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(54) Title: ARYL PIPERIDINE DERIVATIVES AS VLA-1 INTEGRIN ANTAGONISTS AND USES THEREOF

(57) Abstract: Compounds that are VLA-1 integrin antagonists are disclosed. Also disclosed are compositions containing such compounds and methods of using such compounds in treating diseases mediated, at least in part, by the VLA-1 integrin.



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**ARYL PIPERIDINE DERIVATIVES AS VLA-1
INTEGRIN ANTAGONISTS AND USES THEREOF**

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of
5 U.S. provisional patent application Serial No.
60/495,740, filed August 14, 2003.

FIELD OF THE INVENTION

BACKGROUND OF THE INVENTION

This invention relates to compounds which
10 are VLA-1 integrin antagonists. This invention also
relates to compositions containing such compounds
and methods of treatment using such compounds in
treating diseases mediated, at least in part, by the
VLA-1 integrin.

15 **STATE OF THE ART**

Integrins are heterodimeric cell surface
proteins composed of two noncovalently linked poly-
peptide chains, α and β . Integrins are the major
receptor for cell adhesion to the extracellular
20 matrix and play important roles in certain cell-cell
and cell-matrix adhesion events. These integrin-
mediated adhesion events are critical for both nor-
mal and pathophysiological processes during cell
activation, migration, proliferation, and differen-
25 tiation (for reviews see Hynes (1992) *Cell* 69:11;

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Springer (1994) *Cell* 76:301; Hynes (2002) *Cell* 110:673).

VLA-1 (very late antigen-1) is an integrin heterodimer composed of an alpha chain (CD49a, $\alpha 1$) and a beta chain (CD29, $\beta 1$). VLA-1 is one member of a family of four $\beta 1$ integrin molecules that have been shown to bind to the extracellular matrix proteins, collagen, and laminin. The $\beta 1$ integrin collagen receptors include $\alpha 1\beta 1$ (VLA-1), $\alpha 2\beta 1$ (VLA-2), $\alpha 10\beta 1$ and $\alpha 11\beta 1$. These four collagen receptors share overlapping, but distinct, expression profiles. They also appear to have distinct ligand preferences *in vitro* (Tulla et al. (2001) *J. Biol. Chem.* 51:48206). For example, $\alpha 1\beta 1$ has been shown to bind more effectively to type IV collagen than type I collagen while $\alpha 2\beta 1$ binds to type I collagen better than to type IV collagen (Dickeson et al., (1999) *J. Biol. Chem.* 274:32182).

VLA-1 is expressed on smooth muscle cells, microvascular endothelial cells, fibroblasts, osteoblasts, and chondrocytes. In addition, VLA-1 is also expressed on activated cells of the immune system including effector T cells, macrophages, and NK cells (de Fougerolles et al. (2000) *J. Clin. Invest.* 105:721); however, it does not appear to be expressed on B cells or neutrophils. VLA-1 is expressed on T cells in various disease states including in the joints of arthritis patients (Hemler et al. (1986) *J. Clin. Invest.* 78:696), lesions of giant cell arteritis patients (Schaufelberger et al. (1993) *Clin. Exp. Immunol.* 91:421), arterioscler-

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otic plaques, thyroid infiltrates of patients with autoimmune thyroid disease (Paolieri et al. (1992) *J. Endocrinol. Invest.* 15:63), and lungs of chronic bronchitis (Saetta et al. (1993) *Am. Rev. Respir. Dis.* 147:301), sarcoidosis (reviewed in HemLer. (1990) *Annu. Rev. Immunol.* 8:365), and asthma patients (Corrigan et al. (1991) *Int. Arch. Allergy Appl. Immunol.* 94:270).

Despite this broad expression profile, $\alpha 1$ null mice generated by homologous recombination are viable and fertile and have no overt phenotype, demonstrating that the molecule is not required for development (Gardner et al. (1996) *Dev. Biol.* 175:301). In addition, no increased incidence of infection was noted in the mutant mice. While embryonic fibroblasts derived from mutant animals show a striking absence of adhesion to collagen IV, they show no deficit in adhesion to collagen I. Despite the absence of an overt phenotype, no compensatory upregulation of other collagen binding receptors could be identified, suggesting instead that VLA-1 may have redundant roles during development. Together these data suggest that inhibiting VLA-1 function should be nontoxic.

Inhibiting VLA-1 function using $\alpha 1$ null mice and/or blocking anti- $\alpha 1$ antibodies has shown efficacy either prophylactically or therapeutically or both in several animal models of inflammatory disease including 1) delayed-type hypersensitivity as a model of general inflammatory disease (de Fougerolles et al. (2000) *J. Clin. Invest.* 105:721);

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- 2) contact hypersensitivity as a model for skin allergic reactions (de Fougerolles et al. (2000) *J. Clin. Invest.* 105:721); 3) anti-collagen mAb-induced arthritis as a model of rheumatoid arthritis (de Fougerolles et al. (2000) *J. Clin. Invest.* 105:721); and 4) TNBS- and DSS-induced colitis as models of inflammatory bowel disease (Fiorucci et al. (2002) *Immunity* 17:769; Krieglstein et al. (2002) *J. Clin. Invest.* 110:1773).
- The mechanism for the reduction in inflammation seen with the blocking anti- $\alpha 1$ mAb and in $\alpha 1$ null mice results from multiple effects. VLA-1 has been shown to mediate adhesion to and migration across collagen matrix. Therefore, VLA-1 expression may be critical for allowing the effector cells to enter the site of inflammation. mAbs against $\alpha 1$ have also been shown to block collagen-induced cytokine release, including release of TNF- α , a key mediator in arthritis (Miyake et al. (1994) *Eur. J. Immunol.* 24:2000). In addition, VLA-1 also regulates matrix metalloproteinase (MMP) expression (Gardner et al. (1996) *Dev. Biol.* 175:301; Pozzi et al. (2000) *Proc. Natl. Acad. Sci. USA* 97:2202; Pozzi et al. (2002) *Oncogene* 21:272; Lochter et al. (1999) *Mol Biol Cell* 10:271). Therefore, inhibiting VLA-1 provides a way of reducing inflammation through the synergistic action of a variety of mechanisms (i.e., VLA-1 is an upstream regulator of multiple disease promoting factors).
- Fibrosis is a common response to chronic injury and represents a paradigm for the cycle of

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parenchymal wound healing in a variety of tissues (reviewed in Bataller et al. (2001) *Semin. Liver Dis.* 21:437; Bissell. (1998) *J. Gastroenterol.* 33:295). When overactive, this wound healing process can result in pathologic tissue scarring, which results from the progression of several defined steps. First, an infiltrate, consisting of inflammatory cells and platelets and resident "myofibroblasts" (identified as hepatic stellate cells in the liver and differentiated mesangial cells in the kidney), accumulates at the site of injury. Second, the local extracellular matrix (ECM) is altered by *de novo* production of collagen by the myofibroblasts. Third, the myofibroblasts migrate and align within the wound site and proliferate. Finally, the myofibroblasts contract the collagen, forming the fibrotic scar which contributes to tissue dysfunction. It is generally believed that a similar process results in scarring within tissues of the liver, kidney, lung, and skin.

VLA-1 is expressed on myofibroblasts *in vitro* and *in vivo* and is believed to regulate their pathologic functions. Alport syndrome is a genetic disorder characterized by progressive glomerulonephritis resulting in fibrosis of the kidneys and ultimately kidney failure. Alport syndrome affects approximately 1 in 5000 people and is caused by mutations in the type IV collagen genes. This condition has been mimicked in mice by knocking out the gene of the $\alpha 3$ chain of type IV collagen (Alport mouse). Double knockout mice for both type IV collagen and

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$\alpha 1$ integrin have a delayed onset and slowed progression of glomerular disease (Cosgrove et al. (2000) *Am. J. Pathol.* 157:1649). In addition, inhibition of TGF- $\beta 1$ with a soluble receptor construct had a synergistic effect with the inactivation of $\alpha 1$, slowing the onset and severity of glomerular disease. These results correlated with a dramatic decrease in the accumulation of myofibroblasts and macrophages in the tubular interstitium of double knockout mice (Sampson et al. (2001) *J. Biol. Chem.* 276:34182). Another report studying the effects of $\alpha 1$ expression in transfected glomerular mesangial cells showed that VLA-1 expression levels influenced the cell growth, cell size, and collagen matrix remodeling ability of these cells (Kagami et al. (2000) *Kidney Int.* 58:1088). In addition, $\alpha 1$ mAb blocks hepatic stellate cell adhesion to collagen and endothelin-stimulated hepatic stellate cell-mediated contraction of collagen lattices *in vitro*, and VLA-1 is the sole integrin utilized by contracting hepatic stellate cells *in vivo* (Racine-Sampson et al. (1997) *J. Biol. Chem.* 272:30911). Furthermore, blocking anti- $\alpha 1$ antibody has shown efficacy therapeutically in two independent models of fibrotic kidney disease (Kagami et al. (2002) *Lab. Invest.* 82:1219; Cook et al. (2002) *Am. J. Pathol.* 161:1265).

VLA-1 may also play a role in regulation of tumor vascularization (angiogenesis) and tumor cell metastasis in many forms of cancer. For example, VLA-1 may regulate tumor angiogenesis by two

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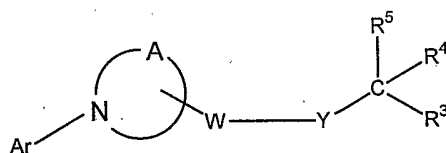
distinct mechanisms: 1) by regulating the proliferation potential of the vascular endothelial fibroblasts (Pozzi et al. (1998) *J. Cell. Biol.* 142:587; Senger et al. (2002) *Am. J. Pathol.* 160:195), and 2) by regulating the production of matrix metalloproteinase 9 which in turn regulates the activity of angiostatin, a potent angiogenesis inhibitor (Pozzi et al. (2000) *PNAS* 97:2202; Pozzi et al. (2002) *Oncogene* 21:272). Furthermore, the metastatic potential of malignant melanoma cell lines correlates with the expression level of VLA-1 (Schadendorf et al. (1996) *Br. J. Cancer* 74:194), and blocking VLA-1 binding inhibits tumor cell invasion across reconstituted basement membrane through inhibition of matrix metalloproteinase 3 (stromelysin-1) expression (Lochter et al. (1999) *Mol. Biol. Cell* 10:271).

Currently, there are only two descriptions for VLA-1 inhibitors in the patent literature, and both describe large molecular weight polypeptides. The first is a mAb to VLA-1 (WO 02/083854-A2) and the second is a disintegrin isolated from cobra venom (WO 02/22571-A2). Therefore, there still exists a need in the art for low molecular weight antagonists, specific inhibitors of VLA-1-dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties, such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention, or suppression of various pathologies mediated by VLA-1 binding and cellular adhesion, migration, activation or differentiation.

SUMMARY OF THE INVENTION

The present invention provides aryl piperidine compounds that are antagonists to the VLA-1 integrin.

5 In one of its composition aspects, this invention is directed to a compound of Formula I:



(I)

wherein Ar is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

A, together with the nitrogen atom bound thereto, forms a 4-8 membered nitrogen containing heterocyclic group containing 1 to 2 nitrogen atoms, wherein said heterocyclic group may be optionally substituted with 1 to 3 additional substituents each independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, hydroxy, alkoxy, thioalkyl, and halo,

wherein the one or more alkyl and substituted alkyl substituents, if present, may be attached to either a carbon or a nitrogen atom in said heterocyclic group,

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wherein the one or more hydroxy and alkoxy substituents, if present, may be attached to a carbon atom in said heterocyclic group,

wherein the one or more thioalkyl and the one or more halo substituents, if present, may not be attached to a nitrogen atom in said heterocyclic group,

and wherein the one or more halo, thioalkyl, and the one or more hydroxy substituents, if present, may not be attached to a carbon atom which is adjacent to a nitrogen atom in said heterocyclic group;

W is selected from the group consisting of -C(X)-NH and -NH-C(X)-, wherein X is oxygen or sulfur,

Y is selected from the group consisting of a bond, alkylene, and substituted alkylene;

R³ and R⁴ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aminocarbonyloxy, oxycarbonylamino, aminoacyl, acylamino, aminocarbonylamino, aminosulfonylamino, aminosulfonyl, sulfonylamino, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkoxy, substituted alkoxy, carboxyl, and carboxyl esters; or R³-C-R⁴ forms a cycloalkyl, substituted cycloalkyl, heterocyclic, or substituted heterocyclic group;

R⁵ is selected from the group consisting of CR^aR^aCO₂R^a, COCO₂R^a, carboxyl, carboxyl esters,

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-CONR^aOR^a, -CONR^aSO₂R^a, heterocyclic, cyano, and hydroxyalkyl; wherein R^a is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, heterocyclic (e.g., tetrazolyl), and substituted heterocyclic;

with the proviso that when Y is a bond and W is C(O)NH, then R³ and/or R⁴ are not amino, substituted amino, hydroxy, or alkoxy;

and pharmaceutically acceptable salts, prodrugs, and any and all tautomers thereof.

In a preferred embodiment of this invention, A and the nitrogen atom pendent thereto form a piperidine ring.

In another preferred embodiment, W is -C(O)-NH- or -NH-C(O)-.

In still another preferred embodiment, Y is a bond or methylene, R⁴ is hydrogen, and R⁵ is -CO₂H.

In yet another preferred embodiment, R³ is alkyl or substituted alkyl.

Particularly preferred Y groups include a bond, methylene, and substituted methylene.

Particularly preferred R³ groups include methyl, N-benzylimidazol-4-ylmethylene, and phenylacetamidomethylene.

In still another preferred embodiment, Ar is selected from the group consisting of:

5-(2,3-dichlorophenyl)pyridin-3-yl;

4-(2,3-dichlorophenyl)pyridin-2-yl;

5-(2,3-dichlorophenyl)pyridin-2-yl;

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- 3-methyl-5-(2,3-dichlorophenyl)pyridin-2-yl;
3-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl;
5 5-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl;
5-(2,3-dichlorophenyl)pyridin-2-yl;
6-methyl-3-(2,3-dichlorophenyl)phenyl;
4-(2,3-dichlorophenyl)thiazol-2-yl;
10 5-bromo-pyridin-3-yl;
pyridin-3-yl;
3-(2,3-dichlorophenyl)phenyl;
6-methyl-3-(2,3-dichlorophenyl)phenyl;
3-methylphenyl;
15 3-ethylphenyl;
3-isopropylphenyl;
3-trifluoromethylphenyl;
3-dimethylaminophenyl;
3-(4-fluorophenoxy)phenyl;
20 3-fluoro-5-trifluoromethylphenyl;
3,5-trifluoromethylphenyl;
2-methylquinolin-6-yl;
3,4-dichlorophenyl;
2,3-dichlorophenyl;
25 6,7-dichlorobenzo[b]thiophen-5-yl;
3,5-dichlorophenyl;
benzo[1,3]dioxol-6-yl;
4-t-butylphenyl;
3-chloro-6-nitrophenyl;
30 5-bromo-4-fluoro-2-nitrophenyl;
5-(N-morpholino)-2-nitro-phenyl;

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3-(trifluoromethylthio)phenyl;
 3-(trifluoromethoxy)phenyl;
 3-(trifluoromethoxy)phenyl;
 quinolin-3-yl
 5 quinolin-3-yl;
 isoquinolin-3-yl;
 isoquinolin-3-yl;
 (4-fluorophenyl)oxy)benz-3-yl;
 3-(4-fluorophenyl)oxy)ethylphenyl;
 10 quinolin-3-yl; and
 phenyl.

