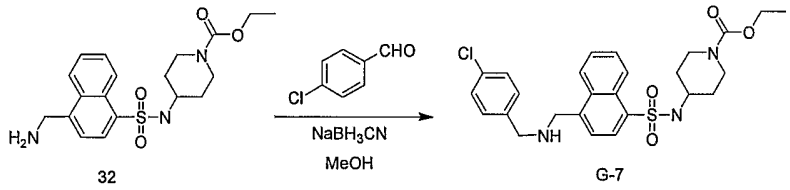
the resultant solution was concentrated *in vacuo* to give the crude product. Purification using reverse phase HPLC provided the title compound (**G-1**). LCMS showed *m/z*: 510 $(M + H)^+$.



4-{4-[(2,3-Dimethyl-benzoylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-2)

The title compound was made following general procedure in scheme 10, substituting 2,3-dimethyl-benzoyl chloride for 2-methyl-benzoyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (m, 1H), 8.18 (t, 2H), 7.65 (m, 2H), 7.52 (d, 1H), 7.32 (t, 2H), 7.04 (m, 1H), 6.80 (m, 1H), 5.10 (s, 2H), 4.00 (q, 2H), 3.80 (d, 2H), 3.20 (m, 1H), 2.70 (t, 2H), 2.26 (s, 3H), 2.23 (s, 3H), 1.55 (m, 2H), 1.20 (m, 2H), 1.14 (t, 3H); LC/MS *m/z* 524 $(M + H)^+$

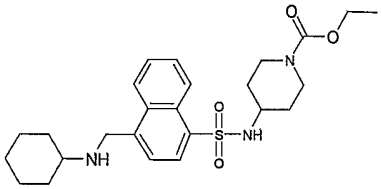
Scheme 13



4-{4-[(4-Chloro-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-7)

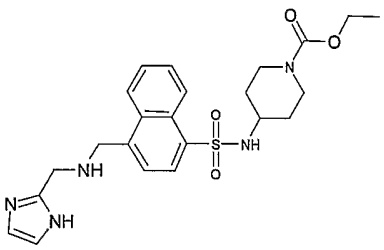
4-(4-Aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**32**) was prepared according to the procedure in Scheme 12. To a 25 °C solution of 4-(4-aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**32**) (62 mg, 0.159 mmol) in MeOH (4 mL) was added 4-chloro-benzaldehyde (45 mg, 0.318 mmol) and sodium cyanoborohydride (50 mg, 0.795 mmol). After stirring for 2h at 25 °C, the solution was concentrated *in vacuo*

to give a solid. The resultant solid was purified by reverse phase HPLC providing 4-{4-[(4-chloro-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester formate salt (**G-7**). ^{1}H NMR (300 MHz, MeOD) δ 8.76 (m, 1H), 8.38 (s, br, 1H), 8.24 (d, 1H), 8.18 (m, 1H), 7.51 (m, 3H), 7.44 (m, 4H), 4.52 (s, 2H), 4.12 (s, 2H), 4.04 (q, 2H), 3.60 (d, 2H), 3.40 (m, 1H), 2.72 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 516 $(M + H)^+$.



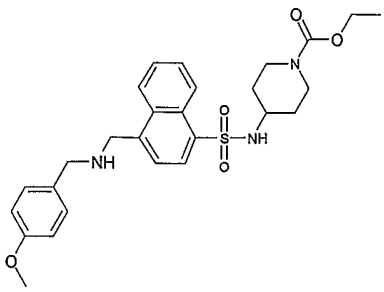
4-(4-Cyclohexylaminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-8)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting cyclohexanone for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1H), 8.25 (s, br, 1H), 8.17 (s, 1H), 8.04 (t, 2H), 7.70 (d, 1H), 7.57 (m, 2H), 6.15 (d, 1H), 4.48 (s, 2H), 4.04 (q, 2H), 3.80 (d, 2H), 3.25 (s, br, 1H), 3.00 (t, 1H), 2.70 (s, br, 1H), 2.60 (s, 1H), 2.10 (d, 2H), 1.80 (d, 2H), 1.50 (m, 5H), 1.20 (m, 7H); LC/MS *m/z* 475 $(M + H)^+$



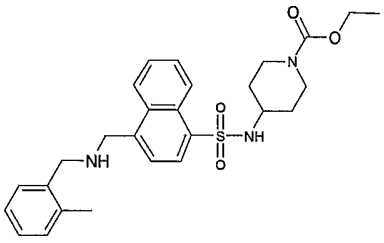
4-(4-{[(1H-Imidazol-2-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-9)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 1*H*-imidazole-2-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (m, 1H), 8.40 (s, br, 1H), 8.22 (m, 2H), 7.67 (m, 3H), 7.09 (s, 2H), 4.32 (s, 2H), 4.04 (m, 4H), 3.80 (d, 2H), 3.20 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 472 $(M + H)^+$



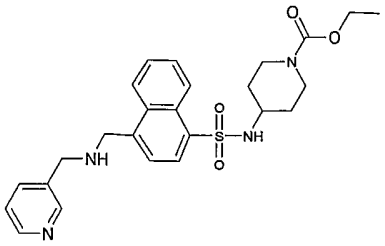
4-{4-[(4-Methoxy-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-10)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 4-methoxy-benzaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.73 (d, 1H), 8.22 (d, 1H), 8.14 (d, 1H), 7.66 (m, 3H), 7.33 (d, 2H), 6.92 (d, 2H), 4.30 (s, 2H), 4.12 (s, 2H), 4.04 (q, 2H), 3.90 (s, 2H), 3.80 (m, 5H), 3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 512 $(M+H)^+$



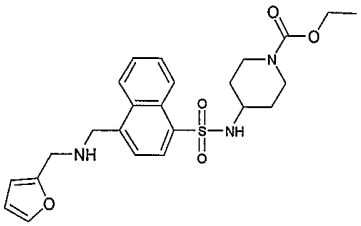
4-{4-[(2-Methyl-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-11)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 2-methyl-benzaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.76 (d, 1H), 8.22 (m, 2H), 7.70 (m, 3H), 7.38 (m, 1H), 7.21 (m, 3H), 4.51 (s, 2H), 4.05 (m, 4H), 3.80 (d, 2H), 3.20 (m, 1H), 2.75 (m, 2H), 2.30 (s, 3H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 496 $(M+H)^+$



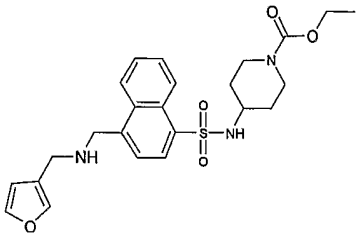
4-(4-{[(Pyridin-3-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-12)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting pyridine-3-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (dd, 1H), 8.57 (s, 1H), 8.44 (d, 1H), 8.22 (m, 2H), 7.90 (d, 1H), 7.64 (m, 3H), 7.42 (dd, 1H), 4.30 (s, 2H), 4.05 (q, 2H), 3.95 (s, 2H), 3.68 (d, 2H), 3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 483 $(M + H)^+$



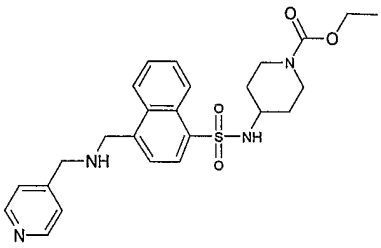
4-(4-{[(Furan-2-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-13)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting furan-2-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (dd, 1H), 8.18 (m, 2H), 7.65 (m, 3H), 7.49 (m, 1H), 6.39 (m, 1H), 6.34 (m, 1H), 4.28 (s, 2H), 4.05 (q, 2H), 3.92 (s, 2H), 3.80 (d, 2H), 3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 472 $(M + H)^+$



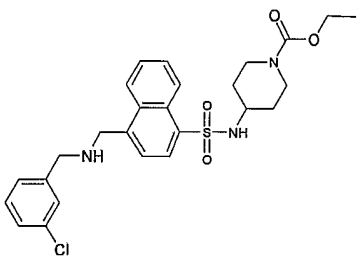
4-(4-{[(Furan-3-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-14)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting furan-3-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.76 (m, 1H), 8.22 (m, 2H), 7.64 (m, 5H), 6.56 (m, 1H), 4.42 (s, 2H), 4.05 (q, 2H), 3.95 (s, 2H), 3.80 (d, 2H), 3.20 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 472 $(M + H)^+$



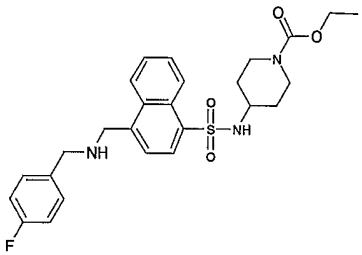
4-(4-{[(Pyridin-4-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-15)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting pyridine-4-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.70 (m, 1H), 8.54 (s, 1H), 8.24 (m, 4H), 7.68 (m, 2H), 7.45 (m, 1H), 7.14 (m, 1H), 4.70 (m, 2H), 4.55 (m, 2H), 4.05 (q, 2H), 3.80 (d, 2H), 3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.18 (t, 3H); LC/MS *m/z* 483 $(M + H)^+$



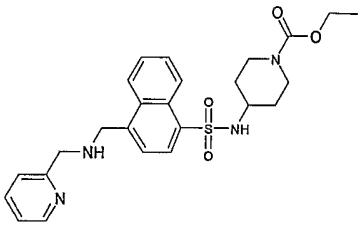
4-{4-[(3-Chloro-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-16)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 3-chloro-benzaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.20 (m, 2H), 7.66 (m, 3H), 7.45 (s, 1H), 7.30 (m, 3H), 4.25 (s, 2H), 4.05 (q, 2H), 3.90 (s, 2H), 3.78 (d, 2H), 3.20 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 516 $(M + H)^+$



4-{4-[(4-Fluoro-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-17)

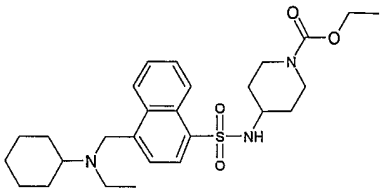
The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 4-fluoro-benzaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.19 (m, 2H), 7.66 (m, 3H), 7.40 (m, 2H), 7.06 (m, 2H), 4.25 (s, 2H), 4.05 (q, 2H), 3.85 (s, 2H), 3.78 (d, 2H), 3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 500 $(M + H)^+$



4-(4-{[(Pyridin-2-ylmethyl)-amino]-methyl}-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (G-18)

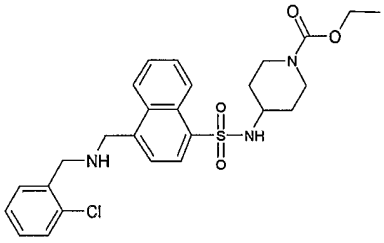
The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting pyridine-2-carbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.52 (m, 1H), 8.24 (m, 2H), 7.80 (t, 1H), 7.67 (m, 3H), 7.52 (d, 1H), 7.30 (t, 1H), 4.30 (s, 2H), 4.00 (m, 4H), 3.80 (d, 2H),

3.18 (m, 1H), 2.75 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 483 $(M + H)^+$



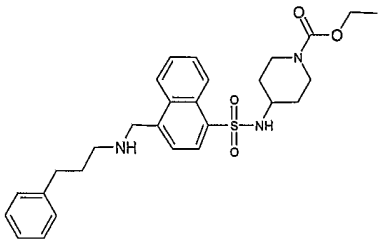
4-{4-[(Cyclohexyl-ethyl-amino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-20)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting acetaldehyde for 4-chloro-benzaldehyde, and substituting 4-(4-cyclohexylaminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester (**G-8**) for 4-(4-aminomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester. ^{1}H NMR (300 MHz, MeOD) δ 8.79 (m, 1H), 8.36 (m, 2H), 8.27 (dd, 1H), 7.77 (m, 3H), 4.62 (s, 2H), 4.05 (q, 2H), 3.80 (d, 2H), 3.25 (m, 1H), 3.05 (m, 3H), 2.75 (m, 2H), 2.10 (d, 2H), 1.80 (d, 2H), 1.65 (m, 3H), 1.48 (m, 2H), 1.22 (m, 11H); LC/MS *m/z* 502 $(M + H)^+$



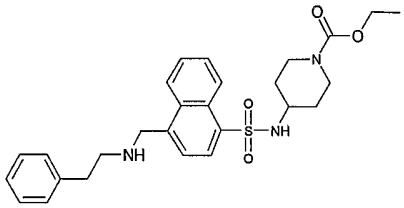
4-{4-[(2-Chloro-benzylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-21)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 2-chloro-benzaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.72 (d, 1H), 8.15 (d, 2H), 7.66 (m, 3H), 7.52 (m, 1H), 7.38 (m, 1H), 7.28 (m, 2H), 4.30 (s, 2H), 4.00 (m, 4H), 3.78 (d, 2H), 3.18 (m, 1H), 2.72 (m, 2H), 1.50 (m, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 516 $(M + H)^+$



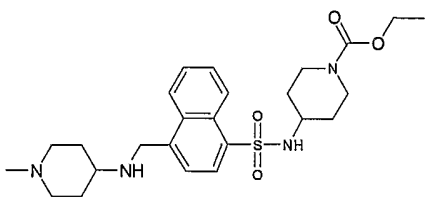
4-{4-[(3-Phenyl-propylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-23)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 3-phenyl-propionaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (m, 1H), 8.25 (m, 1H), 8.20 (d, 1H), 7.70 (m, 2H), 7.59 (m, 1H), 7.19 (m, 5H), 4.33 (s, 2H), 4.05 (q, 2H), 3.78 (d, 2H), 3.18 (m, 1H), 2.73 (m, 6H), 1.90 (m, 2H), 1.48 (m, 2H), 1.23 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 510 $(M + H)^+$



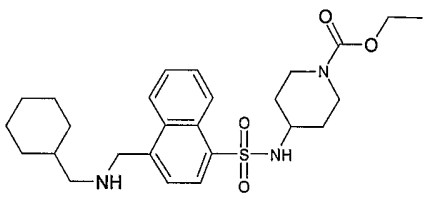
4-[4-(Phenethylamino-methyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (G-24)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting phenyl-acetaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (m, 1H), 8.19 (m, 2H), 7.67 (m, 2H), 7.59 (m, 1H), 7.22 (m, 5H), 4.35 (s, 2H), 4.05 (q, 2H), 3.78 (d, 2H), 3.18 (m, 1H), 2.92 (m, 4H), 2.62 (m, 2H), 1.90 (m, 2H), 1.48 (m, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 496 $(M + H)^+$



4-{4-[(1-Methyl-piperidin-4-ylamino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-25)

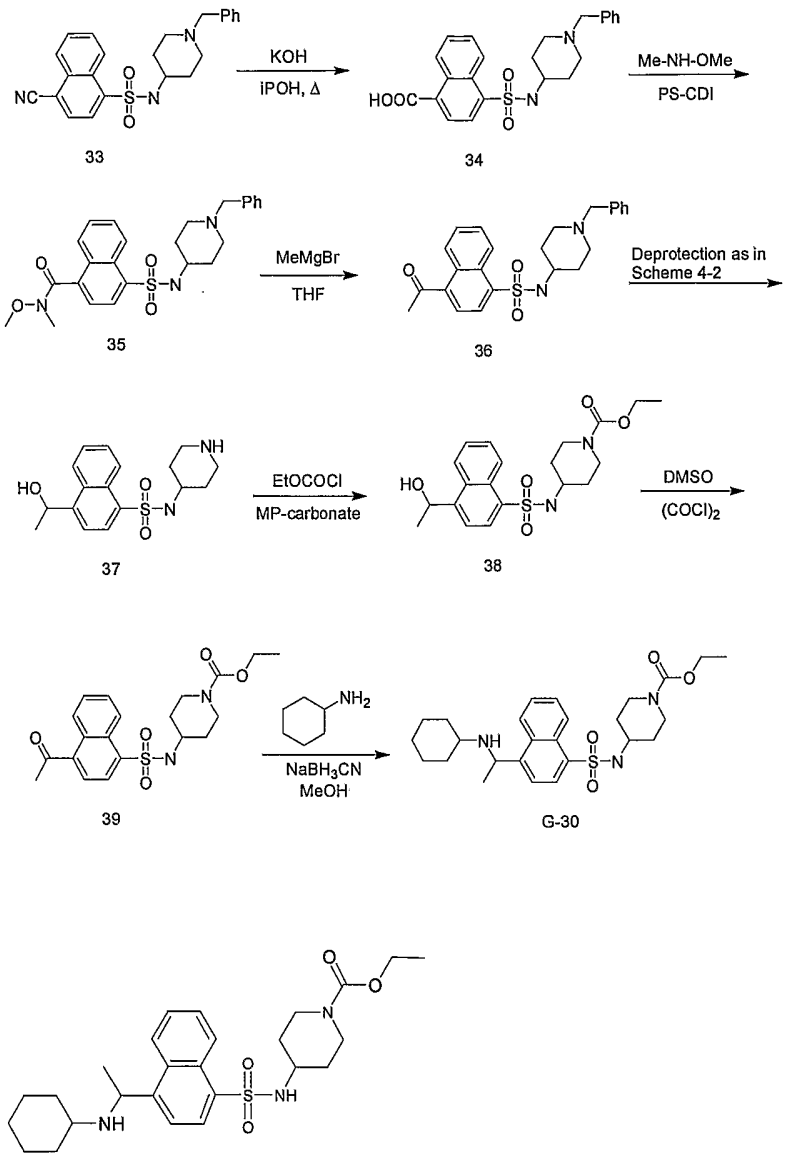
The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting 1-methyl-piperidin-4-one for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (m, 1H), 8.45 (s, 1H), 8.28 (m, 1H), 8.22 (d, 1H), 7.70 (m, 3H), 4.40 (s, 2H), 4.05 (q, 2H), 3.80 (d, 2H), 3.45 (d, 2H), 3.20 (m, 1H), 3.00 (m, 3H), 2.78 (s, 3H), 2.72 (m, 2H), 2.25 (d, 2H), 1.80 (m, 2H), 1.50 (d, 2H), 1.25 (m, 2H), 1.17 (t, 3H); LC/MS *m/z* 487 $(M + H)^+$



4-{4-[(Cyclohexylmethyl-amino)-methyl]-naphthalene-1-sulfonylamino}-piperidine-1-carboxylic acid ethyl ester (G-27)

The title compound was prepared as its formate salt following the general procedure in Scheme 13, substituting cyclohexanecarbaldehyde for 4-chloro-benzaldehyde. ^{1}H NMR (300 MHz, MeOD) δ 8.76 (m, 1H), 8.52 (s, 1H), 8.26 (m, 2H), 7.72 (m, 3H), 4.49 (s, 2H), 4.05 (q, 2H), 3.80 (d, 2H), 3.20 (m, 1H), 2.75 (m, 4H), 1.75 (m, 6H), 1.50 (d, 2H), 1.25 (m, 5H), 1.18 (t, 3H), 1.00 (m, 2H); LC/MS *m/z* 488 $(M + H)^+$

Scheme 14



33 34 35 36 37 38 39 G-30

4-[4-(1-Cyclohexylamino-ethyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (G-30)

4-Cyano-naphthalene-1-sulfonic acid (1-benzyl-piperidin-4-yl)-amide (**33**) was prepared according to the general procedure in Scheme 11, substituting 1-benzyl-piperidin-4-ylamine for 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. To a solution of 4-cyano-naphthalene-1-sulfonic acid (1-benzyl-piperidin-4-yl)-amide **33** (3.0 g, 7.43 mmol) in H_2O (70 mL) was added KOH (4.2 g, 75 mmol). After stirring at 100 °C overnight, the resultant mixture became a clear solution. The aqueous layer was washed with CH_2Cl_2 twice and acidified to pH 4 by adding hydrochloric

acid. After filtration, the resultant solid was dried to give 1.8 g of crude 4-(1-benzyl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid **34** in 57% yield. LCMS showed *m/z*: 425 $(M + H)^+$. This material was used without further purification.

To a solution of 4-(1-benzyl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid **34** (212 mg, 0.5 mmol) in DCE (5 mL), was added *O,N*-dimethyl-hydroxylamine hydrochloride (59 ul, 0.6 mmol), PS-carbodiimide (1.9g, 2.5 mmol), triethyl amine (140 uL, 1 mmol) and HOAt (102 mg, 0.75 mmol). After stirring at 50 °C overnight, the resultant solution was filtered and concentrated *in vacuo* to give the crude product 4-(1-benzyl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid methoxy-methyl-amide **35**. LCMS showed *m/z*: 468 $(M + H)^+$. This material was used without further purification.

To a 0 °C solution of 4-(1-benzyl-piperidin-4-ylsulfamoyl)-naphthalene-1-carboxylic acid methoxy-methyl-amide **35** (200 mg, 0.43 mmol) in THF (5 mL) was slowly added methylmagnesium bromide (5.71 mL, 17.1 mmol, 1M THF solution). After stirring at 25 °C for 4h, the resultant mixture was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product. The crude material was purified by Flash column chromatography (hexane/EtOAc) to provide 118 mg of 4-acetyl-naphthalene-1-sulfonic acid (1-benzyl-piperidin-4-yl)-amide **36** in 56% overall yield (for two steps).LCMS showed *m/z* : 423 $(M + H)^+$.

Following the general procedure in Scheme 4-2, deprotection of 4-acetyl-naphthalene-1-sulfonic acid (1-benzyl-piperidin-4-yl)-amide **36** occurred concomitant with reduction of the ketone group to afford 4-(1-hydroxy-ethyl)-naphthalene-1-sulfonic acid piperidin-4-ylamide acetic acid salt **37** as product. LCMS showed *m/z*: 334 $(M + H)^+$. This material was used without further purification.

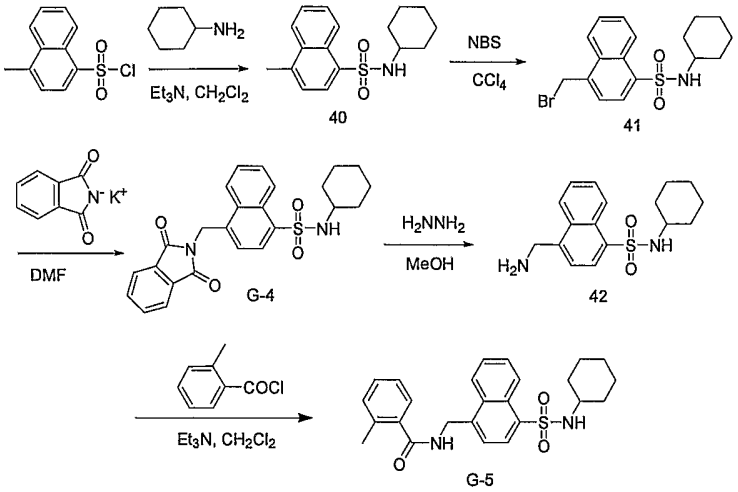
To a solution of 4-(1-hydroxy-ethyl)-naphthalene-1-sulfonic acid piperidin-4-ylamide acetic acid salt **37** (290 mg, 0.74 mmol) in MeOH (10 mL) was added MP-Carbonate (1.45 g, 3.69 mmol, 2.54 mmol/g). After shaking at 25 °C for 1h, the solution was filtered. To the resultant solution was added ethyl chloroformate (120 mg, 1.11 mmol). After stirred for another 2h at 25 °C, the solution was concentrated *in vacuo to* give a solid. The crude material was purified by Flash column chromatography (CH_2Cl_2: MeOH) to provide 4-[4-(1-hydroxy-ethyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester **38**. LCMS showed *m/z* : 407 $(M + H)^+$.

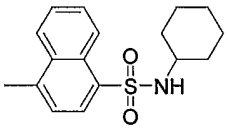
To a -78 °C solution of oxalyl dichloride (85 mg, 0.665 mmol) in CH_2Cl_2 (10 mL) was added DMSO (104 mg, 1.33 mmol). After stirred at -78 °C for 10 min, a solution of 4-[4-(1-hydroxy-ethyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester **38** (180 mg, 0.443 mmol) in CH_2Cl_2 was added into the mixture by dropwise. The resultant mixture was stirred at -78 °C for another 30 min, then was added triethyl amine (224 mg, 2.22 mmol). The reaction mixture was warmed up to room temperature and stirred for 2h. The resultant mixture was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give the crude product. The crude material was purified by Flash column chromatography (CH_2Cl_2: MeOH) to provide 45 mg of 4-(4-acetyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester **39** in 25% yield. LCMS showed *m/z* : 409 $(M + H)^+$.

To a 25 °C solution of 4-(4-acetyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid ethyl ester **39** (45 mg, 0.11 mmol) in MeOH (4 mL) was added cyclohexylamine (31 mg, 0.22 mmol) and sodium cyanoborohydride (34 mg, 0.69 mmol). After stirring for 2h at 25 °C, the solution was concentrated *in vacuo* to give a solid. The resultant solid was purified by reverse phase HPLC providing the title compound (**G-30**). ^1H NMR (300 MHz, MeOD) δ 8.84 (m, 1H), 8.42 (s, br, 1H), 8.35 (m, 2H), 7.82 (m, 3H), 5.55 (d, 1H), 4.02 (q, 2H), 3.80 (d, 2H), 3.22(m, 1H),

3.00 (m, 1H), 2.77(s, br, 2H), 2.19 (d, 1H), 2.05 (d, 1H), 1.78 (m, 4H), 1.50 (m, 5H), 1.24 (m, 9H); LC/MS *m/z* 488 $(M+H)^+$.