Aryl piperidine amide derivatives within
 the scope of this invention are exemplified by those
 set forth in Tables I and II as follows:

15

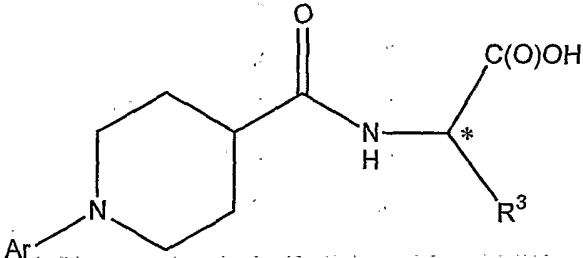
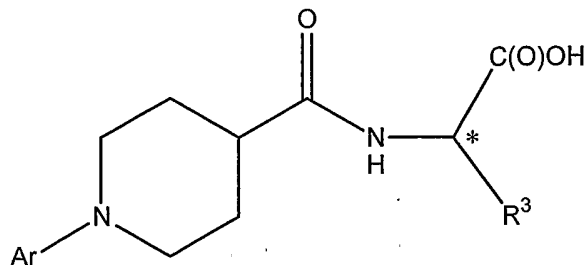
TABLE I		
		
* unless otherwise indicated, the stereochemistry at this site corresponds to L-amino acids		
Ex. No.	Ar	R ³
1	4-(2,3-dichlorophenyl)pyridin-2-yl	methyl
2	4-(2,3-dichlorophenyl)pyridin-2-yl	N-benzylimidazol-4-ylmethylene
3	5-(2,3-dichlorophenyl)pyridin-2-yl	methyl
4	3-methyl-5-(2,3-dichlorophenyl)pyridin-2-yl	methyl

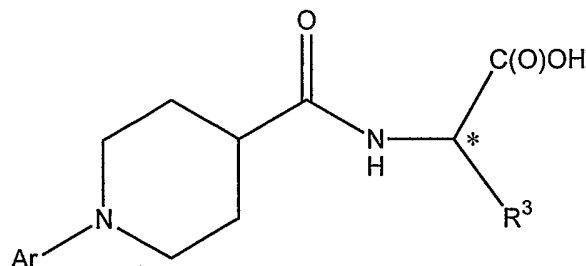
TABLE I



* unless otherwise indicated, the stereochemistry at this site corresponds to L-amino acids

Ex. No.	Ar	R ³
5	3-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl	methyl
	5-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl	
6	5-(2,3-dichlorophenyl)pyridin-2-yl	methyl
7	5-(2,3-dichlorophenyl)pyridin-3-yl	methyl
8	5-(2,3-dichlorophenyl)pyridin-3-yl	N-benzylimidazol-4-ylmethylene
9	5-(2,3-dichlorophenyl)pyridin-3-yl	phenylacetamidomethylene
10	5-bromo-pyridin-3-yl	methyl
11	5-bromo-pyridin-3-yl	phenylacetamidomethylene
12	5-bromo-pyridin-3-yl	N-benzylimidazol-4-ylmethylene
13	pyridin-3-yl	methyl
14	pyridin-3-yl	N-benzylimidazol-4-ylmethylene
17	3-(2,3-dichlorophenyl)phenyl	methyl
18	6-methyl-3-(2,3-dichlorophenyl)-phenyl	methyl
19	4-(2,3-dichlorophenyl)thiazol-2-yl	methyl
20	4-(2,3-dichlorophenyl)thiazol-2-yl	N-benzylimidazol-4-ylmethylene
21	3-methylphenyl	N-benzylimidazol-4-ylmethylene
22	3-ethylphenyl	N-benzylimidazol-4-ylmethylene
23	3-isopropylphenyl	N-benzylimidazol-4-ylmethylene
24	3-trifluoromethylphenyl	N-benzylimidazol-4-ylmethylene
25	3-dimethylaminophenyl	N-benzylimidazol-4-ylmethylene
26	3-(4-fluorophenoxy)phenyl	N-benzylimidazol-4-ylmethylene

TABLE I

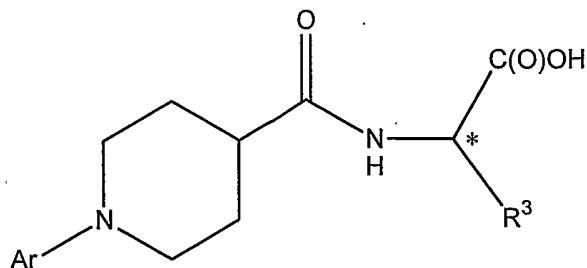


* unless otherwise indicated, the stereochemistry at this site corresponds to L-amino acids

Ex. No.	Ar	R ³
27	3-fluoro-5-trifluoromethylphenyl	N-benzylimidazol-4-ylmethylene
28	3,5-trifluoromethylphenyl	N-benzylimidazol-4-ylmethylene
29	2-methylquinolin-6-yl	N-benzylimidazol-4-ylmethylene
30	3,4-dichlorophenyl	N-benzylimidazol-4-ylmethylene
31	2,3-dichlorophenyl	N-benzylimidazol-4-ylmethylene
32	6,7-dichlorobenzo[b]thiophen-5-yl	N-benzylimidazol-4-ylmethylene
33	3,5-dichlorophenyl	N-benzylimidazol-4-ylmethylene
34	benzo[1,3]dioxol-6-yl	N-benzylimidazol-4-ylmethylene
35	4-t-butylphenyl	N-benzylimidazol-4-ylmethylene
36	3-chloro-6-nitrophenyl	N-benzylimidazol-4-ylmethylene
37	5-bromo-4-fluoro-2-nitrophenyl	N-benzylimidazol-4-ylmethylene
38	5-(N-morpholino)-2-nitro-phenyl	N-benzylimidazol-4-ylmethylene
39	3-(trifluoromethylthio)phenyl	N-benzylimidazol-4-ylmethylene
40	3-(trifluoromethoxy)phenyl	N-benzylimidazol-4-ylmethylene
41	3-(trifluoromethoxy)phenyl	phenylacetamidomethylene
42	quinolin-3-yl	N-benzylimidazol-4-ylmethylene
43	quinolin-3-yl	phenylacetamidomethylene
44	isoquinolin-3-yl	N-benzylimidazol-4-ylmethylene
45	isoquinolin-3-yl	phenylacetamidomethylene

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TABLE I

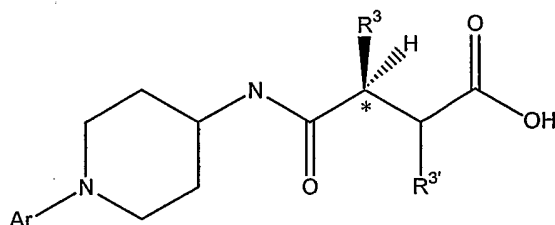


* unless otherwise indicated, the stereochemistry at this site corresponds to L-amino acids

Ex. No.	Ar	R ³
46	3-(4-fluorophenyloxymethyl)phenyl	N-benzylimidazol-4-ylmethylene
47	3-(4-fluorophenyl)oxyethylphenyl	N-benzylimidazol-4-ylmethylene
49	3-(6,7-dichlorobenzo[b]thiophen-5-yl)phenyl	N-benzylimidazol-4-ylmethylene
	4-isoxazolyl(3,5-dimethyl)-pyridin-3-yl	N-benzylimidazole-4-yl-methylene

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TABLE II



* both R and S configurations are contemplated,
though the illustrated stereoisomer is generally preferred

Ex. No.	Ar	R ³	R ^{3'}
48	quinolin-3-yl	methyl	hydrogen
15	5-(2,3-dichlorophenyl)pyridin-3-yl	methyl	hydrogen
16a	5-(2,3-dichlorophenyl)pyridin-3-yl	methyl	hydrogen
16b	5-(2,3-dichlorophenyl)pyridin-3-yl	hydrogen	methyl
	3-(6,7-dichlorobenzo[b]thiophen-5-yl)phenyl-pyridin-3-yl	methyl	hydrogen
	5-chloro-3-dimethyl-2-benzo[b]thiophen-pyridin-3yl	methyl	hydrogen

Specific compounds within the scope of
 5 this invention are exemplified by the following:
 2-([4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid;
 3-(1-Benzyl-1H-imidazol-4-yl)-2-([4'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-
 10 carbonyl]-amino)-propionic acid;
 2-([6'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid;
 2-([6'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-
 15 propionic acid;
 2-([4'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-

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propionic acid/2-{[4'-(2,3-Dichloro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

5 2-{[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[5'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

10 3-Benzoylamino-2-{[5'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-[(5'-Bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

15 3-Benzoylamino-2-[(5'-bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(5'-bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

20 2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

25 N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic acid;

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic/N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']-

30 bipyridinyl-4-yl]-2-methyl-succinamic acid;

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- 2,3-Dichloro-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid;
- 2,3-Dichloro-4'-methyl-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid;
- 5 2-({1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl}-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[4-(2,3-dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl}-amino)-propionic acid;
- 10 3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-m-tolyl-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-ethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-isopropyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 15 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-dimethyl-amino-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 20 3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluorophenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluorophenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid;
- 25 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-fluoro-5-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3,5-bis-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 30

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3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(2-methyl-quinolin-6-yl)-piperidine-4-carbonyl]-amino}-propionic acid;

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3,4-dichloro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(2,3-dichloro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

10 3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(6,7-dichloro-benzo[b]thiophen-5-yl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3,5-dichloro-phenyl)-piperidine-4-carbonyl]-amino}-propionic
15 acid;

2-[(1-Benzo[1,3]dioxol-5-yl-piperidine-4-carbonyl)-amino]-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(4-tert-butyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic
20 acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(5-chloro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(5-bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;
25

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(5-morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

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- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethylsulfanyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-Benzoylamino-2-([1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-Benzoylamino-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-Benzoylamino-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-[3-(4-fluorophenoxy)methyl]-phenyl]-piperidine-4-carbonyl)-amino)-propionic acid;
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-{3-[1-(4-fluorophenoxy)-ethyl]-phenyl}-piperidine-4-carbonyl)-amino]-propionic acid;
- 3-([5'-(1-Methyl-1H-indol-5-yl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino)-butyric acid;
- 3-Methyl-N-(1-quinolin-3-yl-piperidin-4-yl)-succinamic acid; and
- 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-[3-(6,7-dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carbonyl]-amino)-propionic acid.

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In a preferred embodiment are compounds of Formula I having an IC_{50} of less than or about 50 μM using the method described in Example A or Example B herein. In a more preferred embodiment are compounds of Formula I having an IC_{50} of less than or about 40 μM using the method described in Example A or Example B herein. In a still more preferred embodiment are compounds of Formula I having an IC_{50} of less than or about 20 μM using the method described in Example A or Example B herein.

In another aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I as defined herein.

In one of the method aspects, this invention is directed to a method for assaying a biological sample from a mammalian patient suspected of having a disease, condition, or disorder mediated, at least in part, by VLA-1, which method comprises obtaining a biological sample from said patient and assaying said sample for the presence of VLA-1.

In another aspect, this invention is directed to a method for inhibiting adhesion of mammalian cells to the extracellular matrix mediated, at least in part, by VLA-1, which method comprises contacting said cells with a compound or pharmaceutical composition of this invention.

In another one of its method aspects, this invention is directed to a method for treating a disease, condition, or disorder whose progression is

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regulated, at least in part, by VLA-1 expression or activity in a mammalian patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound or composition of this invention.

In a preferred embodiment, said disease, disorder, or condition is selected from the group consisting of asthma, trachoma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, tumor migration, and/or tumor growth, proliferation of fibroblasts in cancer, solid tumors, meningitis, encephalitis, stroke, cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia, acute leukocyte-mediated lung injury, and fibrotic diseases.

In another preferred embodiment, said disease, disorder, or condition is a fibrotic disease.

In still another preferred embodiment, said fibrotic disease is selected from the group consisting of systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, and myositis.

In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic vascular intimal hypertrophy and is selected from the group consisting of vasculitis, polyarteritis nodosa, and temporal arteritis.

In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic

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hypertrophy of skin and/or muscle tissue and is selected from the group consisting of scleroderma, eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus, and surgical adhesions.

5 In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic hypertrophy of nerve tissue and is selected from the group consisting of cerebroscclerosis, annular sclerosis, diffuse sclerosis, and lobar sclerosis.

10 In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of lung tissue and is selected from the group consisting of pulmonary fibrosis, idiopathic pulmonary fibrosis, the fibrotic element of pneumoconiosis, pulmonary sarcoidosis, fibrosing alveolitis, the fibrotic or hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, and emphysema.

20 In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of prostate, liver, the pleura, or pancreas, and is selected from the group consisting of benign prostatic hypertrophy (BPH), nonalcoholic steato hepatitis, and fibrosis of the liver.

 In yet another preferred embodiment, said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of the kidney, and is selected from the group consisting of chronic renal fail-

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ure, lupus nephritis, alport syndrome, glomerulo-nephritis, and diabetic nephritis.

In another preferred embodiment, the invention is directed to a method for ameliorating
5 cancers whose progression is regulated, at least in part, by VLA-1 expression or activity in a mammalian patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound or composition of this invention.

10 In a preferred embodiment, said cancer is a tumor or a neoplasm selected from the group consisting of carcinomas, adenocarcinomas, and sarcomas.

In another preferred embodiment, said cancer is selected from the group consisting of growth
15 of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, human soft tissue carcinoma, cancer metastases, squamous cell carcinoma, esophageal squamous cell carcinoma, oral
20 carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, non-small cell cancers, breast cancer, gastrointestinal cancers, urological cancers, malignancies of the female genital
25 tract, malignancies of the male genital tract, kidney cancer, brain cancer, bone cancers, skin cancers, thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer,
30 trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

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In still yet another preferred embodiment, said cancer is a cell proliferative disorder, and is selected from the group consisting of angiogenesis-mediated diseases, benign tumors, acoustic neuromas, neurofibromas, pyogenic granulomas, biliary tract cancer, choriocarcinoma, esophageal cancer, gastric cancer, intraepithelial neoplasms, lung cancer, and neuroblastomas.

A compound or composition of this invention may be administered to the mammal by any suitable route, such as orally, intravenously, parenterally, transdermally, topically, rectally, or intranasally.

Mammals include, for example, humans and other primates, pet or companion animals, such as dogs and cats, laboratory animals, such as rats, mice and rabbits, and farm animals, such as horses, pigs, sheep, and cattle.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Overview

As discussed above, the present invention is directed to novel aryl piperidine derivatives.

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to limit the scope of the present invention. It must be noted that as used herein and in the claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates other-

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wise. In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

5 As used herein, "alkyl" refers to monovalent alkyl groups having from 1 to 10 carbon atoms, and more preferably 1 to 6 carbon atoms, even more preferably 1 to 4 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl, and the like.

 "Substituted alkyl" refers to an alkyl group having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, 15 aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxy, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, thiol, thioalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and 20 oxycarbonylamino.

 "Hydroxyalkyl" refers to an alkyl group having from 1 to 3 hydroxy substituents provided that there is no more than one hydroxy group per 25 carbon atom.

 "Hydroxy" refers to the group -OH.

 "Alkylenes" refers to divalent alkylenes groups having from 1 to 10 carbon atoms, and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene, n-heptylene, 30 1,3-octylene, and the like.

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"Substituted alkylene" refers to an alkylene group as defined above substituted with from 1 to 3 substituents as described for substituted alkyl.

5 "Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

10 "Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-.

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and where each R is optionally joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring.

30 "Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, aryl-C(O)O-, substituted

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aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O-.

5 "Alkenyl" refers to monovalent alkenyl groups having from 2 to 10 carbon atoms, and more preferably 2 to 6 carbon atoms, and having at least 1 site, and preferably from 1-2 sites, of alkenyl unsaturation.

10 "Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, 15 aryl, substituted aryl, aryloxy, substituted aryl-oxy, cyano, halogen, hydroxy, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, thiol, thioalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and 20 oxycarbonylamino, provided that the hydroxy or the thio group is not pendent to an unsaturated carbon atom.

"Amino" refers to the group -NH₂.

"Substituted amino" refers to the group 25 -NRR where each R is independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where 30 each R is optionally joined to form together with the nitrogen atom a heterocyclic or substituted

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heterocyclic ring provided that both R groups are not hydrogen.

"Aminoacyl" refers to the groups -NRC(O)-alkyl, -NRC(O)substituted alkyl, -NRC(O)alkenyl, 5 -NRC(O)substituted alkenyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic, where R is hydrogen or 10 alkyl.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-substituted aryl, -NRC(O)O-het- 15 eroaryl, -NRC(O)O-substituted heteroaryl, -NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic, where R is hydrogen or alkyl.

"Aminosulfonyl" refers to the group -SO₂Q where Q is amino or substituted amino, as defined 20 herein.

"Aminosulfonylamino" refers to the group QSO₂Q where each Q is independently amino or substituted amino, as defined herein.

"Oxycarbonylamino" refers to the group 25 -OC(O)Q where Q is amino or substituted amino, as defined herein.

"Aminocarbonylamino" refers to the group -QC(O)Q where each Q is independently amino or substituted amino, as defined herein.

30 "Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon

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atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7yl, and the like) provided that the point of attachment is on an aromatic carbocyclic group atom. Preferred aryls include phenyl and naphthyl.

"Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, amino, substituted amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, carboxyl, carboxyl esters, cyano, thiol, thioalkyl, substituted thioalkyl, cycloalkyl, substituted cycloalkyl, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Carboxyl" refers to the group -COOH, and salts thereof.

"Carboxyl esters" refer to the group -COOR where R is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, carboxyl-substituted

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heteroaryl, heterocyclic, and substituted heterocyclic.

"Cycloalkyl" refers to monovalent cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like.

"Substituted cycloalkyl" refers to a cycloalkyl, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the same group of substituents as defined for substituted alkyl as well as oxo (=O) and thioxo (=S) groups.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo, and preferably is fluoro, chloro, or bromo.

"Heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizyl or benzothienyl) provided that the point of attachment is to a heteroaryl group atom and further provided that the heteroaryl group contains five ring atoms. Preferred heteroaryls include pyridyl, pyrrolyl, indolyl, and furyl.

"Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group of substituents defined for substituted aryl.

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"Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated, but not aromatic, group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms, and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl, provided that the heterocyclic ring has at least 4 atoms and further provided that the point of attachment is to a heterocyclic ring atom.

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group of substituents defined for substituted cycloalkyl.

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranlyl, and the like.

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"Thiol" refers to the group -SH.

"Thioalkyl" refers to the group -S-alkyl.

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

5 "Sulfonylamino" refers to the group QSO₂ where Q is amino or substituted amino, as defined herein.

10 "Tautomers" refers to chemical compounds that exist as a mixture of two interconvertible isomers in equilibrium.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, 15 potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate, 20 and the like.

"Prodrugs" as used herein, are compounds which convert (e.g., hydrolyze, metabolize, etc.) *in vivo* to a compound of the invention. The effectiveness of an orally administered drug is dependent 25 upon the drug's efficient transport across the mucosal epithelium and its stability in entero-hepatic circulation. Drugs that are effective after parenteral administration but less effective orally, or 30 whose plasma half-life is considered too short, may be chemically modified into a prodrug form. A pro-

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drug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other *in vivo* processes to the parent bioactive form. The prodrug should have a pharmacokinetic profile that is different from that of the parent, enabling easier absorption across the mucosal epithelium, better salt formulation and/or solubility, and or improved systemic stability (for an increase in plasma half-life, for example). Many chemical modifications may be suitable for the creation of prodrugs according to the invention, including:

(1) Ester or amide derivatives which may be cleaved by, for example, esterases or lipases. For ester derivatives, the ester is derived from the carboxylic acid moiety of the drug molecule by known means. For amide derivatives, the amide may be derived from the carboxylic acid moiety or the amine moiety of the drug molecule by known means.

(2) Peptides that may be recognized by specific or nonspecific proteinases. A peptide may be coupled to the drug molecule via amide bond formation with the amine or carboxylic acid moiety of the drug molecule by known means.

(3) Derivatives that accumulate at a site of action through membrane selection of a prodrug form or modified prodrug form.

(4) Any combination of 1 to 3.

It will further be appreciated by those skilled in the art that certain moieties known to

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those skilled in the art as "pro-moieties," for example as described in Bundgaard, (1985) *Design of Prodrugs* (Elsevier), may be placed on appropriate functionalities when such functionalities are present in compounds of the invention also to form a "prodrug." Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives, and prodrugs, of the compounds of the invention are included within the scope of the invention.