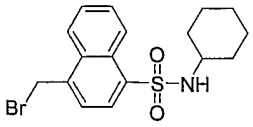
Scheme 15





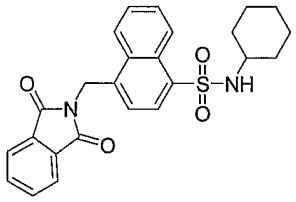
4-Methyl-naphthalene-1-sulfonic acid cyclohexylamide (40)

To a solution of 4-methyl-naphthalene -1-sulfonyl chloride (2.4 g, 10.0 mmol) in CH_2Cl_2 (30 mL), was added cyclohexylamine (1.4 g, 11.0 mmol) and triethylamine (2.8 mL, 20.0 mmol) and the resultant solution was stirred at room temperature overnight. The solution was quenched with water and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by Flash column chromatography (hexane/ethyl acetate, gradient elution) to give the title compound **40** (2.0 g) as a yellow solid. ^1H NMR (300 MHz, CDCl3) δ 8.63 (d, 1H), 8.18 (d, 1H), 8.10 (d, 1H), 7.64 (m, 2H), 7.38 (d, 1H), 3.08 (m, 1H), 2.76 (s, 3H), 1.52 (m, 5H), 1.09 (m, 5H); LC/MS *m/z* 304 $(M+H)^+$.



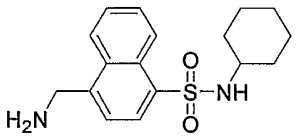
4-Bromomethyl-naphthalene-1-sulfonic acid cyclohexylamide (41)

To a solution of 4-methyl-naphthalene-1-sulfonic acid cyclohexylamide **40** (3.0 g, 10 mmol) in CCl_4 (100 mL) was added NBS (2.1 g, 12.0 mmol) and benzoyl peroxide (240 mg, 1.0 mmol), The reaction mixture was heated at reflux overnight. The solid was filtered and the filtrate was concentrated *in vacuo*. The title compound was a yellow residue (2.5 g, solidified on standing) which was used directly in the next step without further purification. ^{1}H NMR (300 MHz, CDCl3) δ 8.70 (m, 1H), 8.25 (m, 2H), 7.70 (m, 2H), 7.60 (d, 1H), 4.94 (s, 2H), 4.58 (m, 1H); 3.15 (m, 1H), 1.55 (m, 5H), 1.05 (m, 5H); LC/MS *m/z* 356 $(M + H)^+$ 382.



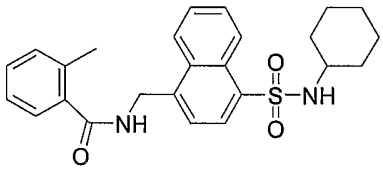
4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-naphthalene-1-sulfonic acid cyclohexylamide (G-4)

To a solution of 4-bromomethyl-naphthalene-1-sulfonic acid cyclohexylamide **41** (150 mg, 0.39 mmol) in DMF (5 mL) was added potassium phthalimide (109 mg, 0.58 mmol). The resultant solution was stirred at room temperature and then heated to 100^{0}C for 3 hr. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layers were dried and concentrated *in vacuo*. HPLC purification of the residue gave the title compound (**G-4**) (63 mg) as white foam. ^{1}H NMR (300 MHz, MeOD) δ 8.67 (d, 1H), 8.42 (d, 1H), 8.22 (d, 1H), 7.88 (m, 23H), 7.76 (m, 4H), 5.48 (s, 2H), 4.48 (d, 1H), 3.12 (d, 1H), 1.58 (m, 6H), 1.10 (m, 4H); LC/MS *m/z* 449 $(M + H)^+$.



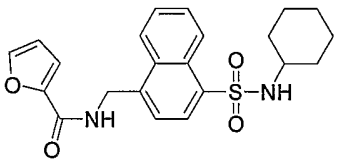
4-Aminomethyl-naphthalene-1-sulfonic acid cyclohexylamide (42)

To a solution of 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-naphthalene-1-sulfonic acid cyclohexylamide (**G-4**) (1.6 g, 3.57 mmol) in methanol (30 mL) was added hydrazine (2 mL). The resultant solution was stirred at room temperature overnight. A precipitate was formed and filtered. The solid was further washed with small amount of methanol. The filtrate was collected and solvent was removed *in vacuo*. Flash chromatography of the residue with Flash column ($MeOH/CH_2Cl_2$: 5-10%) gave the title compound (**42**) as white solid (0.7 g). ^1H NMR (300 MHz, DMSO) δ 8.68 (d, 1H), 8.24 (d, 1H), 8.13 (d, 1H), 7.60 (m, 3H), 5.00 (s, 1H), 4.39 (s, 2H), 3.10 (s, 1H), 2.03 (m, 2H), 1.59 (m, 4H), 1.08 (m, 4H); LC/MS *m/z* 319 $(M + H)^+$.



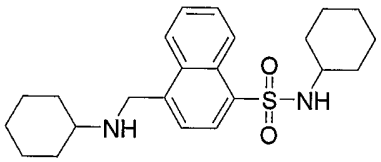
***N*-(4-Cyclohexylsulfamoyl-naphthalen-1-ylmethyl)-2-methyl-benzamide (G-5)**

To a solution of naphthalenyl methylamine **42** (100 mg, 0.32 mmol) in DMF (2 mL) was added o-tolylchloride (49 □L, 0.38 mmol) and triethylamine (88 □L, 0.63 mmol). The resultant solution was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified using HPLC to give the title compound (**G-5**) (30 mg) as pale yellow solid. ^1H NMR (300 MHz, MeOD) δ 8.78 (d, 1H), 8.34 (d, 1H), 8.20 (d, 1H), 7.72 (m, 2H), 7.63 (d, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 5.07 (s, 2H), 2.95 (s, 1H), 2.34 (s, 3H), 1.55 (m, 5H), 1.05 (m, 5H),; LC/MS *m/z* 437 $(M + H)^+$.



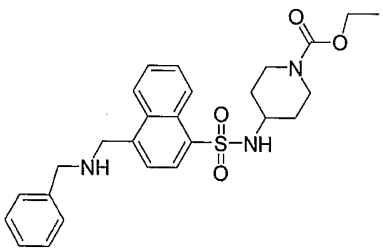
Furan-2-carboxylic acid (4-cyclohexylsulfamoyl-naphthalen-1-ylmethyl)-amide (G-6)

The title compound was made following general procedure in Scheme 15, substituting furan-2-carboxylic chloride for o-tolyl chloride. ^{1}H NMR (300 MHz, MeOD) δ 8.76 (d, 1H), 8.26 (d, 1H), 8.18 (d, 1H), 7.67 (d, 1H), 7.50 (d, 1H), 7.16 (d, 1H), 6.58 (m, 1H), 5.08 (s, 2H), 2.87 (s, 1H), 1.52 (m, 5H), 1.11 (m, 5H),; LC/MS *m/z* 413 $(M+H)^+$.



4-Cyclohexylaminomethyl-naphthalene-1-sulfonic acid cyclohexylamide (G-31)

The title compound was prepared according to the general procedure in Scheme 15, substituting cyclohexylamine and potassium carbonate for potassium phthalimide. HPLC purification of the residue gave the title compound (77 mg) as white foam. ^{1}H NMR (300 MHz, MeOD) δ 8.80 (m, 1H), 8.37 (s, 1H), 8.26 (d, 2H), 7.78 (m, 3H), 4.79 (s, 2H), 3.36 (m, 1H), 2.96 (m, 1H), 2.30 (m, 2H), 1.90 (m, 2H), 1.72 (m, 1H), 1.48 (m, 10H), 1.10 (m, 2H); LC/MS *m/z* 401$(M+H)^+$.



4-[4-(Benzylamino-methyl)-naphthalene-1-sulfonylamino]-piperidine-1-carboxylic acid ethyl ester (G-32)

The intermediate 4-(4-methyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester was prepared according to the general procedure in Scheme 15, substituting 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester for cyclohexylamine.

The intermediate 4-(4-bromomethyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester was prepared according to the general procedure in

Scheme 15 substituting 4-(4-methyl-naphthalene-1-sulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester for 4-methyl-naphthalene-1-sulfonic acid cyclohexylamide (**40**).

The title compound was prepared according to the general procedure in Scheme 15, substituting phenylamine and potassium carbonate for potassium phthalimide. HPLC purification gave the title compound (15 mg) as a white solid. ^{1}H NMR (300 MHz, MeOD) δ 8.73 (d, 1H), 8.29 (s, 1H), 8.22 (m, 1H), 8.04 (m, 1H), 7.68 (m, 3H), 7.20 (m, 2H), 4.59 (s, 2H), 4.23 (s, 2H), 3.97 (AB q, 2H), 3.67 (m, 2H), 3.16 (m, 1H),2.70 (m, 2H), 1.44 (m, 2H), 1.22 (m, 2H), 1.13 (t, 3H); LC/MS *m/z* 482 (M + H)$^+$.

The Sulfonamides Inhibit CCR8:

This whole cell binding screen evaluates the ability of compounds to inhibit biotinlyated human I309 binding to the cloned human CCR8 receptor stably expressed in L1.2 cells. Human CCR8 gene was amplified by PCR using PFU polymerase under standard conditions from human genomic DNA purchased from Stratagene. The PCR primers used were:

5' CCR8

5'tttggatccatggattatacacttgacctcagtgtg3' (SEQ ID NO: 1)

3' CCR8

5'tttgcggccgctcacaaaatgtagtctacgctggagg3' (SEQ ID NO: 2)

The 5' and 3' primers contained flanking enzyme sites (Bam Hi and Not 1,respectively), which were used to subclone the gene into pcDNA3.1. The vector containing the CCR8 gene was sequenced by manual sequencing and matched to the reported hCCR8 sequence. The CCR8 vector was then transfected into L1.2 cells (murine pre-B cells) by electroporation. Positive clones were selected by functional chemotaxis and binding to the ligand I309.

Compounds were screened using the FMAT™ 8100 HTS System (purchased from Applied Biosystems).

A suspension was prepared of L1.2/hCCR8 cells at 4.0 x 10^5 cells/mL in a binding buffer (Buffer consisting of Hanks Balanced Salt Solution (without phenol red), 10mM HEPES, 0.1% Fatty Acid Free BSA, 0.02% Sodium Azide). A solution of 0.375 nM of Human I-309 (Biotinylated at the C-terminus of the ligand after an additional lysine residue using the Applied Biosystems 433 peptide synthesizer) and 0.375 nM of mouse Cy-5 Mab-□-Biotin (Jackson ImmunoResearch Laboratories, Inc., Code Number 200-172-096) was prepared in binding buffer immediately prior to the assay.

Dilution series of 10 mM stock concentrations of the test compounds were prepared in DMSO and further diluted into binding buffer defined above) to three times the final assay concentration.

10 point concentration response curve is constructed for each compound, starting at 10 μM (final assay concentration in Binding Buffer). 25 μl of each concentration of test were transferred into the appropriate wells of a 384 plate. 25 μl of cold 100 nM I-309 (R and D Systems: Catalog Number 272-I/CF) were then transferred into empty wells to serve as a control for non-specific binding. 25μl of the 0.375nM Biotinylated Human I-309/ 0.375nM Cy5-□-Biotin solution were then transferred into each well of the same 384 well plate, followed by addition of 25 μl of the resuspended cell solution into each well. The components were mixed in wells by covering the plate with aluminum foil and rotating for 0.5 hours. The plates was allowed to incubate at room temperature for approximately 1-2 hours and then read on FMAT™ 8100 HTS System (PMT= 490/518 or 537/568, Set threshold = 1SD MAT). Average fluorescence reported for each concentration was normalized to percent inhibition based on negative (no inhibitor) and positive (100 nM excess unlabeled I309 (R and D Systems) controls.

Table 1: Ki of compounds to inhibit I-309 binding to CCR8 (uM)

No	*Ki, uM*	No	*Ki, uM*
A-1	<0.5	A-13	<30
A-2	<30	A-14	<0.5
A-3	<0.5	A-16	<30
A-7	<1	A-17	<0.5
A-9	<30	A-18	<0.5
A-10	<1	A-19	<0.5
A-11	<30	A-20	--
No	***Ki, uM***	**No**	***Ki, uM***
A-21	<1	A-31	<0.5
A-22	<30	A-32	<0.5
A-23	<0.5	A-34	<30
A-24	<0.5	A-35	<0.5
A-25	<0.5	A-37	<0.5
A-26	<0.5	A-38	<0.5
A-27	<1	A-40	<0.5
A-28	<0.5	A-41	--
A-29	<30	A-42	--
A-30	<30	A-43	<0.5
No	***Ki, uM***	**No**	***Ki, uM***
A-44	--	A-48	<30
A-45	<30	A-49	--
A-46	<30	A-50	--
A-47	<30		

No	*Ki, uM*	No	*Ki, uM*
B-2	<0.5	B-12	<0.5
B-3	<30	B-13	<1
B-4	<0.5	B-14	<0.5
B-5	<1	B-15	<0.5
B-6	<30	B-16	<1
B-7	<0.5	B-17	<30
B-8	<1	B-18	<30
B-9	<30	B-19	<0.5
B-10	<30	B-20	<1
B-11	<0.5	B-21	<30
No	***Ki, uM***	**No**	***Ki, uM***
B-22	<30	B-27	<0.5
B-23	<30	B-28	<0.5
B-24	<0.5	B-33	<30
B-26	<0.5		

No	*Ki, uM*	No	*Ki, uM*
C-1	<1	C-14	<0.5
C-2	<0.5	C-15	<0.5
C-4	<0.5	C-16	<0.5
C-5	<0.5	C-17	<0.5
C-7	<0.5	C-18	<0.5
C-9	<1	C-19	<0.5
C-10	<0.5	C-20	<0.5
C-11	<0.5	C-21	<0.5
C-12	<0.5	C-22	<0.5
C-13	<0.5	C-23	<30
No	***Ki, uM***	**No**	***Ki, uM***
C-24	<0.5	C-34	<0.5
C-25	<0.5	C-35	<0.5
C-26	<0.5	C-36	<0.5
C-27	<0.5	C-37	<0.5
C-28	<1	C-38	<0.5
C-29	<0.5	C-39	<0.5
C-30	<0.5	C-40	<0.5
C-31	<0.5	C-41	<0.5
C-32	<1	C-42	<0.5
C-33	<1	C-43	<0.5

No	*Ki, uM*	No	*Ki, uM*
C-44	<1	C-54	<0.5
C-45	<0.5	C-55	<0.5
C-46	<0.5	C-56	<0.5
C-47	<0.5	C-57	<0.5
C-48	<0.5	C-58	<0.5
C-49	<0.5	C-59	<0.5
C-50	<0.5	C-60	<0.5
C-51	<0.5	C-61	--
C-52	<0.5	C-62	--
C-53	<0.5	C-63	--
No	***Ki, uM***	**No**	***Ki, uM***
C-64	<0.5	C-74	<30
C-65	<0.5	C-75	<0.5
C-66	<0.5	C-76	<0.5
C-67	<0.5	C-77	<30
C-68	<30	C-78	<30
C-69	<1	C-79	<30
C-70	<1	C-80	<0.5
C-71	<1	C-81	<0.5
C-72	<1	C-82	<0.5
C-73	<1	C-83	<30

5

No	*Ki, uM*	No	*Ki, uM*
C-84	--	C-94	--
C-85	--	C-95	--
C-86	--	C-96	--
C-87	--	C-97	--
C-88	--	C-98	<1
C-89	--	C-99	<0.5
C-90	--	C-100	<0.5
C-91	--	C-101	<0.5
C-92	--	C-102	<0.5
C-93	--	C-103	<0.5
No	***Ki, uM***	**No**	***Ki, uM***
C-104	<0.5	C-114	<0.5
C-105	<0.5	C-115	<0.5
C-106	<1	C-116	--
C-107	<30	C-117	--
C-108	--	C-118	--
C-109	<1	C-119	--
C-110	<0.5	C-120	<0.5
C-111	<0.5	C-121	<0.5
C-112	<1	C-122	<0.5
C-113	<0.5	C-123	<0.5

5

No	*Ki, uM*	No	*Ki, uM*
C-124	<0.5	C-134	--
C-125	<0.5	C-135	--
C-126	<0.5	C-136	<0.5
C-127	--	C-137	<0.5
C-128	--	C-138	<1
C-129	--	C-139	<0.5
C-130	--	C-140	<0.5
C-131	--	C-141	<1
C-132	--	C-142	<0.5
C-133	--	C-143	<30
No	***Ki, uM***	**No**	***Ki, uM***
C-144	<30		
C-145	<1		
C-146	--		
C-147	<0.5		
C-148	<30		

No	*Ki, uM*	No	*Ki, uM*
D-1	<30	D-11	<30
D-2	<30	D-12	<30
D-3	<0.5	D-13	<30
D-4	<0.5	D-14	<0.5
D-5	<0.5	D-15	<0.5
D-6	<0.5	D-16	<0.5
D-7	<0.5	D-17	<30
D-8	<0.5	D-18	<0.5
D-9	<0.5	D-19	<0.5
D-10	<0.5	D-20	<0.5
No	***Ki, uM***	**No**	***Ki, uM***
D-21	<30	D-23	<30
D-22	<30	D-24	<30

No	*Ki, uM*	No	*Ki, uM*
E-1	<0.5	E-11	<0.5
E-2	<0.5	E-12	<0.5
E-3	<0.5	E-13	<1
E-4	<1	E-14	<1
E-5	<0.5	E-15	<0.5
E-6	<0.5	E-16	<0.5
E-7	<30	E-17	<0.5
E-8	<0.5	E-18	<0.5
E-9	<0.5	E-19	<0.5
E-10	<0.5	E-20	<0.5

No	*Ki, uM*	No	*Ki, uM*
E-21	<0.5	E-31	<0.5
E-22	<0.5	E-32	<0.5
E-23	<0.5	E-33	<0.5
E-24	<1	E-34	--
E-25	<30	E-35	--
E-26	<1	E-36	--
E-27	<0.5		
E-28	<0.5		
E-29	<0.5		
E-30	<0.5		

No	*Ki, uM*	No	*Ki, uM*
F-1	<1	F-11	<0.5
F-2	<30	F-12	<0.5
F-3	<0.5	F-13	<0.5
F-4	<0.5	F-14	<1
F-5	<30	F-15	<30
F-6	<0.5	F-16	<30
F-7	<0.5	F-17	<30
F-8	<0.5	F-18	<30
F-9	<0.5	F-19	<0.5
F-10	<0.5	F-20	<0.5
No	***Ki, uM***	**No**	***Ki, uM***
F-21	<0.5	F-27	<0.5
F-22	<0.5	F-28	<0.5
F-23	<0.5	F-29	--
F-24	<1	F-30	--
F-25	<0.5	F-31	--
F-26	<0.5		

5

No	*Ki, uM*	No	*Ki, uM*
G-1	<0.5	G-12	<0.5
G-2	<0.5	G-13	<0.5
G-4	<30	G-14	<0.5
G-5	<1	G-15	<1
G-6	<1	G-16	--
G-7	<0.5	G-17	--
G-8	<0.5	G-18	--
G-11	<0.5	G-20	<0.5
G-9	<30	G-21	<0.5
G-10	<0.5		
No	***Ki, uM***	**No**	***Ki, uM***
G-24	<0.5	G-30	--
G-25	<30	G-31	<0.5
G-27	<0.5	G-32	<0.5

5

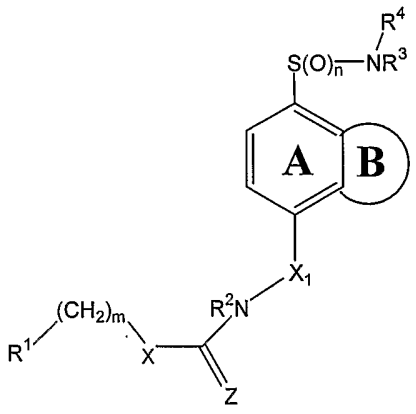
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is a covalent bond, C=O or CR^aR^b;

X is a covalent bond, O, or NR^5;

C=Z is C=O, CH_2, C=NH, C=S or absent, provided that when X_1 is a covalent bond then C=Z is not CH_2, provided that when C=Z is absent then X is a covalent bond, and provided that when X is NR^5 and C=Z is C=O then R^4 is not an aliphatic or substituted aliphatic group;

R^a and R^b are independently H or a C1-C3 alkyl;

R^1 is: i) a substituted or unsubstituted aromatic group; ii) a substituted or unsubstituted non-aromatic ring; or iii) when X is NR^5, then NR^5-$(CH_2)_mR^1$, taken together, is optionally a substituted or unsubstituted non-aromatic heterocyclic group;

R^2 is –H or a C1-C3 alkyl group;

R^3 is –H; and R^4 is: i) a substituted or unsubstituted aliphatic group; ii) a substituted or unsubstituted aromatic group; iii) a substituted or unsubstituted non-aromatic ring or a substituted or unsubstituted non-aromatic bridged bicyclic group; or iv) R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic

heterocyclic group;

R^5 is –H, or a C1-C3 alkyl group;

Ring **B** is phenyl group or five or six membered carbocyclic non-aromatic ring fused to Ring A;

Rings **A** and **B** are optionally substituted with alkyl, halolkyl, alkoxy, haloalkoxy, hydroxy, halogen, cyano or nitro;

m is 0, 1, 2 or 3;

n is 1 or 2;

each substitutable carbon atom of the aromatic group represented by R^1 is optionally substituted with a group represented by R^{10}, wherein R^{10} is halogen, -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH_2(Ph), substituted -CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R^o$, -$NR'C(O)R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$, -CO_2R^o, -$C(O)R^o$, -$C(O)N(R^o)_2$, -$OC(O)R^o$, -$OC(O)N(R^o)_2$, -$S(O)_2R^o$, -$SO_2N(R')_2$, -$S(O)R^o$, -$NR'SO_2N(R')_2$, -$NR'SO_2R^o$, -$C(=S)N(R')_2$, -$(CH_2)_yN(R')_2$, -$C(=NH)$-$N(R')_2$, haloalkyl, -V-R^o, -V-OH, -V-OR^o, -V-SH, -V-SR^o, -V-NO_2, -V-CN, -V-$N(R')_2$, -V-$NR'CO_2R^o$, -V-$NR'C(O)R^o$, -V-$NR'NR'C(O)R^o$, -V-$N(R')C(O)N(R')_2$, -V-$NR'NR'C(O)N(R')_2$, -V-$NR'NR'CO_2R^o$, -V-$C(O)C(O)R^o$, -V-$C(O)CH_2C(O)R^o$, -V-CO_2R^o, -V-$C(O)R^o$, -V-$C(O)N(R^o)_2$, -V-$OC(O)R^o$, -V-$OC(O)N(R^o)_2$, -V-$S(O)_2R^o$, -V-$SO_2N(R')_2$, -V-$S(O)R^o$, -V-$NR'SO_2N(R')_2$, -V-$NR'SO_2R^o$, -V-$C(=S)N(R')_2$, -V-$(CH_2)_yN(R')_2$, or -V-$C(=NH)$-$N(R')_2$, and each group represented by R^{10} is independently selected;

each substitutable carbon atom of the aliphatic group represented by R^4 is optionally substituted with a group represented by R^{11}, wherein R^{11} is halogen, -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH_2(Ph), substituted -CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R^o$, -$NR'C(O)R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$,

-C(O)R°, -C(O)N(R°)$_2$, -OC(O)R°, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO$_2$N(R')$_2$, -S(O)R°, -NR'SO$_2$N(R')$_2$, -NR'SO$_2$R°, -C(=S)N(R')$_2$, -(CH$_2$)$_y$N(R')$_2$, -C(=NH)-N(R')$_2$, haloalkyl, -V-R°, -V-OH, -V-OR°, -V-SH, -V-SR°, -V-NO$_2$, -V-CN, -V-N(R')$_2$, -V-NR'CO$_2$R°, -V-NR'C(O)R°, -V-NR'NR'C(O)R°, -V-N(R')C(O)N(R')$_2$, -V-NR'NR'C(O)N(R')$_2$, -V-NR'NR'CO$_2$R°, -V-C(O)C(O)R°, -V-C(O)CH$_2$C(O)R°, -V-C(O)R°, -V-C(O)N(R°)$_2$, -V-OC(O)R°, -V-OC(O)N(R°)$_2$, -V-S(O)$_2$R°, -V-SO$_2$N(R')$_2$, -V-S(O)R°, -V-NR'SO$_2$N(R')$_2$, -V-NR'SO$_2$R°, -V-C(=S)N(R')$_2$, -V-(CH$_2$)$_y$N(R')$_2$, -V-C(=NH)-N(R')$_2$, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$ (alkyl), or =NR*, and each group represented by R^{11} is independently selected;