The terms "substituted" as used with, for example, "substituted alkyl" does not include polymers derived therefrom but are limited to a maximum of 3 substituents groups, e.g., alkyl-Ar-Ar-Ar.

15 Compound Preparation

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups

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may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and

5 deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in Greene and Wuts, (1991) *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, and references cited therein.

10 Furthermore, the compounds of this invention may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as

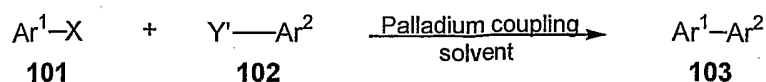
15 stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active

20 starting materials or stereoselective reagents well known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

25 Compounds in the present invention may be better understood by the following synthetic Schemes that illustrate methods for the synthesis of compounds of the invention.

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Scheme 1

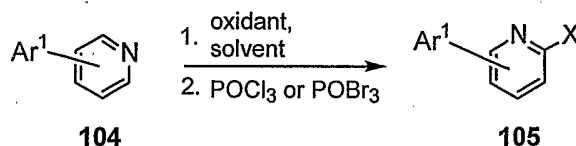


Scheme 1 above, wherein Ar¹, Ar² can be aryl, substituted aryl, heteroaryl, or substituted aryl, describes the synthesis of a typical substituted biaryl, compound 103, via palladium coupling. Such biaryls are useful starting materials for the preparation of compounds of formula I above where Ar is Ar¹-Ar². The coupling (Suzuki et al. (1995) *Chem. Rev.* 95:457; *Org. React.* (1997) 50:1) can be performed using compound 101, wherein X is a halogen, (e.g., 3-chloroiodo-benzene or 2-chloropyridine or the like) and compound 102, wherein Y' is a boronic acid, boronic ester, or an organo stannane of an aryl, substituted aryl, heteroaryl, and substituted heteroaryl (e.g., 3-nitrophenylboronic acid or 2-tributylstannyl pyridine) in the presence of a base (e.g., cesium carbonate or tripotassium phosphate) in a nonprotic solvent (e.g., dioxane, DME, toluene) or protic solvent (e.g., DMF, acetone/water), together with a palladium catalyst (e.g., Pd(PPh₃)₄, Pd₂(dba)₃, Pd(OAc)₂). This reaction is run at a temperature of about 25°C to about 90°C for a time sufficient for the reaction to go to completion, typically about 1 to about 12 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation

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and/or purification. The reaction also can be performed in the reverse direction by switching the halide and transition metal of the aryl groups.

Scheme 2



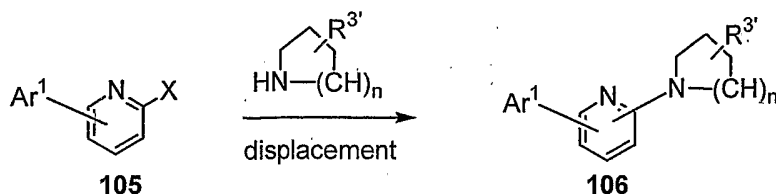
Scheme 2, for illustrative purposes only, describes how a halopyridine such as compound 105, can be synthesized by treating a pyridine biaryl compound useful in the preparation of compounds of formula I, for example compound 104, with an oxidizing agent (e.g., *m*-CPBA, hydrogen peroxide, etc.), in a suitable solvent (e.g., DCM, DCE, CCl₄). The *N*-oxide intermediate is then reacted with a phosphorus oxyhalide (e.g., POCl₃, POBr₃) to furnish the halopyridine. The halopyridine of this reaction may be optionally substituted with substituents suitable for use in the subsequent reactions. Step 1 of the reaction shown in Scheme 2 is run at a temperature of about -10°C to about 30°C for a time sufficient for the reaction to go to completion, typically about 1 to about 18 hours. Step 2 of the reaction shown in Scheme 2 is run at a temperature of about 25°C to about 90°C for a time sufficient for the reaction to go to completion, typically about 1 to about 18 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and

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the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

Scheme 3



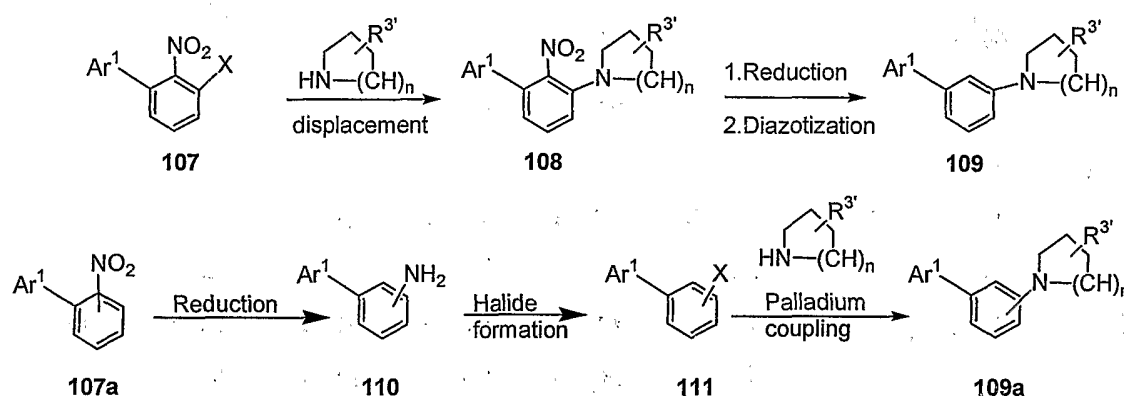
In scheme 3 above, Ar¹ is defined above, R^{3'} is either a carboxylic acid with a suitable protecting group (OCOPg, where Pg may be alkyl, or more specifically, *t*-butyl) or an amine with a suitable protecting group (NHPg*, where Pg* may be boc, cbz, or fmoc), n is 0 to 4, and the halopyridine may be optionally substituted with substituents suitable for use in the subsequent reaction. Scheme 3 illustrates a method for converting a halopyridine, such as compound 105, [e.g., 2-(4-methoxyphenyl)pyridine], to a 2-aminopyridine, compound 106, through a melt reaction using various amines (e.g., ethyl or methyl isonipecotate or 4-(*t*-butyloxycarbonylamino)piperidine or methyl azetidine-3-carboxylate). This reaction is typically run neat, preferably using an excess of amine, at a suitable temperature, from about 25°C to about 90°C in an inert atmosphere in a closed tube. The reaction is run for a time sufficient for the reaction to go to completion, typically about 1 to 50 hours. The product can be recovered using standard techniques such as filtra-

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tion, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

5

Scheme 4



In Scheme 4 above, Ar¹, R^{3'}, n, and X are defined above and the phenyl group is further optionally substituted with a group suitable for use in subsequent reactions. As shown, substituted nitrohaloarene analogs, such as compound 107, can be reacted with various amines (ethyl or methyl isonipecotate or 4-(*t*-butyloxycarbonyl-amino) piperidine or methyl azetidine-3-carboxylate, etc.) to form the nitro aniline compound 108. This reaction is typically run neat, preferably using an excess of amine, at a suitable temperature, from about 25°C to about 90°C. The reaction is run for a time sufficient for the reaction to go to completion, typically about 1 to about 20 hours. The product can be recovered using standard techniques such as filtra-

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tion, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

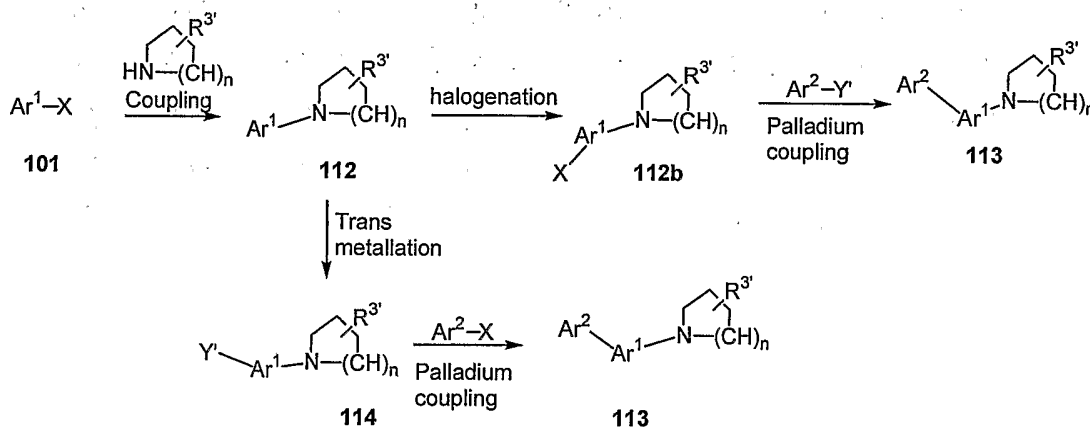
5 The nitro group of compound 108 may be reduced to form the aniline, (compound not shown), using a suitable reducing conditions (e.g., zinc in acetic acid or $\text{FeSO}_4 \cdot (\text{H}_2\text{O})_7$ in THF) followed by formation of a diazo salt (NaNO_2 , sulfuric acid, or
10 HNO_2). The resulting diazonium salt may be reduced (H_3PO_4 or HMPA in ethanol or sodium stannite, see Ruchardt et al. (1977) *Chem. Ber.* 110:2494) to the hydrido product compound 109. This reaction is run at a temperature of about 0° to about 90°C for a
15 time sufficient for the reaction to go to completion, typically about 1 to 24 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may
20 be used in the next step without further isolation and/or purification.

 Biaryl halides, such as compound 111, (2,3-methyl-3'-iodo-biphenyl, etc.) can also be synthesized from biaryl nitro compounds, such as
25 compound 107a, (e.g., 2,3-dichloro-3'-nitro-biphenyl, and the like). Reduction of the nitro group of compound 107a leads to an aniline derivative, compound 110. This intermediate can then be converted to an aryl halide, such as compound 111, by first
30 converting the aniline to a diazo salt by the method described above, followed by displacement with a

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halide such as NaI or CuBr₂ (*J. Chem. Soc., Perkin Trans. 1* (1987) 645). Furthermore, halopyridines, such as compound 105, or aryl halides such as compound 111, (e.g., 3 bromobiphenyl, 2,3-dichloro-3'-iodo-biphenyl, 2-chloro-4-(*m*-tolyl)-pyridine)), can be converted to various substituted aminoaryls, such compounds 106, 109, 109a, (and, as illustrated in Scheme 5 below, compound 112) by a palladium mediated coupling (WO 00/39081; Old et al. (1998) *J. Am. Chem. Soc.* 120(91):9122; Prim et al. (2002) *Tetrahedron* 58:2041). The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

Scheme 5

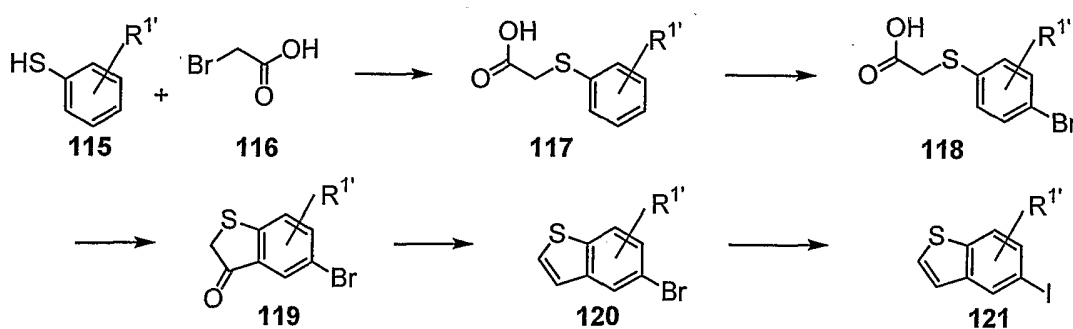


Alternatively the coupling partners can be reversed, as shown in Scheme 5 above, wherein Ar¹, Ar², R^{3'}, n, X, and Y' are defined herein above. The coupling can be performed as described in Schemes 3

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and 4 to give compound 112. Compound 112 may be halogenated by using techniques described herein and/or by methods well known in the art, to give compound 112a, where Y' is a boronic acid, boronic ester, or an organo stannane. Furthermore, compound 112a can be coupled to Ar²-Y' when Y' is a boronic acid, boronic ester, or an organo stannane via copper mediated Chan-Lam coupling (see Lam et al. (2002) *Tetrahedron Lett.* 43:3091; Chan et al. (2003) *Tetrahedron Lett.* 44:3863). A second palladium coupling (as indicated in Scheme 1) can provide compound 113 from compound 112a. Alternatively, compound 112 may be transmetallated to give compound 114, (Miyaura et al. (1995) *J. Org. Chem.* 60:7508-7510), which can then be coupled as in Scheme 1 to other aromatic halides to give compound 113. The above reactions are run under conditions described herein or using techniques well known in the art.

Scheme 6



Substituted benzothiophenes were synthesized according to Scheme 6. One method entails the alkylation of bromoacetic acid compound 116 with

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substituted thiophenols compound 115 (3-methyl thiohenol, 2,3-dichloro thiophenol, etc.) in aqueous solvent and in the presence of a base (NaOH, Cs₂CO₃, and the like) to afford compound 117.

5 Bromination (e.g., using iron filings and Br₂, or CuBr₂) in acidic solvent (e.g., acetic acid) then affords compound 118. The reaction is typically performed at room temperature for 1 to 96 hours.

The carboxylic acid is activated, for
10 example by conversion to the corresponding acid chloride (thionyl chloride, oxalyl chloride, or the like, with catalytic DMF in a halogenated solvent, e.g., DCM, DCE) at a temperature in the range of 0°C to 110°C for about 1 to 48 hours. The volatiles are
15 then removed under reduced pressure and the residue is dissolved in an appropriate solvent, typically dichloromethane, and subjected to Friedel-Crafts cyclization to afford ketone compound 119 by treatment with a Lewis acid such as AlCl₃ or polyphosphoric acid. The reaction is generally carried out
20 at -78°C to 25°C.

Reduction of the ketone is afforded by a reducing agent (NaBH₄, LiAlH₄, or DIBAL-H, or the like), in a solvent such as ethanol, at a temperature of about -10°C to about 10°C for a period of
25 time sufficient for completion of the reaction. The intermediate alcohol is eliminated to benzothiophene compound 120 using techniques well known in the art. The product can be recovered using standard techniques such as filtration, chromatography, distilla-
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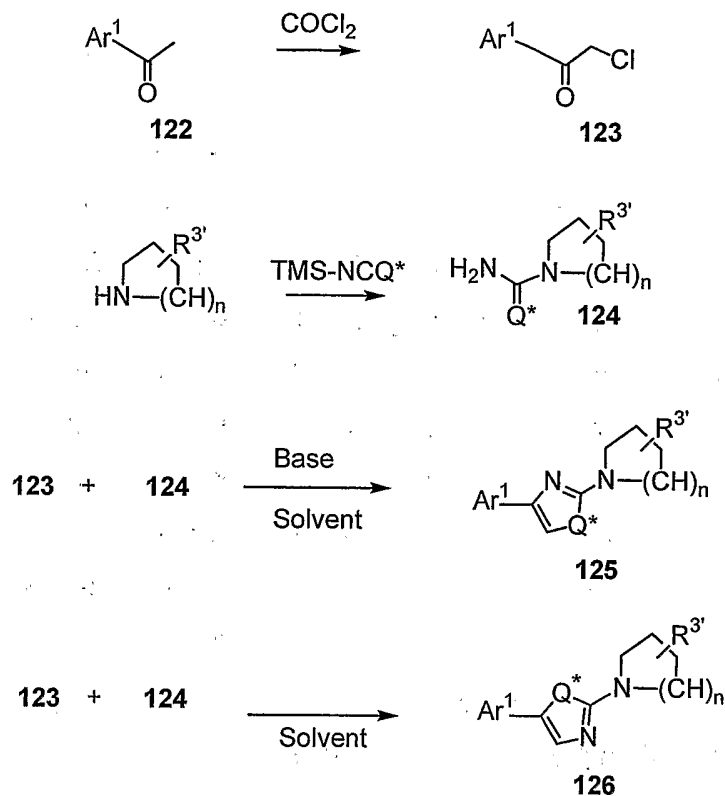
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tion, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

In order to increase the reactivity of the
5 aryl halide towards palladium coupling reactions,
the bromide can be converted to the corresponding
iodide compound 121 (Buchwald et al. (2002) *J. Am.*
Chem. Soc. 124:14844-14845). The product can be re-
covered using standard techniques such as filtra-
10 tion, chromatography, distillation, extraction, and
the like. Alternatively, the product may be used in
the next step without further isolation and/or pur-
ification.