each substitutable carbon atom of the aromatic group represented by R^4 is optionally substituted with a group represented by R^{12}, wherein R^{12} is halogen, -R°, -OH, -OR°, -O(haloalkyl), -SH, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH$_2$(Ph), substituted -CH$_2$(Ph), -CH$_2$CH$_2$(Ph), substituted -CH$_2$CH$_2$(Ph), -CN, -NR'CO$_2$R°, -NR'NR'C(O)R°, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO$_2$R°, -C(O)C(O)R°, -C(O)CH$_2$C(O)R°, -CO$_2$R°, -C(O)R°, -OC(O)R°, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO$_2$N(R')$_2$, -S(O)R°, -NR'SO$_2$N(R')$_2$, -NR'SO$_2$R°, -C(=S)N(R')$_2$, -(CH$_2$)$_y$N(R')$_2$, -C(=NH)-N(R')$_2$, haloalkyl, -V-R°, -V-OH, -V-OR°, -V-SH, -V-SR°, -V-CN, -V-NR'CO$_2$R°, -V-NR'NR'C(O)R°, -V-N(R')C(O)N(R')$_2$, -V-NR'NR'C(O)N(R')$_2$, -V-NR'NR'CO$_2$R°, -V-C(O)C(O)R°, -V-C(O)CH$_2$C(O)R°, -V-CO$_2$R°, -V-C(O)R°, -V-OC(O)R°, -V-OC(O)N(R°)$_2$, -V-S(O)$_2$R°, -V-SO$_2$N(R')$_2$, -V-S(O)R°, -V-NR'SO$_2$N(R')$_2$, -V-NR'SO$_2$R°, -V-C(=S)N(R')$_2$, -V-(CH$_2$)$_y$N(R')$_2$ or -V-C(=NH)-N(R')$_2$, and each group represented by R^{12} is independently selected;

each substitutable carbon atom of: i) the non-aromatic ring represented by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from NR^5(CH$_2$)$_m$R^1; iii) the nitrogen-containing non-aromatic heterocyclic group formed from NR^{3}R^4; and iv) the non-aromatic bridged bicyclic group represented by R^4 is optionally and independently substituted with -R°, -OH, -OR°, -O(haloalkyl), -SH, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph),

substituted -O(Ph), -CH_2(Ph), substituted –CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -CN, -NO_2, -$N(R')_2$, -$C(O)N(R^o)_2$, -$NR'C(O)R^o$, -$NR'C(O)R^o$, -V-$N(R')_2$, -V-$NR'C(O)R^o$, -V-$C(O)N(R^o)_2$, -$NR'CO_2R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$, -CO_2R^o, -$C(O)R^o$, -$OC(O)R^o$, -$OC(O)N(R^o)_2$, -$S(O)_2R^o$, -$SO_2N(R')_2$, -$S(O)R^o$, -$NR'SO_2N(R')_2$, -$NR'SO_2R^o$, -$C(=S)N(R')_2$, -$(CH_2)_yN(R')_2$, -$C(=NH)$-$N(R')_2$, haloalkyl, -V-R^o, -V-OH, -V-OR^o, -V-SH, -V-SR^o, -$NR'C(O)R^o$, -V-NO_2, -V-CN, -V-$N(R')_2$, -V-$NR'CO_2R^o$, -V-$NR'C(O)R^o$, -V-$NR'NR'C(O)R^o$, -V-$N(R')C(O)N(R')_2$, -V-$NR'NR'C(O)N(R')_2$, -V-$NR'NR'CO_2R^o$, -V-$C(O)C(O)R^o$, -V-$C(O)CH_2C(O)R^o$, -V-CO_2R^o, -V-$C(O)R^o$, -V-$C(O)N(R^o)_2$, -V-$OC(O)R^o$, -V-$OC(O)N(R^o)_2$, -V-$S(O)_2R^o$, -V-$SO_2N(R')_2$, -V-$S(O)R^o$, -V-$NR'SO_2N(R')_2$, -V-$NR'SO_2R^o$, -V-$C(=S)N(R')_2$, -V-$(CH_2)_yN(R')_2$, -V-$C(=NH)$-$N(R')_2$, =O, =S, =NNHR*, $=NN(R^*)_2$, =NNHC(O)R*, $=NNHCO_2$(alkyl), $=NNHSO_2$ (alkyl) or =NR*;

each R^o is independently hydrogen or substituted or unsubstituted aliphatic group, a substituted or unsubstituted cycloaliphatic, a substituted or unsubstituted non-aromatic heterocyclic group or a substituted or unsubstituted aromatic group selected from phenyl, naphthyl, 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisazolyl;

each R' is independently R^o, -CO_2R^o, -SO_2R^o or -$C(O)R^o$;

each R* is independently hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group;

V is a C1-C6 alkylene group;

each substitutable carbon atom of : i) the aliphatic, cycloaliphatic, non-aromatic heterocyclic group and aromatic group represented by R^o; and ii) the

aliphatic group represented by R* is optionally and independently substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, aminoalkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl;

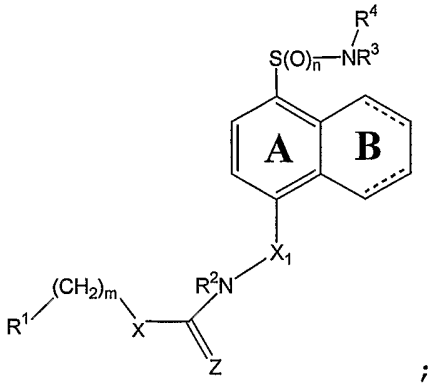
each substitutable nitrogen atom of: i) the non-aromatic ring represented by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from $NR^5(CH_2)_mR^1$; iii) the nitrogen-containing non-aromatic heterocyclic group formed from NR^3R^4; iv) the non-aromatic heterocyclic group represented by $R^{o;}$ and v) the non-aromatic bridged bicyclic group represented by R^4 is optionally and independently substituted with R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, $-NR^+SO_2R^+$, $-C(O)-NHR^+$, $-C(O)-N(R^+)_2$, $-C(O)-CH[N(R^+)_2]R^+$ or $-C(O)-CH[OR^+]R^+$;

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an aliphatic, cycloaliphatic, non-aromatic heterocyclic group, phenyl or benzyl group, wherein each substitutable carbon atom of the aliphatic, cycloaliphatic, non-aromatic heterocyclic ring, phenyl or benzyl group represented by R^+ is optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl or $N(R^+)_2$ is a non-aromatic heterocyclic group; and

each substitutable nitrogen atom of the non-aromatic heterocyclic group represented by R^+ is optionally substituted with alkyl, alkoxycarbonyl, alkylcarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl,

provided that the compound is other than N-[4-[[(4-methoxyphenyl)amino]sulfonyl]-1-naphthalenyl]-benzamide, N-[4-[(2-propenylamino)sulfonyl]-1-naphthalenyl]-benzamide, N-[4-(4-morpholinylsulfonyl)-1-naphthalenyl]-benzamide or N-[4-(1-piperidinylsulfonyl)-1-naphthalenyl]-benzamide.

2. The compound of Claim 1 wherein the compound is represented by the following structural formula:



;

wherein:

C=Z is C=O, CH_2,C=NH or C=S;

Rings **A** and **B** are optionally substituted with alkyl, halolkyl, alkoxy, haloalkoxy, hydroxy, halogen, cyano or nitro;

R^4 is a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group or a substituted or unsubstituted non-aromatic ring;

each substitutable nitrogen atom of: i) the non-aromatic ring represented by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from $NR^5(CH_2)_mR^1$; iii) the nitrogen-containing non-aromatic heterocyclic group formed from R^3, R^4 and the nitrogen atom to which R^3 and R^4 are bonded; and iv) the non-aromatic heterocyclic group represented by R^o are selected from R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$ and $-NR^+SO_2R^+$; and

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an unsubstituted non-aromatic heterocyclic ring or an aliphatic, phenyl or benzyl group optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

3. The compound of Claim 2 wherein:

C=Z is C=O and X_1 is a bond;

X is a bond;

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group optionally substituted with one or more groups R^{10};

R^2 is –H;

R^3 is –H or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl or benzyl group optionally substituted with one or more groups R^{12};

m is 0 or 1; or

n is 2.

4. The compound of Claim 2 wherein:

C=Z is C=O and X_1 is a bond;

X is a bond;

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group optionally substituted with one or more groups R^{10};

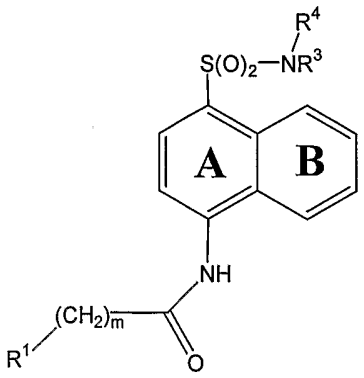
R^2 is –H;

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

m is 0 or 1; and

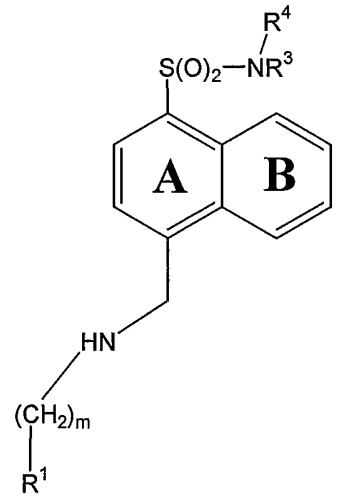
n is 2.

5. The compound of Claim 4 wherein the compound is represented by the following structural formula:



wherein Rings **A** and **B** are unsubstituted.

6. The compound of Claim 1 wherein the compound is represented by the following structural formula:



;

wherein:

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

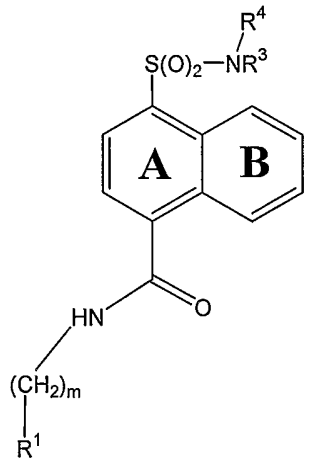
m is 0 or 1;

Rings **A** and **B** are unsubstituted;

each substitutable nitrogen atom in: i) a nitrogen-containing the non-aromatic heterocyclic group formed from $-NR^3R^4$; and ii) the non-aromatic ring represented by R^4 are R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$ and $-NR^+SO_2R^+$; and

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an unsubstituted non-aromatic heterocyclic ring or an aliphatic, phenyl or benzyl group optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

7. The compound of Claim 1 wherein the compound is represented by the following structural formula:



;

wherein:

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

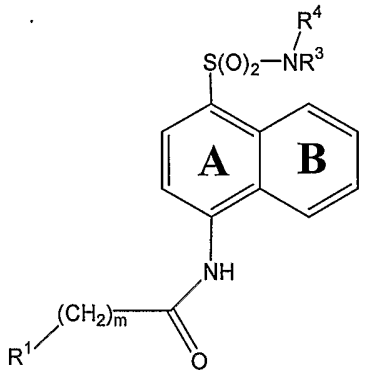
m is 0 or 1; and

Rings **A** and **B** are unsubstituted.

8. The compound of Claim 5 wherein R^4 is a substituted or unsubstituted non-aromatic ring.

9. The compound of Claim 8 wherein R^4 is a piperidinyl group or an *N*-substituted piperidinyl group.

10. The compound of Claim 1 wherein the compound is represented by the following structural formula:



R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H;

R^4 is a piperidinyl group *N*-substituted with R^{15}, -C(O)R^{15}, -C(O)OR^{15}, -C(O)-NHR^{15}, -C(O)-N(R^{15})$_2$, or -C(O)CH[N(R^{16})$_2$]R^{17};

each substitutable carbon of the piperidinyl group represented by R^4 is optionally and independently substituted with an aliphatic group or substituted aliphatic group;

R^{15} is –H, a substituted or unsubstituted non-aromatic ring, or a substituted or unsubstituted aliphatic group or a substituted or unsubstituted C7-C9 aralkyl group, provided that –COOR^{15} is not –COOH, or N(R^{15})$_2$ taken together is a substituted or unsubstituted five or six membered non-aromatic nitrogen-containing heterocyclic group;

R^{16} is –H or an alkyl group;

R^{17} is –H; a C1-C6 alkyl group optionally substituted with –OH or -NH_2; indolyl; imidazolyl; or phenyl or benzyl optionally substituted with –OH;

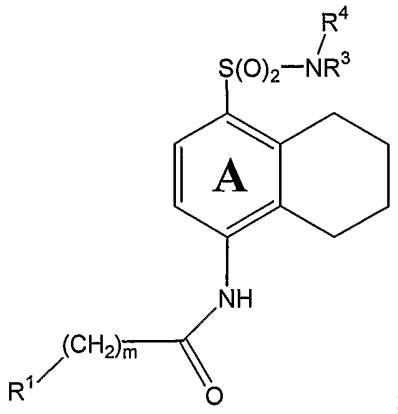
m is 0 or 1; and

Rings **A** and **B** are unsubstituted.

11. The compound of Claim 5 wherein R^4 is a cyclohexyl group, a phenyl group or a benzyl group wherein the phenyl or benzyl group represented by R^4 is optionally substituted with hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_3$, $N(CH_2CH_3)_2$, $N(CH_3)(CH_2CH_3)$, $NH(CH_2CH_2CH_3)$, $N(CH_2CH_2CH_3)_2$, $N(CH_3)(CH_2CH_2CH_3)$ or $N(CH_2CH_3)(CH_2CH_2CH_3)$.

12. The compound of Claim 5 wherein R^1 is a substituted or unsubstituted cyclohexyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted pyridyl group, a substituted or unsubstituted –CH_2-(pyridyl) group, a substituted or unsubstituted –CH_2-(thienyl) group, a substituted or unsubstituted benzothienyl group, a substituted or unsubstituted -CH_2-(benzothienyl) group, a substituted or unsubstituted furanyl group; or a substituted or unsubstituted -CH_2-(furanyl) group; and R^4 is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group; or –NR^3R^4 taken together is a nitrogen-containing non-aromatic heterocyclic ring.

13. The compound of Claim 4 wherein the compound is represented by the following structural formula:



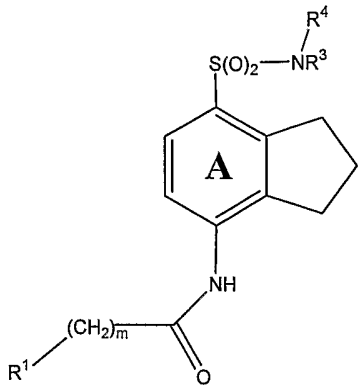
;

wherein Ring **A** is optionally substituted at any one or more substitutable ring carbons with a group selected from alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, halogen, cyano and nitro.

14. The compound of Claim 13 wherein R^4 is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group; or $-NR^3R^4$ taken together is a nitrogen-containing non-aromatic heterocyclic ring.

15. The compound of Claim 13 wherein R^1 is a substituted or unsubstituted cyclohexyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted pyridyl group, a substituted or unsubstituted $-CH_2$-(pyridyl) group, a substituted or unsubstituted thienyl group, a substituted or unsubstituted -CH_2-(thienyl) group, a substituted or unsubstituted benzothienyl group, a substituted or unsubstituted -CH_2-(benzothienyl) group, a substituted or unsubstituted furanyl group or a substituted or unsubstituted $-CH_2$-(furanyl) group; and R^4 is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group; or $-NR^3R^4$ taken together is a nitrogen-containing non-aromatic heterocyclic ring.

16. The compound of Claim 1 wherein the compound is represented by the following structural formula:



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wherein:

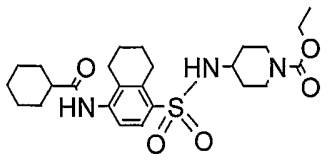
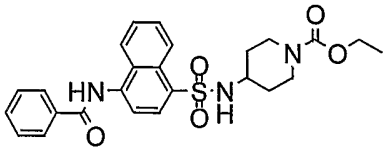
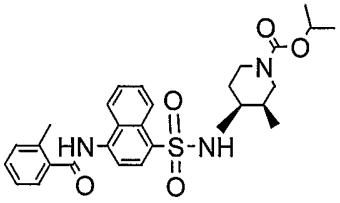
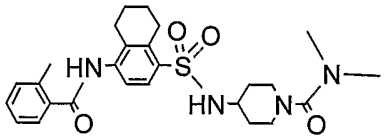
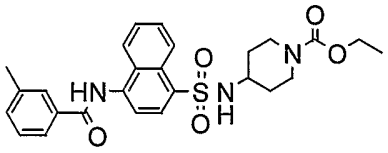
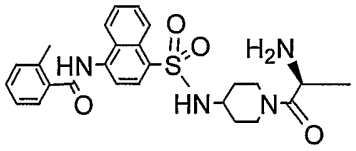
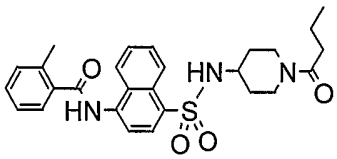
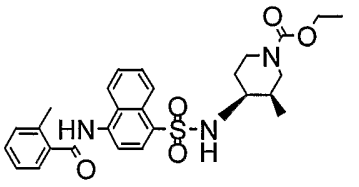
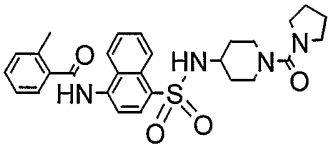
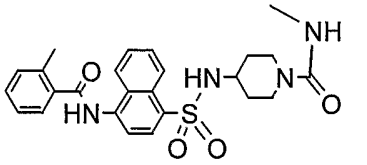
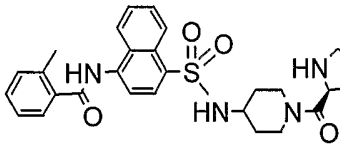
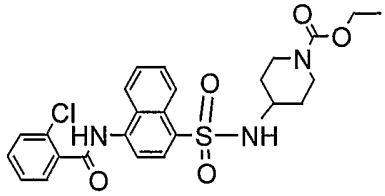
Ring **A** is optionally substituted at any one or more substitutable ring carbons with a group selected from alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, halogen, cyano and nitro;

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

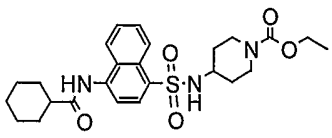
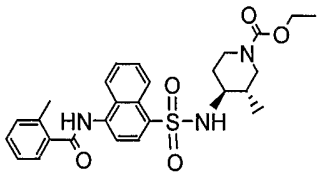
R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group; and

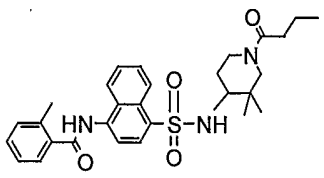
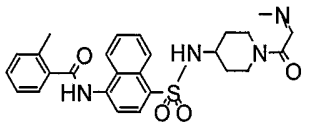
m is 0 or 1.

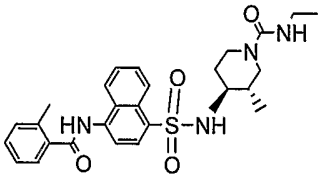
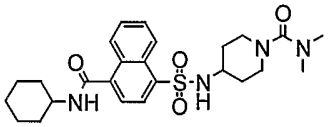
17. The compound of Claim 1 wherein the compound is represented by a structural formula selected from:

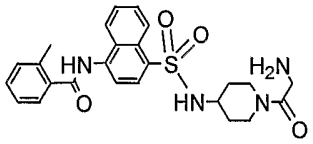
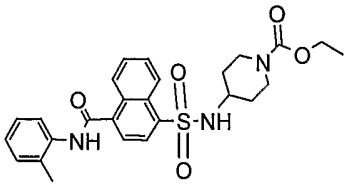

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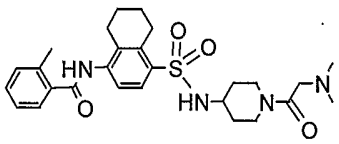
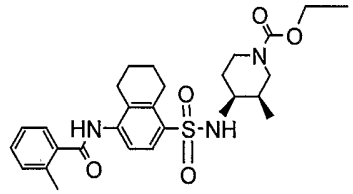
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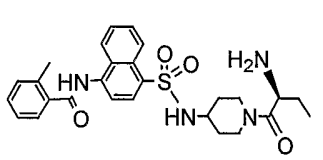
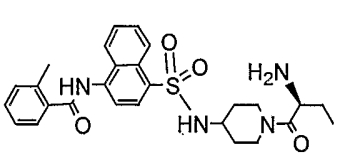

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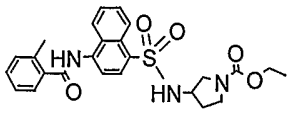
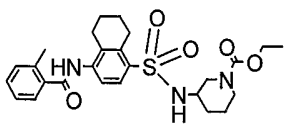

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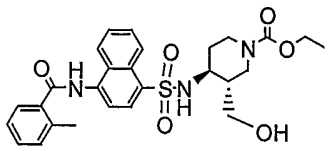
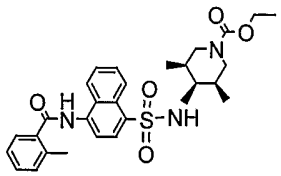

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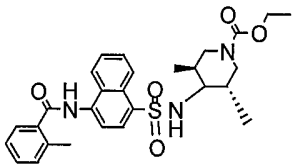
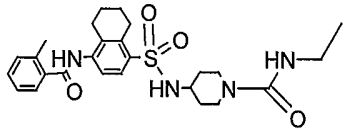

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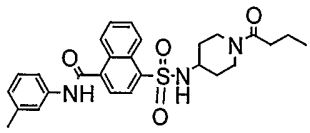
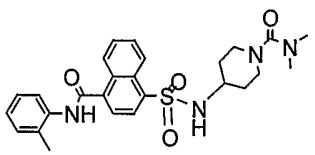

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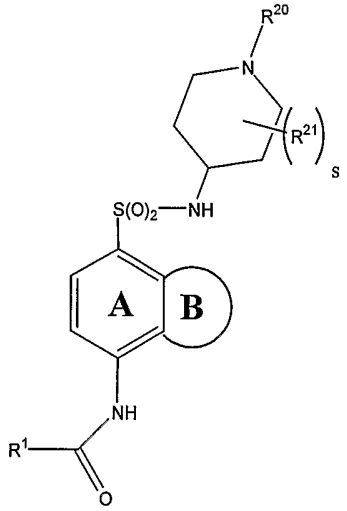

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or a pharmaceutically acceptable salt thereof.

18. A compound represented by the following structural formula:

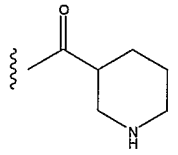
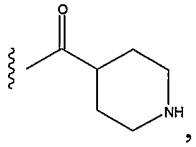
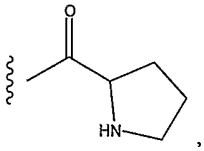
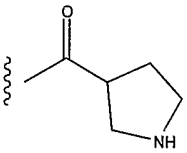
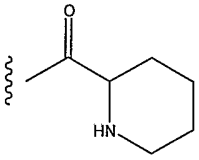


or a pharmaceutically acceptable salt thereof, wherein:

Ring **A** is unsubstituted;

Ring **B** is an unsubstituted phenyl, cyclohexyl or cyclopentyl ring fused to Ring **A**;

R^1 is cyclohexyl or phenyl, furanyl, thienyl or pyridyl optionally substituted with C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, methylenedioxy, ethylenedioxy, halogen, cyano or nitro;

R^{20} is -C(O)R^{22},  ,  ,  ,  ,  ,-C(O)OR^{22}, -C(O)-NHR^{22}, -C(O)-N(R^{22})$_2$ or -C(O)CH[N(R^{23})$_2$]R^{24};

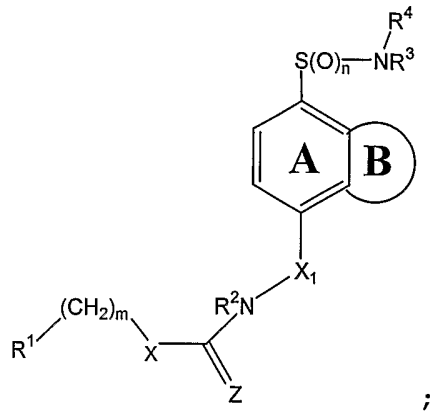
R^{21} is methyl, ethyl, 2-hydroxyethyl or iso-propyl;

R^{22} is –H or C1-C4 alkyl or -N(R^{22})$_2$ taken together is *N*-pyrollidinyl or *N*-piperidinyl, provided that R^{22} is not –H when R^{20} is –COOR^{22};

R^{23} is –H, methyl or ethyl;

R^{24} is –H, methyl, ethyl, phenyl, benzyl, 4-hydroxyphenyl or 4-hydroxybenzyl; and s is 0, 1, 2, 3 or 4.