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Scheme 7



A process for preparing substituted heteroaryl derivatives is illustrated in Scheme 7, following a Hantzsch type synthesis (Beugelmans et al. (1996) *J. Org. Chem.* 61:778), wherein Ar¹, R^{3'}, and n are defined herein above, and Q* is sulfur or oxygen. The starting aryl ketone compound 122 is chlorinated by reaction with oxalyl chloride in toluene yielding compound 123. This reaction is run at a temperature of about 0°C to about 90°C for a time sufficient for the reaction to go to completion, typically about 1 to 24 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extrac-

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tion, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

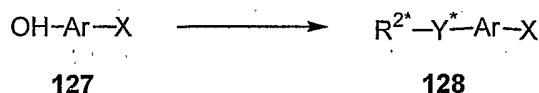
Ureas, such as compound 124, can be synthesized by reaction of an amine (e.g., ethyl or methyl isonipecotate or 4-(*t*-butyloxy-carbonyl-amino)piperidine or methyl azetidine-3-carboxylate, etc.) with (trimethylsilyl) isocyanate or trimethylsilylisothiocyanate in an aprotic solvent (e.g., DCM, toluene). This reaction is run at a temperature of about 0°C to about 90°C for a time sufficient for the reaction to go to completion, typically about 1 to 24 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

Combination of compounds 123 and 124 in the presence of base (LiHMDS, NaH, or the like) results in heteroaryl compounds such as compound 125. When they are combined in the absence of base, heteroaryl compounds analogs such as compound 126 are formed. In either case the reactions are run at a temperature of about 0°C to about 90°C for a time sufficient for the reaction to go to completion,

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typically about 1 to 24 hours. The products can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

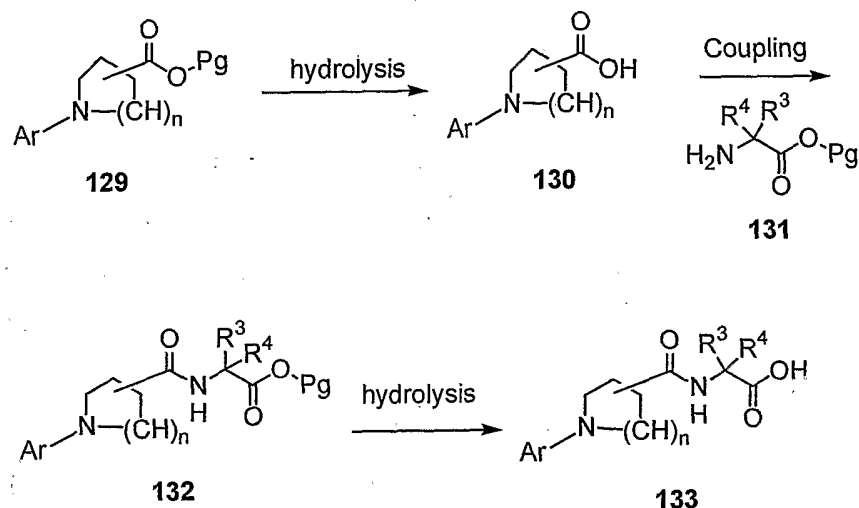
Scheme 8



Scheme 8 illustrates the synthesis of substituted arylethers, arylthioethers and amino derivatives such as compound 128; wherein X is as defined herein, Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, R^{2*} is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Y* is NH, O or S. The Mitsunobu procedure can be utilized on compounds such as compound 127, which are prepared from the corresponding optional substituted Ar-X (Mitsunobu et al. (1967) *Bull. Chem. Soc. Jpn.* 40:2380; Camp et al. (1989) *J. Org. Chem.* 54:3045 and 3049) to furnish substituted aryl ethers such as compound 128.

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Scheme 9



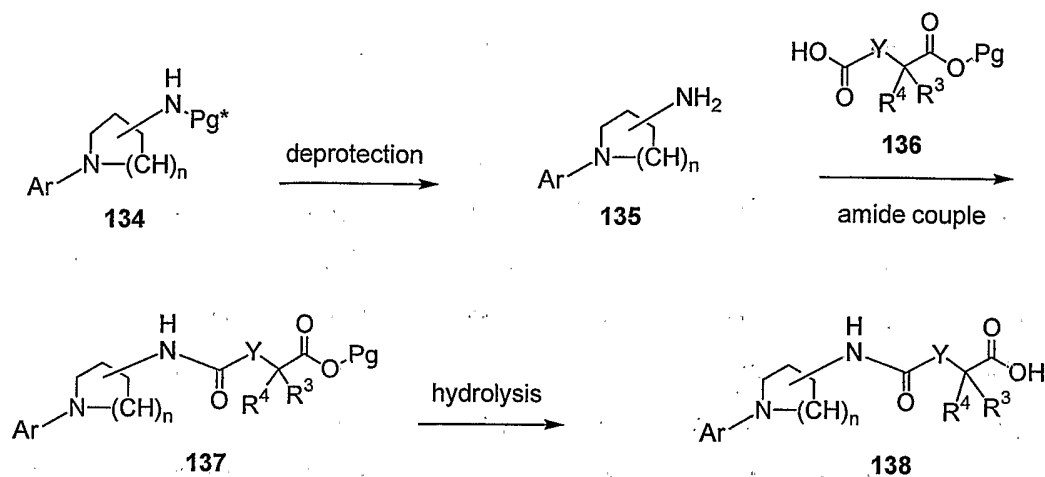
As illustrated in Scheme 9, (wherein Ar, R³, R⁴, and n are as herein defined above, and Pg is a suitable protecting group for a carboxylic acid such as alkyl (e.g., methyl)), hydrolysis of the ester of compound 129 (e.g., compound 113 from Scheme 5), using LiOH or NaOH, or the like, in an aqueous solvent (water-THF, etc.) afforded the carboxylic acid compound 130. This reaction is run at a temperature of about 0°C to about 30°C for a time sufficient for the reaction to go to completion, typically about 1 to 12 hours. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

To prepare coupled amide compounds such as compound 132, amino acid derivatives such as compound 131 are coupled to the carboxylic acids, com-

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pound 130, in an inert solvent (DCM, THF, DMF or the like) using any of a wide variety of well known coupling agents. Suitable coupling agents include, but are not limited to, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP), and diethylcyanophosphate (DECP). Additionally, well known coupling promoters (for example 1-hydroxybenzotriazole (HOBt), *N*-hydroxysuccinimide, and the like) may be used to optimize the yield. Furthermore, the acid may be coupled utilizing solid support resins such as 1% cross linked polystyrene tetrafluoro phenol (PS-TFP), polystyrene dicyclohexylcarbodiimide (PS-DCC) or polystyrene 1-hydroxybenzotriazole (PS-HOBT) by the use of one of the listed coupling reagents in the presence of a base (4-dimethylamino pyridine, triethyl amine, etc.) and solvent (DMF, methylene chloride.) The resin bound acid can then be reacted with a range of amines to furnish the corresponding amide. The coupled amide compound 132 is then subjected to basic hydrolysis conditions listed above to afford the final acid compound 133. The product can be recovered using standard techniques such as filtration, chromatography, distillation, extraction, and the like. Alternatively, the product may be used in the next step without further isolation and/or purification.

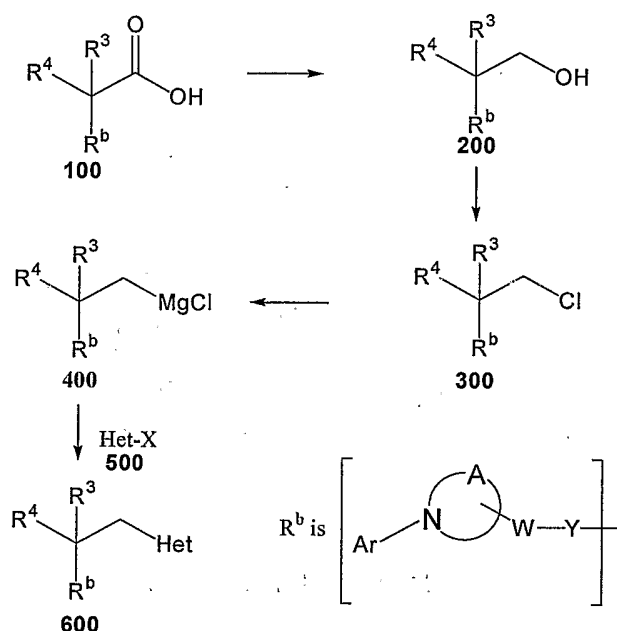
Scheme 10



Scheme 10 depicts the preparation of reversed amide analogs, wherein Ar, R³, R⁴, n, Pg and Pg* are as defined herein above. The protecting group Pg* on the protected amine, compound 134, (also compound 112 or compound 113 from Scheme 5 wherein R^{3'} is an amine protected with a suitable protecting group such as Boc, Cbz, Fmoc, trifluoroacetamide, or the like), is removed using conditions suitable for the protecting group, to afford the amine compound 135. Amine compound 135 is then coupled using conditions listed above to an acid, compound 136, to provide for the amide compound 137. The ester of the resulting amide compound 137 is then hydrolyzed using conditions listed above to yield the acid, compound 138.

Conversion of a methylene carboxylic acid to the corresponding ethylene heteroaryl derivative can be accomplished by well known techniques an example of which is provided in Scheme 11 below:

Scheme 11



Specifically, in Scheme 11 above, (wherein R^3 , R^4 , Y, W, A, Ar and X are as defined herein above, and HET is heteroaryl or substituted hetero-aryl), the carboxyl group of compound 100 is reduced using conventional techniques such as the use of a conventional reducing agent including, for example, lithium aluminum hydride to provide for the corresponding alcohol, compound 200. The reaction is preferably conducted in an inert diluent such as tetrahydrofuran, diethyl ether, and the like at a temperature preferably from about -78°C to about 25°C . The reaction is continued until substantial completion which typically occurs from within 0.5 to 18 hours. Upon completion of the reaction, compound 200 can be recovered by conventional methods including neutralization, extraction, precipitation, chro-

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matography, filtration, and the like or used in the next step of the reaction without purification and/or isolation.

The alcohol, compound 200, is converted to a halo group (e.g., chloro) again by conventional methods such as contact with a suitable halogenating agent to provide for compound 300. Suitable halogenating agents include, for example, inorganic acid halides, such as thionyl chloride, phosphorous tri-
chloride, phosphorous tribromide or phosphorous
pentachloride, under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent,
such as dichloromethane or carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, such as DMF, may also be used in this reaction. Upon completion of the reaction, compound 300 can be recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like or used in the next step of the reaction without purification and/or isolation.

The conversion of compound 300 into a Grignard reagent, compound 400, follows conventional techniques well documented in the literature including Gutsche et al. (1975) *Fundamentals of Organic Chemistry*, Prentice Hall, p. 238 et seq. Specifically, at least an equimolar amount of metallic magnesium is added to compound 3 in a suitable inert diluent such as diethyl ether to form the Grignard

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reagent, compound 400. This compound, typically in a single reaction vessel, is reacted with at least an equimolar equivalent of a heteroaryl or heterocyclic halide, i.e., Het-X (compound 500) to provide
5 for compound 600. Transition-metal catalysts may be used to facilitate this transformation, for example using copper(I) (e.g., copper(I) iodide, copper(I)-bromide dimethylsulfide complex) or palladium complexes.

10 Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of the subject invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of
15 routes including oral, parenteral, transdermal, topical, rectal, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at
20 least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the subject invention above associated with pharmaceutically
25 acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper, or other con-

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tainer. The excipient employed is typically an excipient suitable for administration to human subjects or other mammals. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

15 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

25 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose.
30 The formulations can additionally include: lubri-

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cating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and
5. flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

10 The quantity of active component, that is the compound according to the subject invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the
15. particular compound and the desired concentration.

 The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, usually, about 5 to about 100 mg, occasionally about 10 to about 30 mg, of the
20 active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired
25 therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the subject invention above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than
30 about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

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The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the severity of the condition being treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

In therapeutic use for treating, or combating, inflammation in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered by any appropriate route, such as orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment that will be therapeutically effective. Generally, such therapeutically effective amount of dosage of active component (i.e., an effective dosage) will be in the range of about 0.1 to about 100, more preferably about 1 to about 50, mg/kg of body weight/day.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions

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as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

10 The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

25 The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil,

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sesame oil, coconut oil, or peanut oil, as well as elixirs, and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

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The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

5 **Formulation Example 2**

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/capsule)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

10 The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

15 A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

20 The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

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Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

5 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50°C to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

20 Capsules, each containing 40 mg of medication are made as follows:

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Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, starch and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

10.

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

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Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

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Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

15

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

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Formulation Example 9

A subcutaneous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11

An intravenous formulation may be prepared as follows:

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Ingredient	Quantity
Active Ingredient	250 g
Isotonic saline	1000 mL

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble

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drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

10 Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, (1985), Seventeenth Edition, Mack Publishing Company, Philadelphia, PA.

As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to enhance the *in vivo* serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka et al. U.S. Patent Nos. 25 4,235,871; 4,501,728; and 4,837,028, each of which is incorporated herein by reference.

Utility

The compounds and/or compositions of this invention can be employed to bind VLA-1 in biolog-

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ical samples, for instance in mammalian patients suspected of having a disease, condition, or disorder mediated, at least in part, by VLA-1. Accordingly, these compounds have utility in, for example, assaying such samples for VLA-1 mediated adhesion.

In addition, it is contemplated that compounds of this invention and/or pharmaceutical compositions thereof inhibit, *in vivo*, adhesion of mammalian cells to the extracellular matrix mediated, at least in part, by VLA-1 and; accordingly, can be used in the treatment, prevention, or amelioration of diseases, conditions, or disorders whose progression or symptoms is regulated, at least in part, by VLA-1 expression or activity. Such diseases, conditions, or disorders include, but are not limited to, inflammatory diseases, fibrotic diseases, and cancer.

For example, diseases, conditions, and disorders which are expected to be treatable by the compounds and/or compositions of the present invention include, but are not limited to, asthma, trachoma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, migration, and/or growth (including angiogenesis), proliferation of fibroblasts in cancer, solid tumors, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myo-

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cardial ischemia, acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome, and fibrotic diseases, such as fibrotic diseases of the lung, kidney, liver, and vasculature (including idiopathic pulmonary fibrosis, systemic sclerosis, glomerulonephritis, chronic hepatitis, chronic renal failure, and nonalcoholic steatohepatitis).

Fibrotic diseases which are expected to be treatable by the compounds and/or compositions of the present invention include systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, myositis (e.g., polymyositis, primary idiopathic polymyositis, childhood polymyositis, dermatomyositis, childhood dermatomyositis, primary idiopathic dermatomyositis in adults, inclusion body myositis, polymyositis or dermatomyositis associated with malignant tumors). Dermatomyositis can be associated with fibrosing or hypertrophic aspects, including fibrosing alveolitis and pulmonary fibrosis. Treatment using the compounds or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases. Amelioration includes reducing the rate of progression of a disease.

Among these fibrotic diseases are diseases that have as a manifestation fibrotic vascular intimal hypertrophy. These diseases include vasculitis (including coronary artery vasculitis), polyarteritis nodosa, or temporal arteritis. Treatment

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using the compounds or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate vascular intimal hypertrophy in such diseases.

5 These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of skin and/or muscle tissue. These diseases include scleroderma, eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus, or surgical adhesions. Treatment using the compounds or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such indications, or hypertrophy or fibrosis of skin or muscle tissue.

15 Fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of nerve tissue. These diseases include cerebro sclerosis, annular sclerosis, diffuse sclerosis, and lobar sclerosis. Treatment using the compounds or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy, or fibrosis of nerve tissue in such diseases.

 These fibrotic diseases further include fibrotic lung diseases that have as a manifestation fibrotic hypertrophy or fibrosis of lung tissue. These diseases include pulmonary fibrosis (or interstitial lung disease or interstitial pulmonary fibrosis), idiopathic pulmonary fibrosis, the fibrotic element of pneumoconiosis (which is associated with exposure to environmental hazards such as smoking,

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asbestos, cotton lint, stone dust, mine dust and other particles), pulmonary sarcoidosis, fibrosing alveolitis, the fibrotic or hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, and emphysema. Treatment using the compounds or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Such fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy or fibrosis of prostate, liver, the pleura (e.g., pleurisy, pleural fibrosis), or pancreas.

These diseases include benign prostatic hypertrophy (BPH), nonalcoholic steato hepatitis, and fibrosis of the liver. Treatment using the compounds and/or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy or fibrosis of the kidney, such as chronic renal failure, lupus nephritis, alport syndrome, glomerulonephritis, and diabetic nephritis. Treatment using the compound or compositions of the present invention is expected to treat, prevent, reduce, or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy, or fibrosis of the kidney.

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Cancers which are expected to be treatable by the compounds or compositions of the present invention typically occur in mammals. Mammals include, for example, humans and other primates, pet or companion animals, such as dogs and cats, laboratory animals, such as rats, mice and rabbits, and farm animals, such as horses, pigs, sheep, and cattle.

Tumors or neoplasms include growths of tissue cells in which the multiplication of the cells is uncontrolled and progressive. Some such growths are benign, but others are termed "malignant" and can lead to death of the organism. Malignant neoplasms or "cancers" are distinguished from benign growths in that, in addition to exhibiting aggressive cellular proliferation, they can invade surrounding tissues and metastasize. Moreover, malignant neoplasms are characterized in that they show a greater loss of differentiation (greater "dedifferentiation") and organization relative to one another and to surrounding tissues. This property is called "anaplasia."

Tumors or neoplasms which are expected to be treatable by the compounds or compositions of the present invention include, but are not limited to, solid tumors, i.e., carcinomas, adenocarcinomas, and sarcomas. Carcinomas include those malignant neoplasms derived from epithelial cells which infiltrate (invade) the surrounding tissues and give rise to metastases. Adenocarcinomas are carcinomas derived from granular tissue, or from tissues which

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form recognizable glandular structures. Another broad category of cancers includes sarcomas, which are tumors whose cells are embedded in a fibrillar or homogenous substance like embryonic connective tissue.

VLA-1 may be associated with adult and pediatric oncology in various forms of cancer, for example, growth of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, human soft tissue carcinoma (including Ewing's sarcoma), cancer metastases (including lymphatic metastases), squamous cell carcinoma (particularly of the head and neck), esophageal squamous cell carcinoma, oral carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, non-small cell cancers, breast cancer (including small cell carcinoma and ductal carcinoma), gastrointestinal cancers (including stomach cancer, colon cancer, colorectal cancer, polyps associated with colorectal neoplasia, pancreatic cancer and liver cancer), urological cancers (including bladder cancer, especially primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer and prostate cancer), malignancies of the female genital tract (including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer, and solid tumors in the ovarian follicle), malignancies of the male genital

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tract (including testicular cancer and penile cancer), kidney cancer (including renal cell carcinoma), brain cancer (including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas and metastatic tumor cell invasion in central nervous system), bone cancers (including osteomas and osteosarcomas), skin cancers (including malignant melanoma, tumor progression of human skin keratinocytes and squamous cell cancer), thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma. Cancers and other cell proliferative disorders treatable by the compounds or compositions of the present invention also include angiogenesis-mediated diseases, benign tumors (e.g., hemangiomas), acoustic neuromas, neurofibromas, pyogenic granulomas, biliary tract cancer, choriocarcinoma, esophageal cancer, gastric cancer, intraepithelial neoplasms, lung cancer, and neuroblastomas.

The biological activity of the compounds identified above may be assayed in a variety of systems. For example, extracellular matrix, such as collagen IV, can be immobilized on a solid surface and adhesion of cells expressing VLA-1 can be measured in the presence or absence of compound. Using such formats, large numbers of compounds can be screened. Cells suitable for this assay include smooth muscle cells, microvascular endothelial cells, fibroblasts, osteoblasts, chondrocytes, and

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activated cells of the immune system including effector T cells, macrophages, and NK cells. A number of transfected cell lines can also be used, including, for example, CHO, K562, and the like.

5 The compounds and compositions of the invention can also be tested for the ability to inhibit binding between VLA-1 and extracellular matrix such as collagen IV, or between VLA-1 and a labeled compound known to bind VLA-1 such as a compound and/or composition of this invention or antibodies to VLA-1. In these assays, the extracellular matrix can be soluble or immobilized on a solid surface. VLA-1 may also be expressed as a recombinant fusion protein having acidic and basic leucine-zipper tails so that binding to extracellular matrix may be detected in an immunoassay.

Many assay formats employ labeled assay components. The labeling systems can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labeled by any one of several methods. The most common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P labeled compounds, and the like. Nonradioactive labels include europium, as well as ligands which bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labeled ligand. The choice of label depends on sensitivity required,

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ease of conjugation with the compound, stability requirements, and available instrumentation.

Appropriate *in vivo* models for demonstrating efficacy in treating inflammatory responses include DTH (delayed type hypersensitivity) in mice, rats, guinea pigs, or primates, as well as other inflammatory or fibrotic models dependent upon VLA-1 integrin.

Compounds having the desired biological activity may be modified as necessary to provide desired properties such as improved pharmacological properties (e.g., *in vivo* stability, bioavailability), or the ability to be detected in diagnostic applications. Stability can be assayed in a variety of ways such as by measuring the half-life of the compounds during incubation with peptidases or human plasma or serum.

For diagnostic purposes, a wide variety of labels may be linked to the compounds, which may provide, directly or indirectly, a detectable signal. Thus, the compounds and compositions of the subject invention may be modified in a variety of ways for a variety of end purposes while still retaining biological activity. In addition, various reactive sites may be introduced for linking to particles, solid substrates, macromolecules, and the like.

Labeled compounds can be used in a variety of *in vivo* or *in vitro* applications. A wide variety of labels may be employed, such as radionuclides (e.g., gamma-emitting radioisotopes such as tech-

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netium-99 or indium-111), fluorescers (e.g., fluorescein), enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chemiluminescent compounds, bioluminescent compounds, and the like. Those of ordinary skill in the art will know of other suitable labels for binding to the complexes, or will be able to ascertain such using routine experimentation. The binding of these labels is achieved using standard techniques common to those of ordinary skill in the art.

In vitro uses include diagnostic applications such as monitoring inflammatory responses by detecting the presence of cells expressing VLA-1. The compounds and compositions of this invention can also be used for isolating or labeling such cells. In addition, as mentioned above, the compounds and compositions of the invention can be used to assay for potential inhibitors of VLA-1/Extracellular matrix interactions.

For *in vivo* diagnostic imaging to identify, e.g., sites of inflammation, radioisotopes are typically used in accordance with well-known techniques. The radioisotopes may be bound to the compound either directly or indirectly using intermediate functional groups. For instance, chelating agents such as diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), and similar molecules have been used to bind compounds to metallic ion radioisotopes.

The complexes can also be labeled with a paramagnetic isotope for purposes of *in vivo* diag-

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nosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR), both of which are well known. In general, any conventional method for visualizing diagnostic images can be used. Usually gamma- and positron-emitting radioisotopes are used for camera imaging and paramagnetic isotopes are used for MRI. Thus, the compounds can be used to monitor the course of amelioration of an inflammatory response in an individual. By measuring the increase or decrease in cells expressing VLA-1, it is possible to determine whether a particular therapeutic regimen aimed at ameliorating the disease is effective.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, (1985) Seventeenth Edition, Mack Publishing Company, Philadelphia, PA.

The amount administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the progression or symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use

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will depend on the disease condition being treated, as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, disorder, or condition, the age, weight and general condition of the patient, and the like.

The compounds administered to a patient are typically in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between about 3 and 11, more preferably from about 5 to 9, and most preferably from about 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds and/or compositions of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for oral administration, the dose will typically be in the range of about 100 µg to about 50 mg per kilogram body weight per day, preferably about 5 mg to about 20 mg per kilogram body weight per day. In the alternative, for intravenous administration, the dose will typ-

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ically be in the range of about 20 µg to about 500 µg per kilogram body weight, preferably about 100 µg to about 300 µg per kilogram body weight. Alternative routes of administration contemplated include, but are not limited to, intranasal, transdermal, inhaled, subcutaneous, and intramuscular. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In general, the compounds and/or compositions of the subject invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit large therapeutic indices are preferred.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any

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compound or composition used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC₅₀ (the concentration of the test compound which achieves a half-maximal inhibition of activity) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

Examples

Unless otherwise stated all temperatures are in degrees Celsius. Also, in these examples and elsewhere, abbreviations have the following meanings:

¹ H NMR	=	proton nuclear magnetic resonance
Å	=	Angstroms
acetone-d ₆	=	deuterated acetone
AlCl ₃	=	aluminum trichloride
APCI	=	Atmospheric Pressure Chemical Ionization
aq	=	Aqueous
BINAP	=	(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
boc	=	tert-butoxycarbonyl

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BOP	=	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
br d (or bd)	=	broad doublet
br s (or bs)	=	broad singlet
CBZ or cbz	=	benzyloxycarbonyl
CDCl ₃	=	deuterated chloroform
CDI	=	<i>N,N'</i> -carbonyldiimidazole
d	=	doublet
dba	=	dibenzylideneacetone
DCC	=	dicyclohexylcarbodiimide
DCE	=	dichloroethane
DCM	=	dichloromethane
dd	=	doublet of doublets
DEAD	=	diethyl azodicarboxylate
DECP	=	diethylcyanophosphonate
DIBAL-H	=	diisobutylaluminum hydride
DME	=	1,2-dimethoxyethane
DMF	=	dimethylformamide
DMSO	=	dimethyl sulfoxide
DMSO- <i>d</i> ₆	=	deuterated dimethyl sulfoxide
dppf	=	dichloro[1,1'-bis(diphenylphosphino)ferrocene]
DTPA	=	diethylenetriaminepentaacetic acid
EDC (or EDCI)	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	=	ethylenediaminetetraacetic acid
eq	=	equivalents
ESI	=	electrospray ionization
Et	=	ethyl
EtO ₂	=	diethyl ether
EtOAc	=	ethyl acetate
Fmoc	=	9-fluorenylmethoxycarbonyl
g	=	grams
h	=	hours
HCl	=	hydrochloric acid
HOBt (HOBT)	=	1-hydroxybenzotriazole
HPLC	=	high performance liquid chromatography
Hz	=	hertz
IPA	=	isopropyl alcohol
<i>J</i>	=	coupling constant in hertz
L	=	liters
LC methods	=	liquid chromatography methods

LCMS	=	liquid chromatography mass spectrometry
LDA	=	lithium diisopropylamide
LiAlH ₄ (LAH)	=	lithium aluminum hydride
LiHMDS	=	lithium hexamethyl disilazane
LiOH	=	lithium hydroxide
M	=	molar
m	=	multiplet
m/z	=	mass/charge ratio
mCPBA	=	m-chloroperoxybenzoic acid
Me	=	methyl
mg	=	milligrams
MHz	=	megahertz
Min	=	minutes
mL	=	milliliters
mm	=	millimeter
mM	=	millimolar
mmol	=	millimole
MP-TsOH	=	macroporus poly(styrene-co-divinylbenzene)-p-toluene sulfonic acid
MS (EI)	=	mass spectrometry (electrospray ionization)
MTBE	=	tert-butyl methyl ether
N	=	normal
nm	=	nanometers
nM	=	nanomolar
NMM	=	N-methyl morpholine
NMR	=	nuclear magnetic resonance
o-(Tol) ₃ P	=	tri-o-tolylphosphine
Pd(OAc) ₂	=	palladium acetate
Pd/C	=	palladium on carbon
Pd ₂ (dba) ₃	=	tri(dibenzylideneacetone)dipalladium(0)
Ph	=	phenyl
PS-DCC	=	polystyrene dicyclohexylcarbodiimide
PS-HOBt	=	polystyrene 1-hydroxybenzotriazole
PS-TFP	=	polystyrene tetrafluorophenol
p-TsOH	=	p-toluenesulfonic acid
Q	=	quartet
RP-HPLC	=	reverse phase high pressure liquid chromatography
Rt	=	retention time
rt	=	room temperature
s	=	singlet
sat.	=	saturated

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t	=	triplet
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
δ	=	chemical shift
μ g	=	micrograms
μ L	=	microliters
μ M	=	micromolar
BSA	=	bovine serum albumin
CMF-PBS	=	calcium and magnesium-free Dulbecco's phosphate buffered saline
dH ₂ O	=	distilled water
D-PBS	=	Dulbecco's phosphate buffered saline
FACS	=	fluorescent-activated cell sorting
FBS	=	fetal bovine serum
PMA	=	Phorbol 12-myristate 13-acetate
RPMI	=	Roswell Park Memorial Institute media 1640
TBS	=	tris buffered saline

The following analytical HPLC methods (or LC Methods) are referred to in the Examples. The gradient profiles were straight-line gradients increasing or decreasing linearly over the time period indicated.

Method A: Varian HPLC System: Pumps: Varian ProStar Solvent Delivery System, Model 210; Detector: Varian ProStar UV-VIS Detector, Model 345; Autosampler: Varian ProStar Autosampler, Model 430). Analytical column: YMC ODS-AQ, 4.6 x 50 mm, S3 microns, Waters Corporation. Detection: 220nm and 254nm. Solvent A: H₂O, 0.1% TFA, 1.0% IPA. Solvent B: Acetonitrile, 0.05% TFA, 1.0% IPA. Flow Rate: 2.0 mL/min. Gradient Program: 0.00 min 95% Solvent A, 5% Solvent B; 0.05 min 95% Solvent A, 5% Solvent B; 4.12 min 5% Solvent A, 95% Solvent B;

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4.24 min 5% Solvent A, 95% Solvent B; 4.30 min 95% Solvent A, 5% Solvent B; 5.00 min 95% Solvent A, 5% Solvent B.

Method B: Varian HPLC System: (Pumps:
5 Varian ProStar Solvent Delivery System, Model 210;
Detector: Rainin Dynamax Absorbance Detector, Model
UV-DII; Autosampler: Varian ProStar Autosampler,
Model 430). Analytical column: YMC ODS-AQ, 4.6 x
50 mm, S3 μ , Waters Corporation. Detection: 220nm
10 and 254nm. Solvent A: H₂O, 0.01% HFBA, 1.0% IPA.
Solvent B: Acetonitrile, 0.01%HFBA, 1.0% IPA. Flow
Rate: 2.0 mL/min. Gradient Program: 0.00 min 95%
Solvent A, 5% Solvent B; 0.12 min 95% Solvent A, 5%
Solvent B; 4.00 min 5% Solvent A, 95% Solvent B;
15 4.18 min 5% Solvent A, 95% Solvent B; 4.30 min 95%
Solvent A, 5% Solvent B; 5.30 min 95% Solvent A, 5%
Solvent B.

Method C: Varian HPLC System: (Pumps:
Varian ProStar Solvent Delivery System, Model 210;
20 Detector: Varian ProStar PDA, Model 330;
Autosampler: Varian ProStar Autosampler, Model
430). Analytical column: YMC ODS-AQ, 4.6 x 50 mm,
S3 μ , Waters Corporation. Detection: 220nm and
254nm. Solvent A: H₂O, 0.01% HFBA, 1.0% IPA.
25 Solvent B: Acetonitrile, 0.01%HFBA, 1.0% IPA. Flow
Rate: 2.0 mL/min. Gradient Program: 0.00 min 95%
Solvent A, 5% Solvent B; 0.12 min 95% Solvent A, 5%
Solvent B; 4.00 min 5% Solvent A, 95% Solvent B;
4.18 min 5% Solvent A, 95% Solvent B; 4.30 min 5%
30 Solvent A, 95% Solvent B; 5.00 min 95% Solvent A, 5%
Solvent B 5.30 min 95% Solvent A, 5% Solvent B.

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Method D: Berger SFC (Berger Dual Pump Fluid Control Module, Model FCM-1200; Berger Thermal Control Module, Model TCM-2000; Hewlett Packard 1100 Series DAD, Model G1315A; Alcott Autosampler, Model 718AL). Column: Chiralcel OJ-R 150 X 4.6 mm. Detection: 258nm. SFC Conditions: 2 mL/min, 10% MeOH in CO₂, 35°C, 200 bar.

Method E: Agilent Technologies 1100 HPLC System (Pump: QuatPump Model G1311A; Detector: DAD, Model G1315B; Column Compartment: Model G1216A; Autosampler: ALS, Model G1313A; Degasser: Model G1322A). Analytical column: Chiralcel OD-RH, 150 X 4.6 mm. Detection: 220nm. HPLC Conditions: 1.0 mL/min, Isocratic, 70% (H₂O, 0.01%TFA), 30% (ACN, 0.01%TFA), 35°C.

Method F: Mass Spectrometer: Finnigan LCQTM Duo, APCI. TSP HPLC System: (Pump: TSP SpectraSYSTEM® P4000; Detector: TSP SpectraSYSTEM® UV2000, 220nm and 254 nm; Autosampler: TSP SpectraSYSTEM® AS3000; Degasser: TSP SpectraSYSTEM® Model SCM1000 Solvent Degasser). Detection: 220nm and 254nm. Analytical column: YMC ODS-AQ, 4.6 x 50 mm, 3µm, Waters Corporation. Solvent C: H₂O, 0.01% HFBA, 1.0% IPA. Solvent D: Acetonitrile, 0.01% HFBA, 1.0% IPA. Flow Rate: 2.0 mL/min. Gradient Program: 0.00 min 95% Solvent C, 5% Solvent D; 0.02 min 95% Solvent C, 5% Solvent D; 4.00 min 5% Solvent C, 95% Solvent D; 4.30 min 5% Solvent C, 95% Solvent D; 4.50 min 95% Solvent C, 5% Solvent D; 5.50 min 95% Solvent C, 5% Solvent D.

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Method G: Mass Spectrometer: Finnigan
LCQTM Duo, ESI. TSP HPLC System: (Pump: TSP SpectraSYSTEM® P4000; Detector: TSP SpectraSYSTEM® UV2000, 220nm and 254 nm; Autosampler: TSP SpectraSYSTEM® AS3000; Degasser: TSP SpectraSYSTEM® Model SCM1000 Solvent Degasser). Detection: 220nm and 254nm. Analytical column: YMC ODS-AQ 4.6 x 50 mm S3µ, Waters Corporation. Solvent C: 10 mM Ammonium Acetate in H₂O. Solvent D: 10 mM Ammonium Acetate in Acetonitrile, 1.0% IPA. Flow Rate: 2.0 mL/min. Gradient Program: 0.00 min 75% Solvent C, 25% Solvent D; 0.02 min 75% Solvent C, 25% Solvent D; 4.00 min 5% Solvent C, 95% Solvent D; 4.30 min 5% Solvent C, 95% Solvent D; 4.50 min 75% Solvent C, 25% Solvent D; 5.50 min 75% Solvent C, 25% Solvent D.

Method H: Mass Spectrometer: Finnigan
LCQTM Duo, ESI. TSP HPLC System: (Pump: TSP SpectraSYSTEM® P4000; Detector: TSP SpectraSYSTEM® UV2000, 220nm and 254 nm; Autosampler: TSP SpectraSYSTEM® AS3000; Degasser: TSP SpectraSYSTEM® Model SCM1000 Solvent Degasser). Detection: 220nm and 254nm. Analytical column: Zorbax Extend C18 Rapid Resolution®, 50 x 4.6 mm, 3.5µ, 80Å, Agilent Technologies. Solvent C: 10 mM Ammonium Acetate in H₂O. Solvent D: 10 mM Ammonium Acetate in Acetonitrile, 1.0% IPA. Flow Rate: 2.0 mL/min. Gradient Program: 0.00 min 95% Solvent C, 5% Solvent D; 0.02 min 95% Solvent C, 5% Solvent D; 4.00 min 5% Solvent C, 95% Solvent D; 4.30 min 5% Solvent C, 95% Solvent D.

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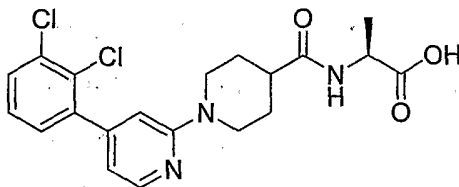
D; 4.50 min 95% Solvent C, 5% Solvent D; 5.50 min 95% Solvent C, 5% Solvent D.

Method I: Mass Spectrometer: Finnigan LCQTM Duo, ESI. TSP HPLC System: (Pump: TSP Spectra-
5 traSYSTEM® P2000; Detector: TSP SpectraSYSTEM® UV2000, 220nm and 254 nm; Autosampler: TSP SpectraSYSTEM® AS3000; Degasser: TSP SpectraSYSTEM® Model SCM1000 Solvent Degasser). Detection: 220nm and
254nm. Analytical column: Zorbax Extend C18 Rapid
10 Resolution®, 50 x 4.6 mm, 3.5µ, 80Å, Agilent Technologies. Solvent A: 10 mM Ammonium Acetate in H₂O.
Solvent B: 10 mM Ammonium Acetate in Acetonitrile, 1.0% IPA. Flow Rate: 2.0 mL/min. Gradient Program: 0.00 min 95% Solvent A, 5% Solvent B; 0.02
15 min 95% Solvent A, 5% Solvent B; 4.00 min 5% Solvent A, 95% Solvent B; 4.30 min 5% Solvent A, 95% Solvent B; 4.50 min 95% Solvent A, 5% Solvent B; 5.50 min 95% Solvent A, 5% Solvent B.