19. A method of treating a subject with a CCR8 mediated disease or condition, said method comprising administering to the subject an effective amount of a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is a covalent bond, C=O or CR^aR^b;

X is a covalent bond, O, or NR^5;

C=Z is C=O, CH_2, C=NH, C=S or absent, provided that when X_1 is a covalent bond then C=Z is not CH_2, provided that when C=Z is absent then X is a covalent bond, and provided that when X is NR^5 and C=Z is C=O then R^4 is not an aliphatic or substituted aliphatic group;

R^a and R^b are independently H or a C1-C3 alkyl;

R^1 is: i) a substituted or unsubstituted aromatic group; ii) a substituted or unsubstituted non-aromatic ring; or iii) when X is NR^5, then NR^5-$(CH_2)_mR^1$, taken together, is optionally a substituted or unsubstituted non-aromatic heterocyclic group;

R^2 is –H or a C1-C3 alkyl group;

R^3 is –H; and R^4 is: i) a substituted or unsubstituted aliphatic group; ii) a substituted or unsubstituted aromatic group; iii) a substituted or unsubstituted non-aromatic ring or a substituted or unsubstituted non-aromatic bridged bicyclic group; or iv) R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R^5 is –H, or a C1-C3 alkyl group;

Ring **B** is a phenyl group or a five or six membered carbocyclic carbocyclic non-aromatic ring fused to Ring **A**;

Rings **A** and **B** are independently substituted or unsubstituted;

m is 0, 1, 2 or 3;

n is 1 or 2;

each substitutable carbon atom of the aromatic group represented by R^1 is optionally substituted with a group represented by R^{10}, wherein R^{10} is halogen, -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH_2(Ph), substituted -CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R^o$, -$NR'C(O)R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$, -CO_2R^o, -$C(O)R^o$, -$C(O)N(R^o)_2$, -$OC(O)R^o$, -$OC(O)N(R^o)_2$, -$S(O)_2R^o$, -$SO_2N(R')_2$, -$S(O)R^o$, -$NR'SO_2N(R')_2$, -$NR'SO_2R^o$, -$C(=S)N(R')_2$, -$(CH_2)_yN(R')_2$, -C(=NH)-$N(R')_2$, haloalkyl, -V-R^o, -V-OH, -V-OR^o, -V-SH, -V-SR^o, -V-NO_2, -V-CN, -V-$N(R')_2$, -V-$NR'CO_2R^o$, -V-$NR'C(O)R^o$, -V-$NR'NR'C(O)R^o$, -V-$N(R')C(O)N(R')_2$, -V-$NR'NR'C(O)N(R')_2$, -V-$NR'NR'CO_2R^o$, -V-$C(O)C(O)R^o$, -V-$C(O)CH_2C(O)R^o$, -V-CO_2R^o, -V-$C(O)R^o$, -V-$C(O)N(R^o)_2$, -V-$OC(O)R^o$, -V-$OC(O)N(R^o)_2$, -V-$S(O)_2R^o$, -V-$SO_2N(R')_2$, -V-$S(O)R^o$, -V-$NR'SO_2N(R')_2$, -V-$NR'SO_2R^o$, -V-$C(=S)N(R')_2$, -V-$(CH_2)_yN(R')_2$, or -V-C(=NH)-$N(R')_2$, and each group represented by R^{10} is independently selected;

each substitutable carbon atom of the aliphatic group represented by $R^4$is optionally substituted with a group represented by R^{11}, wherein R^{11} is halogen, -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH_2(Ph), substituted -CH_2(Ph), -CH_2CH_2(Ph), substituted -CH_2CH_2(Ph), -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R^o$, -$NR'C(O)R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$, -$C(O)R^o$, -$C(O)N(R^o)_2$, -$OC(O)R^o$, -$OC(O)N(R^o)_2$, -$S(O)_2R^o$, -$SO_2N(R')_2$, -$S(O)R^o$, -$NR'SO_2N(R')_2$, -$NR'SO_2R^o$, -$C(=S)N(R')_2$, -$(CH_2)_yN(R')_2$, -C(=NH)-$N(R')_2$, haloalkyl, -V-R^o, -V-OH, -V-OR^o, -V-SH, -V-SR^o, -V-NO_2, -V-CN, -V-$N(R')_2$, -V-$NR'CO_2R^o$, -V-$NR'C(O)R^o$, -V-$NR'NR'C(O)R^o$, -V-$N(R')C(O)N(R')_2$, -V-$NR'NR'C(O)N(R')_2$, -V-$NR'NR'CO_2R^o$, -V-$C(O)C(O)R^o$, -V-$C(O)CH_2C(O)R^o$, -V-$C(O)R^o$, -V-$C(O)N(R^o)_2$, -V-$OC(O)R^o$,

-V-OC(O)N(R^o)$_2$, -V-S(O)$_2R^o$, -V-SO$_2$N(R')$_2$, -V-S(O)R^o, -V-NR'SO$_2$N(R')$_2$, -V-NR'SO$_2R^o$, -V-C(=S)N(R')$_2$, -V-(CH$_2$)$_y$N(R')$_2$, -V-C(=NH)-N(R')$_2$, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$ (alkyl), or =NR*, and each group represented by R^{11} is independently selected;

each substitutable carbon atom of the aromatic group represented by R^4 is optionally substituted at each substitutable carbon atom with a group represented by R^{12}, wherein R^{12} is halogen, -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH$_2$(Ph), substituted –CH$_2$(Ph), -CH$_2$CH$_2$(Ph), substituted -CH$_2$CH$_2$(Ph), -CN, -NR'CO$_2R^o$, -NR'NR'C(O)R^o, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO$_2R^o$, -C(O)C(O)R^o, -C(O)CH$_2$C(O)R^o, -CO$_2R^o$, -C(O)R^o, -OC(O)R^o, -OC(O)N(R^o)$_2$, -S(O)$_2R^o$, -SO$_2$N(R')$_2$, -S(O)R^o, -NR'SO$_2$N(R')$_2$, -NR'SO$_2R^o$, -C(=S)N(R')$_2$, -(CH$_2$)$_y$N(R')$_2$, -C(=NH)-N(R')$_2$, haloalkyl, -V-R^o, -V-OH, -V-OR^o, -V-SH, -V-SR^o, -V-CN, -V-NR'CO$_2R^o$, -V-NR'NR'C(O)R^o, -V-N(R')C(O)N(R')$_2$, -V-NR'NR'C(O)N(R')$_2$, -V-NR'NR'CO$_2R^o$, -V-C(O)C(O)R^o, -V-C(O)CH$_2$C(O)R^o, -V-CO$_2R^o$, -V-C(O)R^o, -V-OC(O)R^o, -V-OC(O)N(R^o)$_2$, -V-S(O)$_2R^o$, -V-SO$_2$N(R')$_2$, -V-S(O)R^o, -V-NR'SO$_2$N(R')$_2$, -V-NR'SO$_2R^o$, -V-C(=S)N(R')$_2$, -V-(CH$_2$)$_y$N(R')$_2$ or -V-C(=NH)-N(R')$_2$, and each group represented by R^{12} is independently selected;

each substitutable carbon atom of: i) the non-aromatic ring represented by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from $NR^5(CH_2)_mR^1$; iii) the nitrogen-containing non-aromatic heterocyclic group formed from NR^3R^4; and iv) the non-aromatic bridged bicyclic group represented by R^4 is optionally and independently substituted with -R^o, -OH, -OR^o, -O(haloalkyl), -SH, -SR^o, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), -CH$_2$(Ph), substituted –CH$_2$(Ph), -CH$_2$CH$_2$(Ph), substituted -CH$_2$CH$_2$(Ph), -CN, -NO$_2$, -N(R')$_2$, -C(O)N(R^o)$_2$, -NR'C(O)R^o, -NR'C(O)R^o, -V-N(R')$_2$, -V-NR'C(O)R^o, -V-C(O)N(R^o)$_2$, -NR'CO$_2R^o$, -NR'NR'C(O)R^o, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO$_2R^o$, -C(O)C(O)R^o, -C(O)CH$_2$C(O)R^o, -CO$_2R^o$, -C(O)R^o, -OC(O)R^o, -OC(O)N(R^o)$_2$, -S(O)$_2R^o$, -SO$_2$N(R')$_2$, -S(O)R^o, -NR'SO$_2$N(R')$_2$, -NR'SO$_2R^o$, -C(=S)N(R')$_2$, -(CH$_2$)$_y$N(R')$_2$,

-C(=NH)-N(R')$_2$, haloalkyl, -V-R°, -V-OH, -V-OR°, -V-SH, -V-SR°, -NR'C(O)R°, -V-NO$_2$, -V-CN, -V-N(R')$_2$, -V-NR'CO$_2$R°, -V-NR'C(O)R°, -V-NR'NR'C(O)R°, -V-N(R')C(O)N(R')$_2$, -V-NR'NR'C(O)N(R')$_2$, -V-NR'NR'CO$_2$R°, -V-C(O)C(O)R°, -V-C(O)CH$_2$C(O)R°, -V-CO$_2$R°, -V-C(O)R°, -V-C(O)N(R°)$_2$, -V-OC(O)R°, -V-OC(O)N(R°)$_2$, -V-S(O)$_2$R°, -V-SO$_2$N(R')$_2$, -V-S(O)R°, -V-NR'SO$_2$N(R')$_2$, -V-NR'SO$_2$R°, -V-C(=S)N(R')$_2$, -V-(CH$_2$)$_y$N(R')$_2$, -V-C(=NH)-N(R')$_2$, =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$ (alkyl), or =NR*;

each R° is independently hydrogen or substituted or unsubstituted aliphatic group, a substituted or unsubstituted cycloaliphatic, a substituted or unsubstituted non-aromatic heterocyclic group or a substituted or unsubstituted aromatic group selected from phenyl, naphthyl, 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisazolyl;

each R' is independently R°, -CO$_2$R°, -SO$_2$R° or -C(O)R°;

each R* is independently hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group;

V is a C1-C6 alkylene group;

each substitutable carbon atom of : i)) the aliphatic, cycloaliphatic, non-aromatic heterocyclic group and aromatic group represented by R°; and ii) the aliphatic group represented by R* is optionally and independently substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, aminoalkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl;

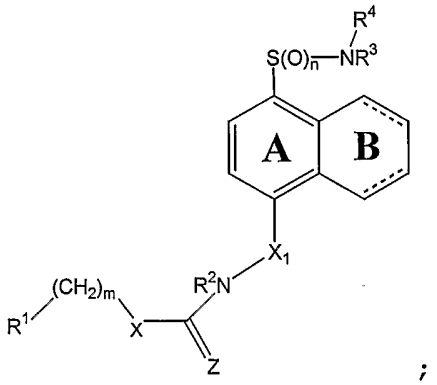
each substitutable nitrogen atom of: i) the non-aromatic ring represented

by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from $NR^5(CH_2)_mR^1$; iii) the nitrogen-containing non-aromatic heterocyclic group formed from NR^3R^4; iv) the non-aromatic heterocyclic group represented by R^4; and v) the non-aromatic bridged bicyclic group represented by R^4 is optionally and independently substituted with R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, $-NR^+SO_2R^+$, $-C(O)-NHR^+$, $-C(O)-N(R^+)_2$, $-C(O)-CH[N(R^+)_2]R^+$ or $-C(O)-CH[OR^+]R^+$;

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an aliphatic, cycloaliphatic, non-aromatic heterocyclic group, phenyl or benzyl group, wherein each substitutable carbon atom of the aliphatic, cycloaliphatic, non-aromatic heterocyclic ring, phenyl or benzyl group represented by R^+ is optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl or $N(R^+)_2$ is a non-aromatic heterocyclic group; and

each substitutable nitrogen atom of the non-aromatic heterocyclic group represented by R^+ is optionally substituted with alkyl, alkoxycarbonyl, alkylcarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl.

20. The method of Claim 19 wherein the compound is represented by the following structural formula:



;

wherein:

C=Z is C=O, CH_2,C=NH or C=S;

Rings **A** and **B** are optionally substituted with alkyl, halolkyl, alkoxy, haloalkoxy, hydroxy, halogen, cyano or nitro;

R^4 is a substituted or unsubstituted aliphatic group, a substituted or unsubstituted aromatic group or a substituted or unsubstituted non-aromatic ring;

each substitutable nitrogen atom of: i) the non-aromatic ring represented by R^1 or R^4; ii) the non-aromatic heterocyclic group formed from $NR^5(CH_2)_mR^1$; iii) the nitrogen-containing non-aromatic heterocyclic group formed from R^3, R^4 and the nitrogen atom to which R^3 and R^4 are bonded; and iv) the non-aromatic heterocyclic group represented by R^o are selected from R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$ and $-NR^+SO_2R^+$; and

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an unsubstituted non-aromatic heterocyclic ring or an aliphatic, phenyl or benzyl group optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

21. The method of Claim 19 wherein the CCR8 mediated disease or condition is asthma, atopic dermatitis, allergic rhinitis, systemic anaphylaxis, a hypersensitivity response, a drug allergy, an insect sting allergy, dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes, glomerulonephritis, autoimmune thyroiditis, Behcet's disease or graft rejection.

22. The method of Claim 21 wherein the CCR8 mediated disease or condition is asthma.

23. The method of Claim 21 wherein:

C=Z is C=O and X_1 is a bond;

X is a bond;

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group optionally substituted with one or more groups R^{10};

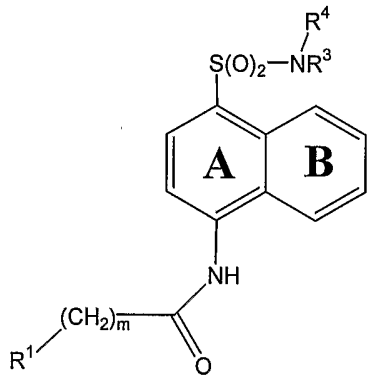
R^2 is –H;

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

m is 0 or 1; and

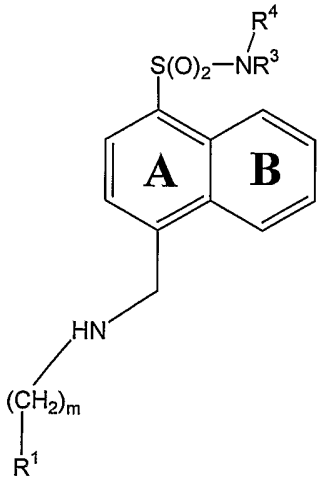
n is 2.