Method J: Mass spectrometers: LCQTM Duo
20 and LCQTM Deca. Pump: Series 1100, Quat pump model G1311A, Agilent Technologies. Detector: Series 1100, Column model G1216A, Agilent Technologies.
Autosampler: Series 1100, ALS model G1313A, Agilent Technologies. Degasser: Series 1100, Degasser
25 model G1322A, Agilent Technologies. ELSD: Sedex model 75, Sedere. Analytical column: YMC ODS-AQ 4.6 x 50 mm S3µ, Waters Corporation. Solvent A: H₂O, 0.01% HFBA, 1.0% IPA. Solvent B: Acetonitrile, 0.01% HFBA, 1.0% IPA. Flow Rate: 2.0 mL/min.
30 Gradient Program: 0.00 min 95% Solvent A, 5% Solvent B; 0.02 min 95% Solvent A, 5% Solvent B;

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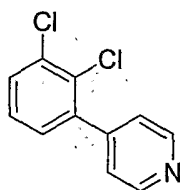
4.10 min 5% Solvent A, 95% Solvent B; 4.30 min 5% Solvent A, 95% Solvent B; 4.50 min 95% Solvent A, 5% Solvent B; 5.50 min 95% Solvent A, 5% Solvent B. Purity based on 220 nm wavelength channel.



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Example 1

2-([4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid



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Example 1A

4-(2,3-Dichloro-phenyl)-pyridine

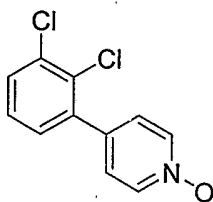
Following the procedure of (Fujita et al. (1995) *Tetrahedron Lett.* 36(29):5247-5250), a stirred solution of 4-tributylstannanyl-pyridine (5.0 g, 13.6 mmol) in 60 mL of anhydrous toluene, lithium chloride (8.24 g, 194 mmol), 1,2-dichloro-3-iodo-benzene (2.65 mL, 9.71 mmol) was made. The mixture was then degassed several times by bubbling nitrogen through the solution via syringe and then trans-dichlorobis(triphenylphosphine)palladium(II) was added. The mixture was heated under nitrogen

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atmosphere at reflux for 96 hours. The reaction mixture was then allowed to cool to ambient temperature and partitioned between toluene and brine. The organic layer was separated and saturated KF was added and the mixture was stirred for 24 h. The organic layer was filtered, and condensed *in vacuo* to provide Example 1A (1.76 g, 80.1%) as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 8.7 (dd, *J*=1.56, 4.69 Hz, 2H), 7.53 (dd, *J*=1.56, 7.81 Hz, 1H), 7.34 (s, *J*=1.56, 4.29 Hz, 2H), 7.29 (t, *J*=8 Hz, 1H), 7.21 (s, *J*=1.56, 7.42 Hz, 1H)



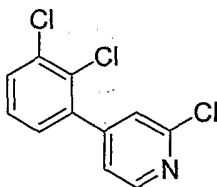
Example 1B

4-(2,3-Dichloro-phenyl)-pyridine N-oxide

15 A flask was charged with 1A (1.50 g, 6.69 mmol) and 15 mL DCM and placed in an ice bath and cooled to 0°C. Next, *m*CPBA (1.62 g, 9.37 mmol) was added and the mixture stirred for 16 h, warming to ambient temperature. After 16 h a second bolus of
20 *m*CPBA (1.62 g, 9.37 mmol) was added at ambient temperature and the mixture stirred for 2 h. The mixture was partitioned between DCM and saturated sodium metabisulfite (2X25 mL), followed by extraction of the organic layer with saturated sodium bi-
25 carbonate/brine. The organic layer was dried over

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sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified via silica gel flash chromatography, eluting with 5% 7 N methanolic ammonia/DCM, to provide Example 1B (1.60 g, 99%) as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ 8.29 (d, J=7.4 Hz, 2H), 7.56 (dd, J=1.6, 8.2 Hz, 1H), 7.4 (d, J=7.4 Hz, 2H), 7.32 (t, J=7.8 Hz, 7H), 7.24 (dd, J=2.0, 7.8 Hz, 1H).



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Example 1C

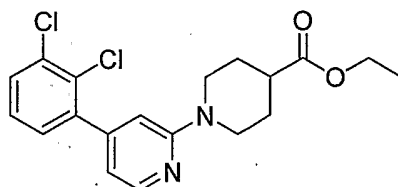
2-Chloro-4-(2,3-dichloro-phenyl)-pyridine

To a flask under nitrogen was added 1B (1.90 g, 7.91 mmol) and phosphorus oxychloride (22.3 g, 185.3 mmol). A reflux condenser was placed on the flask and the mixture was heated to 90°C with stirring for 18h. The mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The remaining slurry was poured over ice chips and neutralized with saturated sodium bicarbonate. The aqueous phase obtained was extracted with CH₂Cl₂ (3X50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to provide the title compound (1.10 g, 7.9 mmol, 54% yield) as an orange solid. ¹H NMR (CDCl₃, 400 MHz) δ 8.48 (d, J=5.06 Hz, 1H), 7.56 (dd, J=1.17, 7.41 Hz,

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1H), 7.39 (s, 1H), 7.31 (t, $J=8.19$ Hz, 3H), 7.3 (dd, $J=1.56, 5.07$ Hz, 1H), 7.22 (dd, $J=1.17, 7.02$ Hz, 1H). HPLC (Method A) $R_t=3.06$ min (92.5 area%, 220 nm).

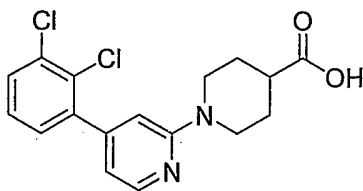


Example 1D

4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methyl ester

To a 25 mL sealable tube was added 1C (1.00 g, 3.87 mmol) and ethyl isonipecotate (6.08 g, 38.68 mmol). The tube was placed under nitrogen, sealed and heated with stirring to 145°C for 24 h. The mixture was cooled to ambient temperature. The mixture was purified by flash chromatography on silica gel eluting with 10% 7N methanolic ammonia/-DCM to provide the title compound (0.890g, 3.87 mmol, 61%). ^1H NMR (CDCl_3 , 400 MHz) δ 8.23 (d, $J=5.08$ Hz, 1H), 7.49 (m, 1H), 7.23 (m, 2H) 6.65 (s, 1H), 6.62 (m, 1H), 4.26 (m, 1H), 4.15 (q, $J=6.9$ Hz, 2H), 3.00 (m, 2H), 2.55 (m, 1H), 2.01 (m, 2H), 1.8 (m, 2H), 1.26 (t, $J=7.22$ Hz, 3H).

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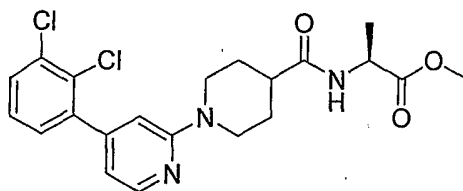


Example 1E

4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

5 To a stirred solution of 1D (0.090 g, 0.246 mmol) in THF (2 mL) was added LiOH monohydrate (0.0062 g, 0.259 mmol) dissolved in 1 mL water. The mixture was stirred for 24 h, concentrated under vacuum and acidified by adding 2.0 eq of HCl (0.1 N) lowering the pH to 3.5. The solution was concentrated by *in vacuo* to provide the title compound 1E (0.085g, 98%) as a light brown solid with salts present. ¹H NMR (CDCl₃, 400 MHz) δ 8.59 (s, 1H), 8.25 (d, *J*=5.08 Hz, 1H), 7.5 (m, 1H), 7.26 (t, *J*=7.61 Hz, 1H), 7.21 (m, 1H), 6.67 (s, 1H), 6.65 (d, *J*=5.08 Hz, 1H), 4.24 (m, 2H), 3.05 (m, 2H), 2.62 (m, 1H), 2.05 (m, 2H), 1.83 (m, 2H). HPLC (Method A) Rt=2.10 min (87.5 area%, 220 nm). LCMS (ESI+ Method F) *m/z* 351(M⁺), 279.2 (M-2Cl); Rt=2.65 min (220 nm, 90 area%).

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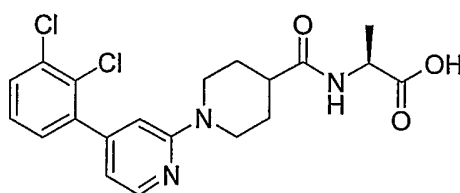


Example 1F

5 2-([4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid methyl ester

To a stirred solution of 1E in DMF (6 mL) was added L-alanine HCl (0.0507 g, 0.363 mmol), HOBT.H₂O (0.0490 g, 0.363 mmol), NMM (0.04 mL, 0.363 mmol), and diisopropyl ethylamine (0.0367 g, 0.363 mmol). After stirring for 5 min, EDCI (0.0564 g, 0.363 mmol) was added and the mixture was stirred for 24 h. Next, 20 mL water was added and the mixture extracted with EtOAc (3X15 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated to obtain the product (0.242 mmol, 61%) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 8.23 (d, J=5.08 Hz, 1H), 7.48 (m, 1H), 7.26 (t, J=7.61 Hz, 1H), 7.2 (m, 1H), 6.66 (s, 1H), 6.63 (m, 1H), 6.14 (d, J=7.03 Hz, 1H), 4.61 (m, 1H), 4.37 (m, 2H), 3.76 (s, 3H), 2.93 (m, 2H), 2.4 (m, 1H), 1.94 (m, 2H), 1.79 (m, 2H), 1.41 (d, J=7.03 Hz, 3H).

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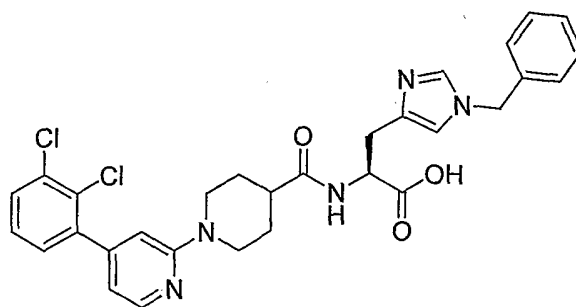
Example 1G

2-([4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid

To a stirred solution of 1F (0.065 g, 0.149 mmol) in THF (5 mL) was added LiOH monohydrate (0.019 g, 0.447 mmol, dissolved in 2 mL water) and stirred for 14 h. The crude product was concentrated *in vacuo* and acidified to pH 2 by dropping in 0.1N HCl until a white precipitate formed. The solid was partitioned between methylene chloride (20 mL) and 0.1 N aqueous HCl (10 mL). The phases were separated, and the aqueous phase was re-extracted with methylene chloride (2x10 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated to provide the title compound (0.045 g, 0.149 mmol, 72%) as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.37 (s, 1H), 8.14 (d, *J*=5.08 Hz, 1H), 8.08 (d, *J*=7.42 Hz, 1H), 7.68 (m, 1H), 7.42 (t, *J*=7.81 Hz, 1H), 7.36 (m, 1H), 6.8 (s, 1H), 6.62 (m, 1H), 4.32 (m, 2H), 4.15 (m, 1H), 2.83 (m, 2H), 2.43 (m, 2H), 1.69 (m, 2H), 1.52 (m, 2H), 1.22 (d, *J*=7.42 Hz, 3H). HPLC (Method B) *R*_t=2.22 min (90.5 area%, 220 nm.) LCMS (ESI+ Method F) *m/z* 422.1 (M⁺), *R*_t=2.19 min (220 nm, 90.5 area%).

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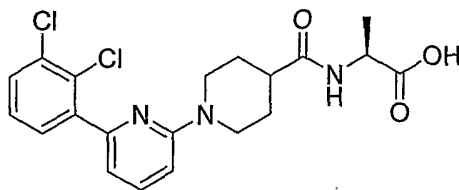


Example 2

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[4'-(2,3-dichloro-
phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-
carbonyl]-amino}-propionic acid

Example 2 was prepared according to the same reaction protocol as described for Example 1 substituting L-N¹-benzyl histidine methyl ester dihydrochloride for L-alanine methyl ester HCl. The procedure provided the title compound (0.036 mmol, 8%) as a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 8.91 (s, 1H), 8.09 (d, J=5.85 Hz, 1H), 7.64 (m, 1H), 7.43 (m, 9H), 7.06 (s, 1H), 6.84 (m, 1H), 5.37 (q, J=14.85, 2.34 Hz, 2H), 4.73 (m, 1H), 4.23 (m, 2H), 3.29 (m, 1H), 3.08 (m, 2H), 2.5 (m, 1H), 1.81 (m, 1H), 1.61 (m, 2H), 1.49 (m, 1H). HPLC (Method C) Rt=2.11 min (100.0 area%, 220 nm). LCMS (ESI-Method E) m/z 576.1 (M-2H)⁻, Rt=2.64 min (220 nm, 95.5 area%).

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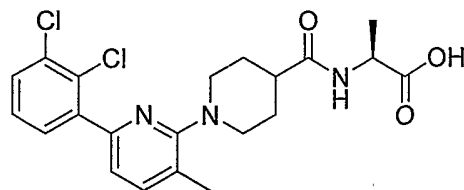


Example 3

2-([6'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid

5 Example 3 was prepared according to the same reaction protocol as described for Example 1 substituting 2-tributylstannanyl-pyridine for 4-tributylstannanyl-pyridine. The procedure resulted in the title compound (0.080 g, 0.190 mmol, 41%) as a
10 white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.44 (s, 1H), 8.08 (d, $J=7.42$ Hz, 1H), 7.66 (m, 1H), 7.6 (m, 1H), 7.43 (m, 2H), 6.86 (d, $J=8.59$ Hz, 1H), 6.8 (d, $J=7.42$ Hz, 1H), 4.32 (m, 2H), 4.15 (m, 1H), 2.83 (m, 2H), 2.44 (m, 1H), 1.71 (m, 2H), 1.53 (m, 2H), 1.23
15 (d, $J=7.42$ Hz, 3H). HPLC (Method B) $R_t=2.78$ min (96.1 area%, 220 nm). LCMS (APCI+ Method D) m/z 422.1 (M^+), $R_t=2.81$ min (220 nm, 98.0 area%).

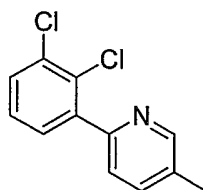
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Example 4

5 2-[[6'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino]-propionic acid

Example 4 was prepared according to the same reaction protocol as described for Example 1 substituting 4A for 1A. The procedure resulted in the title compound (0.020 g, 0.046 mmol, 26%) as a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 12.39 (s, 1H), 8.08 (d, J=7.42 Hz, 1H), 7.66 (m, 1H), 7.58 (d, J=7.42 Hz, 1H), 7.5 (m, 1H), 7.42 (t, J=7.81 Hz, 1H), 7.14 (d, J=7.42 Hz, 1H), 4.18 (m, 1H), 3.5 (m, 2H), 2.69 (m, 2H), 2.31 (m, 1H), 2.30 (s, 3H), 1.74 (m, 3H), 1.23 (m, 5H). HPLC (Method B): Rt=3.11 min (89.0 area%, 220 nm). LCMS (APCI+ Method D) m/z 436.1 (M⁺), Rt=3.13 min (220 nm, 93.4 area%).



Example 4A

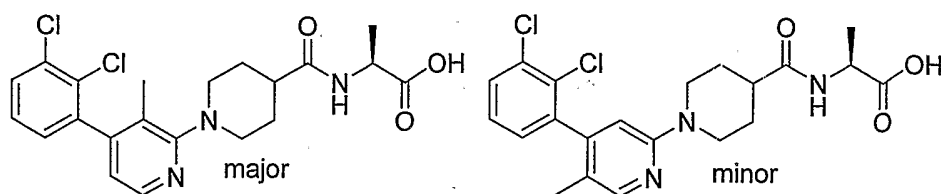
20 2-(2,3-Dichloro-phenyl)-5-methyl-pyridine

To a stirred solution of 2-bromo-5-methylpyridine (1.00 g, 5.81 mmol) and 2,3-dichloro phen-

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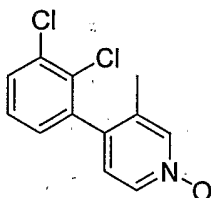
ylboronic acid (1.33 g, 6.98 mmol) in DME (5.8 mL) was added potassium carbonate (1.21 g, 8.7 mmol). The mixture was degassed by bubbling nitrogen with a syringe for 5 min through the mixture, followed by addition of Pd(PPh₃)₄ (0.672 g, 0.58 mmol). A reflux condenser was attached to the flask and the mixture heated to 90°C for 48 h. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and brine. The organic phase was washed with brine (3X20 mL) and dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel eluting with 1:1 ethyl acetate:hexane to provide the title compound (0.380 g, 5.81 mmol, 27% yield) as a light yellow oil which solidified upon standing to an off white solid. ¹H NMR (CDCl₃, 400 MHz) δ 8.54 (m, 1H), 7.58 (m, 1H), 7.5 (s, 2H), 7.44 (dd, J=1.56, 7.42 Hz, 1H), 7.43 (m, 1H), 7.27 (t, J=7.81 Hz, 1H), 2.40 (s, 3H).

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Example 5

2-{{[4'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid/2-{{[4'-(2,3-Dichloro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid



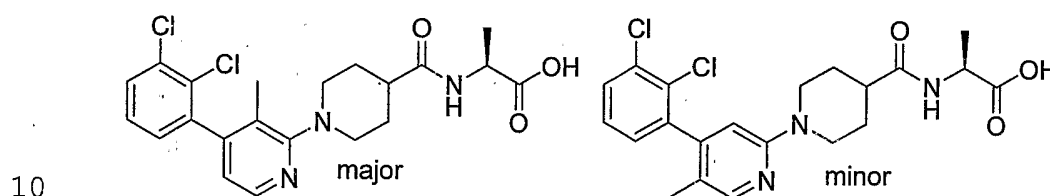
Example 5A

10 4-(2,3-Dichloro-phenyl)-3-methyl-pyridin-n-oxide

To a stirred solution of 4-bromo-3-methylpyridine N-oxide (0.985 g, 5.2 mmol) (prepared from 4-bromo-3-methylpyridine in the same manner as in Example 1B) and 2,3-dichloro phenylboronic acid (1.0 g, 5.2 mmol) in DME (5.8 mL) was added potassium carbonate (0.869 g, 6.3 mmol). The mixture was degassed by bubbling nitrogen with a syringe for 5 min through the mixture, followed by addition of Pd(PPh₃)₄ (0.606 g, 0.52 mmol). A reflux condenser was attached to the flask and the mixture heated to 90°C for 48 h. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and brine. The organic layer was washed with brine

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(3X20 mL) and dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel eluting with 4% 7 N methanolic ammonia/DCM to provide the title compound (0.483 g, 5.24 mmol, 36% yield) as a white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 8.18 (s, 1H), 8.14 (m, 1H), 7.57 (m, 1H), 7.33 (t, $J=8$ Hz, 1H), 7.15 (m, 1H), 7.08 (d, $J=6.64$ Hz, 1H), 2.10 (s, 3H).



Example 5B

2-{{[4'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid/2-{{[4'-(2,3-Dichloro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid

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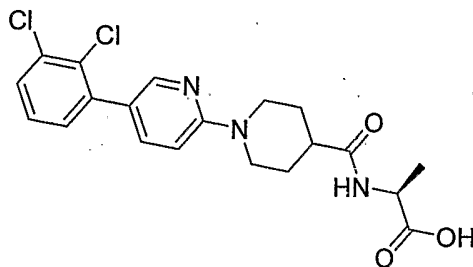
Example 5B (as a 3:2 mixture of regioisomers) was prepared according to the same reaction protocol as described for Example 1 substituting 5A for 1B. The procedure resulted in the title compound (0.060 g, 0.222 mmol, 62%) as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.38 (s, 1.5H), 8.15 (d, $J=5.47$ Hz, 1H), 8.08 (d, $J=7.42$ Hz, 1H), 8.01 (s, 1.5H), 7.69 (m, 1.5H), 7.44 (m, 1.5H), 7.27 (m, 1.5H), 6.79 (d, $J=5.08$ Hz, 1H), 4.19 (m, 4.5H), 3.38 (m, 3.0H), 2.74 (m, 1.5H), 1.92 (s, 3.0H), 1.84 (s, 1.5H), 1.71 (m, 5.0H), 1.52 (m, 1.0H), 1.23 (m, 4.5H). HPLC

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(Method A): Rt=2.24 min (40.1 area%, 220 nm), 2.38 min (58.0 area%, 220 nm). LCMS (APCI+ Method D) m/z 436.1 (M^+), Rt=2.27 min (220 nm, 41.5 area%), Rt=2.41 min (220 nm, 58.5 area%).



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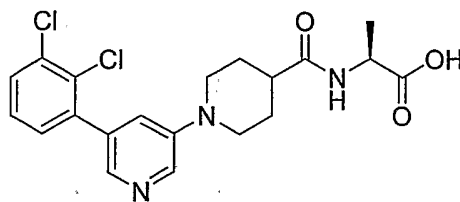
Example 6

2-([5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino)-propionic acid

Example 6 was prepared according to the same reaction protocol as described for Example 1 substituting 3-tributylstannanyl-pyridine for 4-tributylstannanylpiperidine. The procedure resulted in the title compound (0.103 g, 0.246 mmol, 61%) as a white powder. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.4 (s, 1H), 8.14 (d, $J=2.73$ Hz, 1H), 8.11 (d, $J=7.42$ Hz, 1H), 7.61 (m, 2H), 7.4 (m, 2H), 6.9 (d, $J=8.98$ Hz, 1H), 4.36 (m, 2H), 4.17 (m, 1H), 2.88 (m, 2H), 2.44 (m, 1H), 1.73 (m, 2H), 1.53 (m, 2H), 1.24 (d, $J=7.42$ Hz, 3H). HPLC (Method B), Rt=2.54 min (95.0 area%, 254 nm). LCMS (APCI+ Method D) m/z 422.1 (M^+), Rt=2.28 min (220 nm, 95.5 area%).

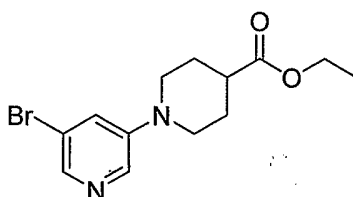
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Example 7

2-([5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino)-propionic acid



Example 7A

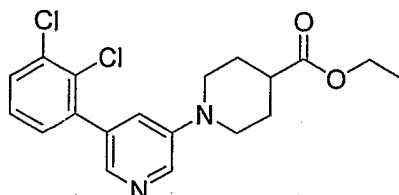
5'-Bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester

To a 250 mL sealable tube was added 3,5-dibromo pyridine (5.00 g, 21.1 mmol), ethyl isonepicotinate (16.0 g, 106 mmol) and cesium carbonate (7.22 g, 22.2 mmol). The tube was vented with N₂ and sealed. The mixture was heated to 150°C for 72 h then cooled to ambient temperature. The crude product was dissolved in toluene and filtered. The organic layer was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 1:1 EtOAc/Hexane to provide the title compound (3.95g, 60%) as a light yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ 8.21 (d, *J*=2.73 Hz, 1H), 8.1 (d, *J*=1.95 Hz, 1H), 7.3 (t, *J*=2.34 Hz, 1H), 4.18 (q, *J*=7.03, 14.43Hz, 2H), 3.66 (m, 2H), 2.89 (m,

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2H), 2.48 (m, 1H), 2.04 (m, 2H), 1.87 (m, 2H), 1.28 (t, $J=7.21$ Hz, 3H).



Example 7B

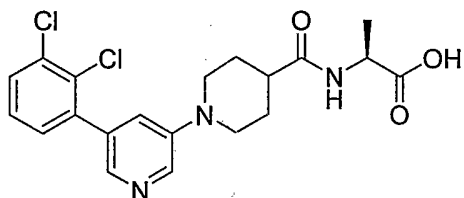
5 5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester

To a stirred solution of 7A (0.800 g, 2.55 mmol) in 10 mL toluene was added 2,3-dichlorophenyl boronic acid (0.975 g, 5.11 mmol) and cesium carbonate (1.33 g, 5.62 mmol). The mixture was degassed with nitrogen for 10 min, then $\text{Pd}(\text{PPh}_3)_4$ (0.148 g, 0.128 mmol) was added. The mixture was heated to 85°C for 18 h then cooled to ambient temperature. The crude product was partitioned between toluene and brine. The organic layer was washed (2 X 30 mL) with brine and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel eluting with 2:1 EtOAc/Hexane to provide the title compound (0.295 g, 30.5%) as a light oil which solidified upon standing to a white solid.

^1H NMR (CDCl_3 , 400 MHz) δ 8.33 (d, $J=2.73$ Hz, 1H), 8.1 (d, $J=1.56$ Hz, 1H), 7.51 (dd, $J=1.95$, 7.80 Hz, 1H), 7.27 (t, $J=3.9$ Hz, 1H), 7.23 (m, 2H), 4.2 (q, $J=7.02$, 14.04 Hz, 2H), 3.71 (m, 2H), 2.91 (m, 2H),

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2.49 (m, 1H), 2.05 (m, 2H), 1.9 (m, 2H), 1.28 (t, $J=7.41$ Hz, 3H).

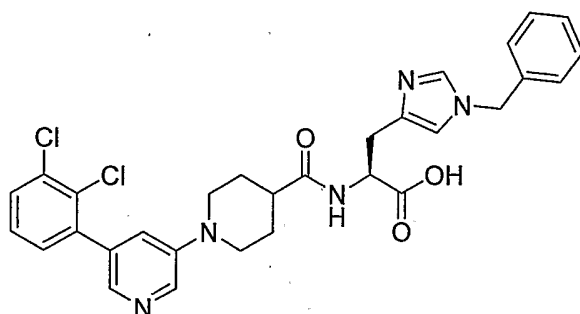


Example 7C

5 2-([5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino)-propionic acid.

Example 7C was prepared according to the same reaction protocol as described for Example 1 substituting 7B for 1D. The procedure resulted in the title compound (0.037 g, 0.286 mmol, 30.7%) as a white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.46 (s, 1H), 8.35 (s, 1H), 8.15 (d, $J=7.41$ Hz, 1H), 7.98 (s, 1H), 7.71 (d, $J=6.63$ Hz, 1H), 7.44 (m, 2H), 7.36 (s, 1H), 4.19 (m, 1H), 3.86 (m, 2H), 2.79 (m, 2H), 2.39 (m, 2H), 1.74 (m, 4H), 1.26 (d, $J=7.02$ Hz, 3H). HPLC (Method C) $R_t=2.19$ min (100.0 area%, 220 nm.) LCMS (ESI+ Method G) m/z 422.2 (M^+), $R_t=2.46$ min (220 nm, 93.6 area%).

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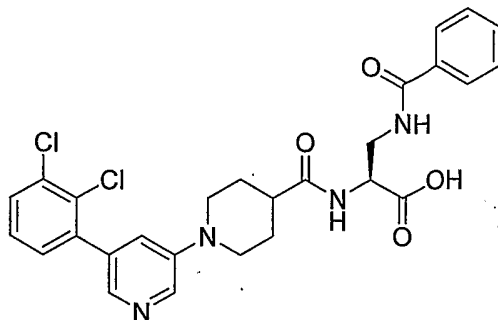


Example 8

3-(1-Benzyl-1H-imidazol-4-yl)-2-([5'-(2,3-dichlorophenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino)-propionic acid

Example 8 was prepared according to the same reaction protocol as described for Example 7 substituting L-N¹-benzyl histidine methyl ester dihydrochloride for L-alanine methyl ester HCl. The procedure resulted in the title compound (0.058 g, 0.286 mmol, 32.1%) as a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 8.34 (m, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.99 (s, 1H), 7.72 (m, 2H), 7.34 (m, 8H), 6.89 (s, 1H), 5.13 (s, 2H), 4.42 (m, 1H), 3.78 (m, 2H), 2.89 (m, 4H), 2.31 (m, 1H), 1.57 (m, 3H), 1.23 (m, 1H). HPLC (Method C) Rt=2.11 min (93.2 area%, 254 nm). LCMS (ESI+ Method G) m/z 578.3 (M⁺), Rt=2.77 min (220 nm, 100.0 area%).

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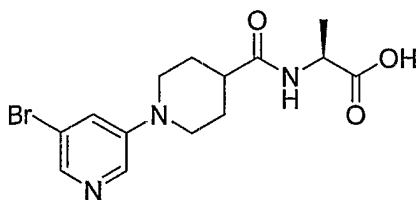


Example 9

3-Benzoylamino-2-([5'-(2,3-dichloro-phenyl)-3,4,5,6-
 tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino)-
 propionic acid

Example 9 was prepared according to the same reaction protocol as described for Example 7 substituting L-2-amino-3-benzoylamino-propionic acid methyl ester HCl for L-alanine methyl ester HCl. The procedure resulted in the title compound (0.062 g, 0.285 mmol, 41%) as a white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.68 (s, 1H), 8.87 (m, 1H), 8.55 (d, $J=7.02$ Hz, 1H), 8.47 (d, $J=2.34$ Hz, 1H), 8.22 (s, 1H), 7.98 (s, 1H), 7.89 (d, $J=7.02$ Hz, 2H), 7.8 (m, 1H), 7.5 (m, 5H), 4.38 (m, 1H), 3.99 (m, 2H), 3.64 (m, 2H), 2.97 (m, 2H), 2.55 (m, 1H), 1.8 (m, 2H), 1.61 (m, 2H). HPLC (Method C) $R_t=2.20$ min (96.5 area%, 220 nm). LCMS (ESI-Method G) m/z 539.0 ($M-2H$) $^-$, $R_t=2.68$ min (220 nm, 100.0 area%).

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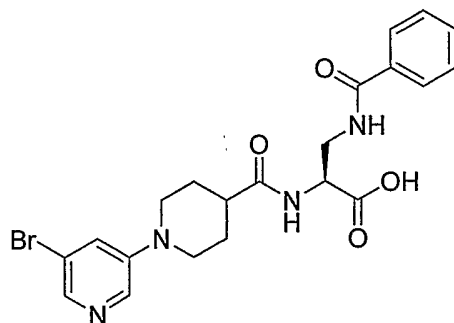


Example 10

2-[(5'-Bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid

5 Example 10 was prepared according to the same reaction protocol as described for Example 1 substituting 7A for 1E. The procedure resulted in the title compound (0.019 g, 0.351 mmol, 15.2%) as a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 12.46 (s, 1H), 8.29 (d, J=2.73 Hz, 1H), 8.14 (d, J=7.41 Hz, 1H), 8 (d, J=1.95 Hz, 1H), 7.52 (t, J=2.14 Hz, 1H), 4.18 (m, 1H), 3.84 (m, 2H), 2.79 (m, 2H), 2.39 (m, 1H), 1.74 (m, 2H), 1.62 (m, 2H), 1.26 (d, J=7.41 Hz, 3H). Analytical: HPLC (Method C) Rt=1.69 (100 area%, 220 nm). LCMS (ESI-Method G) m/z 353.9 (M-2H) Rt=2.77 min (220 nm, 100.0 area%).

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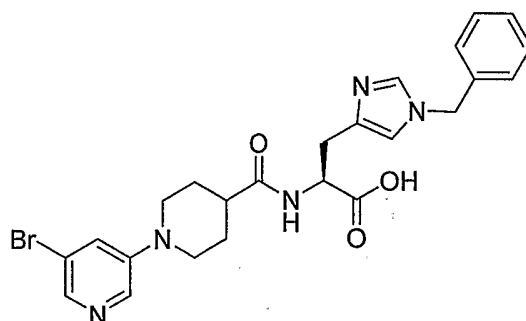


Example 11

3-Benzoylamino-2-[(5'-bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid

5 Example 11 was prepared according to the same reaction protocol as described for Example 10 substituting L-2-amino-3-benzoylamino-propionic acid methyl ester HCl for L-alanine methyl ester HCl. The procedure resulted in the title compound as a
10 white solid (0.110 g, 0.350 mmol, 66.0%). ¹H NMR (DMSO-d₆, 400 MHz) δ 12.7 (s, 1H), 8.53 (t, J=6.04 Hz, 1H), 8.28 (d, J=2.34 Hz, 1H), 8.16 (d, J=8.19 Hz, 1H), 7.99 (d, J=1.95 Hz, 1H), 7.8 (d, J=7.8 Hz, 2H), 7.51 (m, 4H), 4.47 (m, 1H), 3.81 (m, 2H), 3.61
15 (m, 2H), 2.81 (m, 2H), 2.4 (m, 1H), 1.77 (m, 2H), 1.58 (m, 2H). Analytical HPLC (Method C) Rt=2.01 min (99.4 area%, 220 nm). LCMS (ESI-Method G) m/z 473.0 (M-2H)⁻, Rt=2.28 min (220 nm, 100.0 area%).

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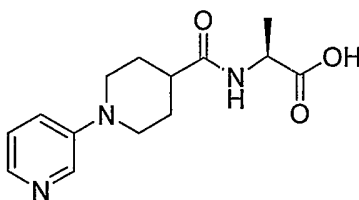


Example 12

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(5'-bromo-3,4,5,6-
 5 tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-
 propionic acid

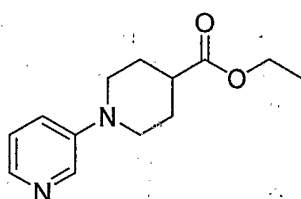
Example 12 was prepared according to the
 same reaction protocol as described for Example 10
 substituting L-N¹-benzyl histidine methyl ester di-
 hydrochloride for L-alanine methyl ester HCl. The
 10 procedure resulted in the title compound (0.101 g,
 0.351 mmol, 57.0%) as a white solid. ¹H NMR (DMSO-
 d₆, 400 MHz) δ 8.27 (d, J=2.34 Hz, 1H), 8.06 (d,
 J=7.8 Hz, 1H), 8 (d, J=1.56 Hz, 1H), 7.67 (s, 1H),
 7.5 (t, J=2.14 Hz, 1H), 7.33 (m, 3H), 7.22 (m, 2H),
 15 6.87 (s, 1H), 5.13 (s, 2H), 4.39 (m, 1H), 3.78 (m,
 2H), 2.87 (m, 1H), 2.77 (m, 3H), 2.32 (m, 1H), 1.68
 (m, 1H), 1.56 (m, 3H). Analytical HPLC (Method C)
 Rt=2.01 min (96.0area%, 220 nm). LCMS (ESI-Method
 G) m/z 548.5 (M+Na)⁺, Rt=3.01 min (220 nm, 100.0
 20 area%).

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Example 13

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid



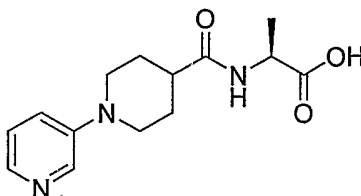
Example 13A

3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester

To a flask was added 7A (1.00 g, 3.19 mmol), dioxane (13 mL), triethyl amine (0.97 g, 9.58 mmol) and pinacol borane (0.613 g, 4.79 mmol). The mixture was degassed with N₂ for 15 min and Pd₂Cl₂-(dppf) dcm (0.132 g, 0.16 mmol) was added. The flask was heated to 90°C for 12 h and cooled to ambient temperature. The crude product was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 15% 7N methanolic ammonia/CM to provide the title compound (400 mg, 45%) ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.31 (d, *J*=2.73 Hz, 1H), 8.09 (m, 1H), 7.18 (m, 2H), 4.16 (dd, *J*=7.02, 14.04 Hz, 2H), 3.67 (m, 2H), 2.85 (m, 2H), 2.46 (m,

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1H), 2.05 (m, 2H), 1.89 (m, 2H), 1.28 (t, $J=7.21$ Hz, 3H).