24. The method of Claim 23 wherein the compound is represented by the following structural formula:



wherein Rings **A** and **B** are unsubstituted.

25. The method of Claim 19 wherein the compound is represented by the following structural formula:



;

wherein:

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

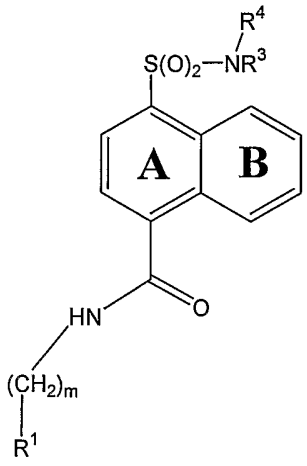
m is 0 or 1;

Rings **A** and **B** are unsubstituted;

each substitutable nitrogen atom in: i) the non-aromatic heterocyclic group formed from $-NR^3R^4$; and ii) the non-aromatic ring represented by R^4 are R^+, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$ and $-NR^+SO_2R^+$; and

each R^+ is independently hydrogen, an unsubstituted heteroaryl or an unsubstituted non-aromatic heterocyclic ring or an aliphatic, phenyl or benzyl group optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

26. The method of Claim 19 wherein the compound is represented by the following structural formula:



;

wherein:

R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H and R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

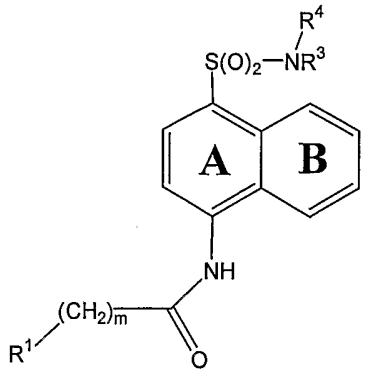
m is 0 or 1; and

Rings **A** and **B** are unsubstituted.

27. The method of Claim 24 wherein R^4 is a substituted or unsubstituted non-aromatic ring.

28. The method of Claim 27 wherein R^4 is a piperidinyl group or an *N*-substituted piperidinyl group.

29. The method of Claim 19 wherein the compound is represented by the following structural formula:



R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H;

R^4 is a piperidinyl group *N*-substituted with R^{15}, -C(O)R^{15}, -C(O)OR^{15}, -C(O)-NHR^{15}, -C(O)-N(R^{15})$_2$, or -C(O)CH[N(R^{16})$_2$]R^{17};

each substitutable carbon of the piperidinyl group represented by R^4 is optionally and independently substituted with an aliphatic group or substituted aliphatic group;

R^{15} is –H, substituted or unsubstituted a non-aromatic ring, or a substituted or unsubstituted aliphatic group or a substituted or unsubstituted C7-C9 aralkyl group, provided that -COOR^{15} is not –COOH, or N(R^{15})$_2$ taken together is a substituted or unsubstituted five or six membered non-aromatic nitrogen-containing heterocyclic group;

R^{16} is –H or an alkyl group;

R^{17} is –H; a C1-C6 alkyl group optionally substituted with –OH or -NH_2; indolyl; imidazolyl; or phenyl or benzyl optionally substituted with –OH;

m is 0 or 1; and

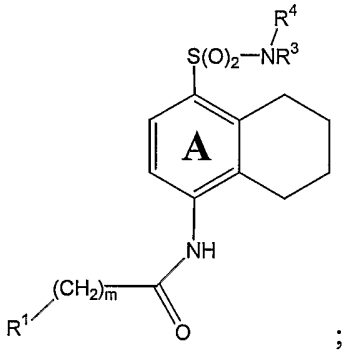
Rings A and B are unsubstituted.

30. The method of Claim 24 wherein R^4 is a cyclohexyl group, a phenyl group or a benzyl group wherein the phenyl or benzyl group represented by R^4 is optionally substituted with hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_3$, $N(CH_2CH_3)_2$, $N(CH_3)(CH_2CH_3)$,

$NH(CH_2CH_2CH_3)$, $N(CH_2CH_2CH_3)_2$, $N(CH_3)(CH_2CH_2CH_3)$ or $N(CH_2CH_3)(CH_2CH_2CH_3)$.

31. The method of Claim 24 wherein R^1 is a substituted or unsubstituted cyclohexyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted pyridyl group, a substituted or unsubstituted $-CH_2$-(pyridyl) group, a substituted or unsubstituted thienyl group, a substituted or unsubstituted $-CH_2$-(thienyl) group, a substituted or unsubstituted benzothienyl group, a substituted or unsubstituted $-CH_2$-(benzothienyl) group, a substituted or unsubstituted furanyl group; or a substituted or unsubstituted $-CH_2$-(furanyl) group; and R^4 is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group; or $-NR^3R^4$ taken together is a nitrogen-containing non-aromatic heterocyclic ring.

32. The method of Claim 23 wherein the compound is represented by the following structural formula:



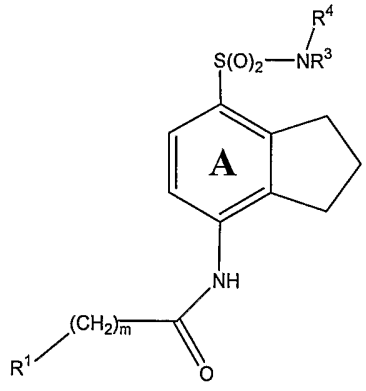
;

wherein Ring **A** is optionally substituted at any one or more substitutable ring carbons a group selected from alkyl, hydroxy, alkoxy, halogen, cyano or nitro.

33. The method of Claim 32 wherein R^1 is a substituted or unsubstituted cyclohexyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted pyridyl group, a substituted or

unsubstituted –CH_2-(pyridyl) group, a substituted or unsubstituted thienyl group, a substituted or unsubstituted -CH_2-(thienyl) group, a substituted or unsubstituted benzothienyl group, a substituted or unsubstituted -CH_2-(benzothienyl) group, a substituted or unsubstituted furanyl group or a substituted or unsubstituted –CH_2-(furanyl) group; and R^4 is a piperidinyl group, an *N*-substituted piperidinyl group, a cyclohexyl group, a substituted cyclohexyl group, an unsubstituted phenyl group, an unsubstituted benzyl group or a phenyl or benzyl group substituted with an electron donating group; or –NR^3R^4 taken together is a nitrogen-containing non-aromatic heterocyclic ring.

34. The method of Claim 19 wherein the compound is represented by the following structural formula:



;

wherein:

Ring **A** is optionally substituted at any one or more substitutable ring carbons a group selected from alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, halogen, cyano or nitro;

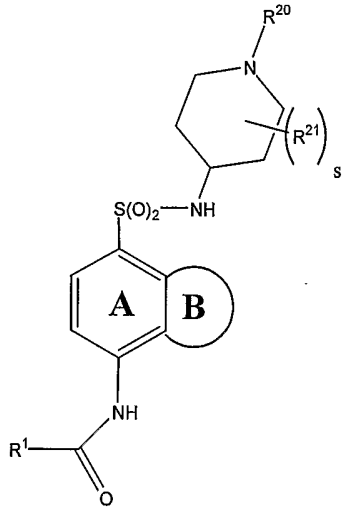
R^1 is a substituted or unsubstituted cycloalkyl group or an aromatic group substituted at zero, one or more substitutable carbon atoms by R^{10};

R^3 is –H or R^3 and R^4 taken together with the nitrogen atom to which they are bonded are a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R^4 is a substituted or unsubstituted non-aromatic ring or a phenyl group or benzyl group optionally substituted with one or more groups R^{12}; and

m is 0 or 1.

35. A method of treating a subject with a CCR8 mediated disease or condition, said method comprising administering to the subject an effective amount of a compound represented by the following structural formula:

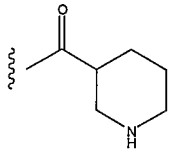


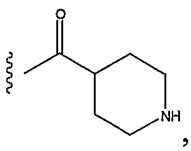
or a pharmaceutically acceptable salt thereof, wherein:

Ring **A** is substituted;

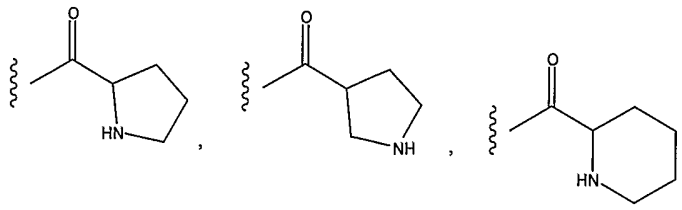
Ring **B** is an unsubstituted phenyl, cyclohexyl or cyclopentyl ring fused to Ring **A**;

R^1 is cyclohexyl or phenyl, furanyl, thienyl or pyridyl optionally substituted with C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, methylenedioxy, ethylenedioxy, halogen, cyano or nitro;

R^{20} is $-C(O)R^{22}$, 

, 

,



, -C(O)OR^{22}, -C(O)-NHR^{22}, -C(O)-N(R^{22})$_2$ or -C(O)CH[N(R^{23})$_2$]R^{24};

R^{21} is methyl, ethyl, 2-hydroxyethyl or iso-propyl;

R^{22} is –H or C1-C4 alkyl or -N(R^{22})$_2$ taken together is *N*-pyrollidinyl or *N*-piperidinyl, provided that R^{22} is not –H when R^{20} is –COOR^{22};

R^{23} is –H, methyl or ethyl;

R^{24} is –H, methyl, ethyl, phenyl, benzyl, 4-hydroxyphenyl or 4-hydroxybenzyl; and

s is 0, 1, 2, 3 or 4.

36. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound of Claim 1.

SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc.
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<120> CCR8 INHIBITORS

<130> 1855.2041-003 PCT

<150> US 60/436,508
<151> 2002-12-23

<160> 2

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INTERNATIONAL SEARCH REPORT

	nal Application No
	PCT/US 03/41199

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/26 C07D213/42 C07D211/58 C07D207/14 C07C311/46
A61K31/18 A61K31/4402 A61K31/4406 A61K31/4409 A61K31/4468
A61K31/40 A61P11/06 A61P29/00 A61P37/08

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)

IPC 7 C07D C07C

Documentation 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, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 038 868 A (BAYER AG) 27 September 2000 (2000-09-27) see defintion of A and examples and formula IV	1-36
A	WO 99/29670 A (BOEHRINGER INGELHEIM PHARMA ;WALTER RAINER (DE); HECKEL ARMIN (DE)) 17 June 1999 (1999-06-17) see definitions of R1-R4 and Y1 and Y2	1-36
X	WO 96/40641 A (TANABE SEIYAKU CO ;SIRCAR ILA (US); SCHOLZ WOLFGANG (US); HU JAMES) 19 December 1996 (1996-12-19) see general formula, definitions of X,Y, R4-R9 and R1 and R2 and examples	1-36

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2004	09/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

1

INTERNATIONAL SEARCH REPORT

	ıal Application No
	PCT/US 03/41199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/07403 A (HALLENBERGER SABINE ;HENNINGER KERSTIN (DE); REEFSCHLAEGER JUERGEN) 1 February 2001 (2001-02-01) see whole document and example 56 and definitions of R4,R9R10 and R8	1-36
A	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280062 order no 5242677, 5242739, 5242752 & "CHEMBRIDGE PRODUCT LIST" 17 January 2002 (2002-01-17) , CHEMBRIDGE CORPORATION,16981 VIA TAZON, SUITE G, SAN DIEGO, CA, 92127, USA	1-36
A	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280063 order no BAS 0371287 & "INTERCHIM INTERMEDIATES" 9 July 2002 (2002-07-09) , INTERCHIM, 213 AVENUE KENNEDY, BP 1140, MONTLUCON, CEDEX, 03103, FRANCE	1-36
A	WO 02/072549 A (WARNER LAMBERT CO ;MILLENNIUM PHARM INC (US)) 19 September 2002 (2002-09-19) the whole document	1-36

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,19 (partly)

Present claims 1, 19 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations, with cascading substitution patterns (see for example R10 as R°, with R° further substituted) that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the examples and the compounds of claims 2-18. It is noted that there appears to be no definition of y in claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/41199

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,19 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

nal Application No
PCT/US 03/41199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1038868 A	27-09-2000	DE 19912638 A1	21-09-2000
		EP 1038868 A2	27-09-2000
		JP 2000319249 A	21-11-2000
WO 9929670 A	17-06-1999	DE 19754490 A1	10-06-1999
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		WO 9929670 A2	17-06-1999
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		WO 02072549 A1	19-09-2002
		US 2003064991 A1	03-04-2003