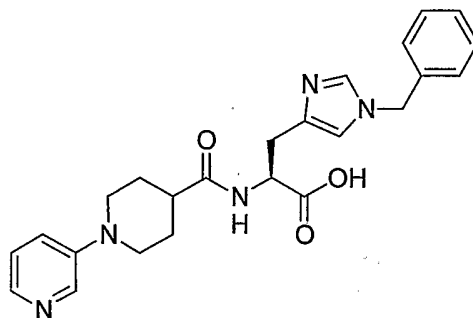
Example 13B

5 2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid

To a flask was added 13A (0.240 g, 1.02 mmol) 5 mL THF and LiOH monohydrate (0.130 g, 3.07 mmol) dissolved in 3 mL water. The mixture was
10 stirred for 18 h and acidified to pH 1 with 0.1 N HCl. All solvents were removed *in vacuo* and the acid obtained was treated with L-alanine methyl ester HCl as described in Example 1F. The resulting methyl ester was hydrolyzed as described in Example
15 1G. The crude product obtained was purified by C-18 reverse phase HPLC eluting with a gradient of 5-95% CH₃CN containing 0.1% TFA to provide the title compound (0.006g, 0.49 mmol, 5.0%) as a white solid.
(¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.42 (d, $J=2.73$ Hz, 1H),
20 8.23 (d, $J=7.41$ Hz, 1H), 8.1 (d, $J=5.07$ Hz, 1H), 7.94 (m, 1H), 7.69 (m, 1H), 4.18 (m, 1H), 3.95 (m, 2H), 2.93 (m, 2H), 2.47 (m, 1H), 1.78 (m, 2H), 1.62 (m, 2H), 1.26 (d, $J=7.41$ Hz, 3H). Analytical HPLC (Method C) $R_t=1.37$ min (52.3 area%, 220 nm), 1.40

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min (47.0 area%, 220 nm). LCMS (ESI-Method G) m/z 276.1 (M-1H)⁻, R_t =1.32 min (220 nm, 100.0 area%).

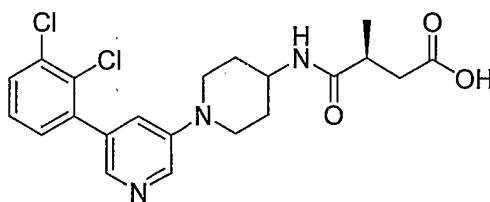


Example 14

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-[(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid

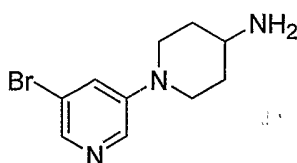
Example 14 was prepared according to the same reaction protocol as described for Example 13 substituting L-N¹-benzyl histidine methyl ester dihydrochloride for L-alanine methyl ester HCl. The procedure resulted in the title compound (0.030 g, 0.48 mmol, 14.0%) as a white solid. Analytical HPLC (Method C) R_t =1.65 min (90.4 area%, 220 nm). LCMS (ESI-Method G) m/z 432.0 (M-2H)⁻, R_t =2.02 min (220 nm, 100.0 area%).

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Example 15

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic acid

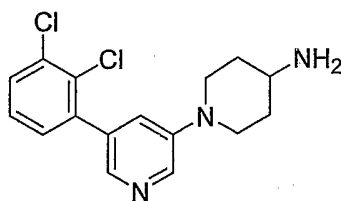


Example 15A

5'-Bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylamine

To a flask was added 3,5-dibromo pyridine
10 (2.00 g, 8.44 mmol), 4-amino piperidine (0.888 g,
8.86 mmol), and cesium carbonate (2.89 g, 8.86
mmol). The mixture was heated under N₂ to 155°C for
24 h. The mixture was cooled to rt and diluted with
toluene (30 mL), filtered, and concentrated *in vacuo*
15 and the crude product obtained was purified by
column chromatography on silica gel eluting with 20%
7 N methanolic ammonia/DCM to provide the title com-
pound (0.440 g, 20.5%) as a yellow oil. LCMS
(ESI+Method G) *m/z* 322.2 (M⁺), *Rt*=2.57 min (220 nm,
20 100.0 area%).

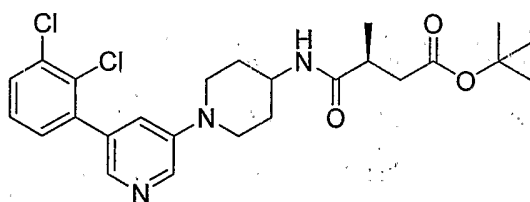
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Example 15B

5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-
[1,3']bipyridinyl-4-ylamine

5 Example 15B was prepared according to the
same reaction protocol as described for Example 7B
substituting 15A for 7A. The procedure resulted in
the title compound (0.160 g, 42.0%) as an off-white
solid. LCMS (ESI+ Method G) m/z 256.3 (M^+), R_t =1.72
10 min (220 nm, 100.0 area%).



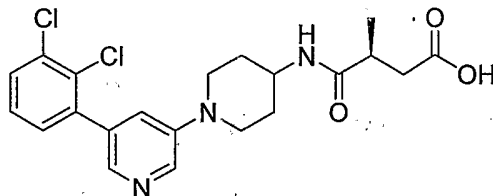
Example 15C

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-
[1,3']bipyridinyl-4-yl]-3-methyl-succinamic acid
15 tert-butyl ester

Example 15C was prepared according to the
same reaction protocol as described for Example 1
substituting 15E for 1E and 15G for L-alanine methyl
ester to provide the title compound (0.145 g, 95%)
20 as an off-white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ
8.33 (d, J =3.12 Hz, 1H), 8.1 (d, J =1.56 Hz, 1H),
7.51 (m, 1H), 7.27 (t, J =7.8 Hz, 1H), 7.24 (d,

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$J=1.95$ Hz, 1H), 7.23 (m, 1H), 5.79 (m, 1H), 3.97 (m, 1H), 3.7 (m, 2H), 2.98 (m, 2H), 2.65 (m, 2H), 2.32 (m, 2H), 2.05 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H), 1.17 (d, $J=6.63$ Hz, 3H.)



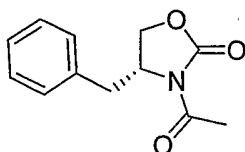
5

Example 15D

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic acid

To a stirred solution of 15C (0.065 g, 0.132 mmol) in 2 mL DCM was added 0.5 mL TFA. The mixture was stirred for 24 h and concentrated *in vacuo*. The residual oil was partitioned between EtOAc and brine. The organic layer was separated and dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the title compound (0.035 mg, 60.0%) as an off-white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.2 (s, 1H), 8.4 (s, 1H), 8.06 (s, 1H), 7.81 (m, 2H), 7.5 (m, 3H), 3.81 (m, 9H), 2.96 (m, 2H), 2.62 (m, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 1.81 (m, 2H), 1.48 (m, 2H), 1.02 (d, $J=6.63$ Hz, 3H) HPLC (Method C) $R_t=2.08$ min (94.6 area%, 220 nm). LCMS (ESI-Method G) m/z 448.7 (M-2H) $^+$ $R_t=3.77$ min (220 nm, 100.0 area%).

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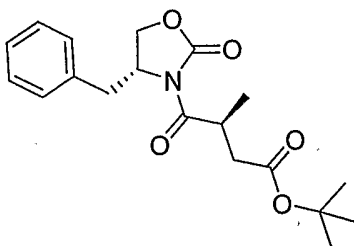


Example 15E

4-Benzyl-3-acetyl-oxazolidin-2-one

The procedure was adapted from Levy et al. (1998) *J. Med. Chem.* 41:199-223. 4-Benzyl-3-propionyl-oxazolidin-2-one was prepared as follows. To an oven dried 2 L flask under N₂ was added (R)-4-benzyl-oxazolidin-2-one (30.0 g, 169.3 mmol) and THF (300 mL by canula, dry, degassed with N₂ for 30 min). The flask was cooled in a dry ice/acetone bath to -78°C (internal probe temperature). Next was added *n*-BuLi (10.84 g, 169.3 mmol, 2.41 M in hexanes) dropwise over a 30 min period to maintain reaction temperature below -68°C. After the addition was complete the mixture was stirred for 30 min and propionyl chloride (17.2 g, 186 mmol) was added over 15 min and the mixture stirred for 1 h. The reaction was allowed to warm to rt over 1 h and quenched by pouring into a 1 L separatory funnel containing 300 mL of saturated aqueous NH₄Cl. The mixture was partitioned with EtOAc (600 mL), separated and the organic layer was washed sequentially with 200 mL saturated aqueous NaHCO₃ and 200 mL brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the title compound (42.18 g, 107%) as a light colored oil.

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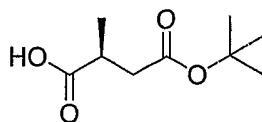
Example 15F

4-(4-Benzyl-2-oxo-oxazolidin-3-yl)-3-methyl-4-oxo-
butyric acid tert-butyl ester

5 To an oven dried 1 L flask under N₂ was added anhydrous THF (250 mL) and diisopropylamine (14.3g, 141 mmol). The flask was cooled to 0°C in an ice bath, and *n*-BuLi (9.06 mL, 2.54 M, 141 mmol) was added over 10 min and the flask was cooled to
10 -78°C in a dry ice/acetone bath. To the resulting LDA solution was added a solution of 15E (30.0 g, 128.6 mmol) in 40 mL dry THF over 30 min. The yellow solution was stirred at -78°C for 2 h. Bromoacetic acid tert-butyl ester (67.7 g, 347 mmol)
15 was added dropwise over 20 min and the mixture was stirred for 30 min at -78°C. The mixture was warmed to 0°C by placing the flask in a water-ice bath for 20 min. The mixture was quenched by pouring into 1 L separatory funnel containing 200 mL of sat. aq NH₄Cl.
20 The mixture was diluted with EtOAc (300 mL), the phases were separated and the organic phase was washed sequentially with 1 N HCl (2X100 mL), sat. aq NaHCO₃ (2X100 mL), and brine (2X100 mL). The organic layer was dried over Na₂SO₄, concentrated and purified
25 on a Biotage 65 column (9:1 hexane: MTBE). The

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title compound was obtained as a white crystalline solid (29.1 g, 65%).



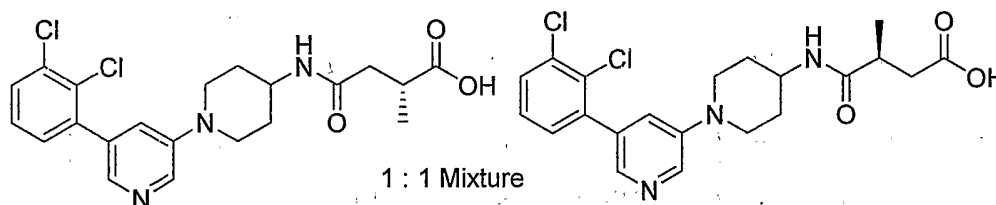
Example 15G

5 2-Methyl-succinic acid 4-tert-butyl ester

To a 1 L flask was added Example 15F (29.0 g, 83.5 mmol) and THF/water (300 mL, 4:1 mixture). The mixture was cooled to 0°C in an ice bath and 30% H₂O₂ (17.0 g, 501 mmol, in water) was added over 10 min with stirring. Next was added LiOH (2 M in water, 4.73 g, 117 mmol) and the reaction was stirred for 4 h in an ice bath. The reaction was quenched by careful dropwise addition of Na₂SO₃ (2.73 M) over 1 h, resulting in slight gas evolution. The THF was removed *in vacuo* and the resulting suspension was extracted with DCM (400 mL). The aqueous phase was reserved (contained desired product) and the DCM was washed with 0.1 N NaOH (100 mL). The organic phase was dried, filtered, and concentrated *in vacuo* to afford the chiral auxiliary (reusable). The combined aqueous phase was cooled in an ice bath and acidified with 2 N HCl to pH 4. The cloudy solution was extracted with EtOAc (300 mL), the EtOAc layer was dried with Na₂SO₄, filtered, and concentrated to give the crude product as a colorless oil, which solidified to a white solid upon standing. The product was purified by a Biotage 40 column, eluting

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with 30% EtOAc/hexanes, to provide the title compound (13.4 g, 85%): $[\alpha]_D = -6.56^\circ$ (-7.0° published) (c 0.86, CHCl_3 , 9 mg/mL), contains minuscule chiral auxiliary which alters the rotation to the + direction. (Lit: Davies et al. (1998) *J. Chem. Soc., Perkin Trans. 1* 17:2635-2644).

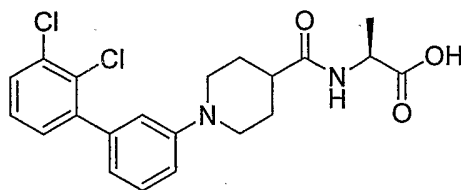


Example 16

10 N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic/N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-2-methyl-succinamic acid

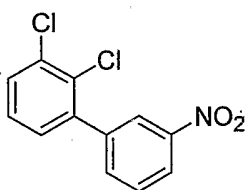
Example 16 was prepared as in Example 1G substituting 15C for 1E. The procedure provided the title compounds as an off-white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.09 (s, 1H), 8.36 (d, $J=2.73$ Hz, 1H), 8 (d, $J=1.95$ Hz, 1H), 7.86 (m, 1H), 7.71 (m, 1H), 7.45 (m, 2H), 3.78 (m, 3H), 2.92 (m, 2H), 2.69 (m, 1H), 2.43 (m, 1H), 2.15 (m, 1H), 1.8 (m, 2H), 1.48 (m, 2H), 1.05 (d, $J=7.02$ Hz, 3H), 1.02 (d, $J=7.02$ Hz, 3H). Analytical HPLC (Method C) $R_t=2.08$ min (92.3 area%, 220 nm). LCMS (ESI-Method G) m/z 448.7 $(\text{M}-2\text{H})^-$ $R_t=3.77$ min (220 nm, 100.0 area%).

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Example 17

2,3-Dichloro-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid



5

Example 17A

2,3-Dichloro-3'-nitro-biphenyl

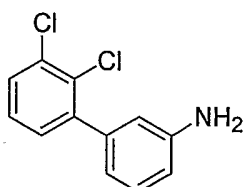
A solution of 2,3-dichloro-iodobenzene (6.00 g, 22.0 mmol) in 60 mL toluene and 20 mL ethanol was treated with 3-nitro-phenylboronic acid (4.22 g, 25.3 mmol) and Na₂CO₃ (2 N in H₂O, 30.0 mL). Then mixture was purged with N₂ for 5 min and Pd(PPh₃)₄ (1.02 g, 0.879 mmol) was added. The mixture was heated to 90°C for 24 h and cooled to ambient temperature and concentrated *in vacuo*. The residual oil was partitioned with Et₂O (80 mL) and washed with dilute brine solution (3x50 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting white solid was recrystallized from hexane and to give the title compound (2.30 g, 39%) as a fluffy white solid. ¹H NMR (CDCl₃, 400 MHz) δ

15

20

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8.29 (m, 2H), 7.76 (m, 1H), 7.63 (t, $J=7.61$ Hz, 1H),
7.55 (m, 1H), 7.31 (t, $J=7.81$ Hz, 1H), 7.26 (m, 1H.)

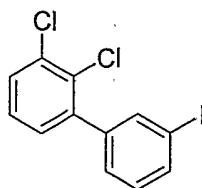


Example 17B

5 2,3-Dichloro-3'-amino-biphenyl

To a solution of 17A (2.30 g, 8.58 mmol) in acetic acid (100 mL) was added zinc dust (5.61 g, 85.8 mmol). The mixture was stirred for 2 h, diluted with DCM (40 mL), and filtered through Celite. 10 The solution was partitioned with NaHCO_3 and extracted with DCM (3 X 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the title compound (1.80 g, 88%) as a light yellow colored oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.44 (m, 1H), 7.22 (m, 2H), 6.78 (m, 1H), 6.71 (m, 2H), 3.73 (s, 15 2H).

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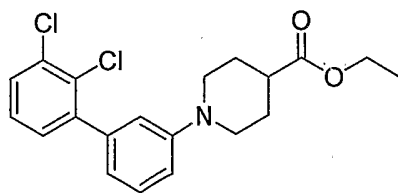


Example 17C

2,3-Dichloro-3'-iodo-biphenyl

A suspension of 17B (4 g, 21.44 mmol) in
5 3N H₂SO₄ (0.15 M) at 0°C was treated with a solution
of NaNO₂ (0.869 g, 12.60 mmol) in water (2 mL) for 1
h. Then KI (2.09 g, 12.60 mmol) and urea (151 mg,
2.52 mmol) in water (2 mL) were added, stirred at
0°C for 1 h and allowed to warm to ambient tempera-
10 ture over 2 h. The reaction mixture was partitioned
with EtOAc (50 mL) and washed with 20% NaHSO₃ (3x20
mL), then saturated NaHCO₃ solution (3x20 mL). The
organic layer was separated, dried (Na₂SO₄), fil-
tered, and concentrated under reduced pressure to
15 provide the title compound (1.02 g, 70%) as a light
red oil. ¹H NMR (CDCl₃, 400 MHz) δ 7.74 (m, 2H),
7.48 (m, 1H), 7.39 (m, 1H), 7.25 (t, J=7.81 Hz, 1H),
7.19 (m, 2H.)

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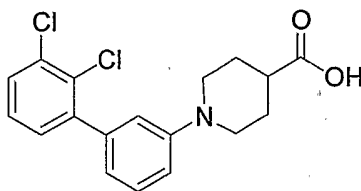


Example 17D

2,3-Dichloro-3'-piperidine-4-carboxylic acid ethyl ester

5 To a solution of 17C (0.850 g, 2.44 mmol) in 5 mL toluene was added Cs_2CO_3 (1.19 g, 3.65 mmol) and ethyl isonipecotate (0.460 g, 2.92 mmol). The mixture was purged with N_2 for 5 min and racemic-BINAP (0.228 g, 0.365 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.112 g, 10 0.122 mmol) were added and the mixture heated to 100°C for 18 h. After cooling to ambient temperature, the mixture was partitioned between dilute brine (30 mL) and toluene (50 mL). The organic layer was washed (3X20 mL) with dilute brine and 15 concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel eluting with 1:20 EtOAc/hexane to give the title compound (0.330 g, 36%) as a light colored oil which solidified upon standing. ^1H NMR (CDCl_3 , 400 MHz) δ 7.41 20 (m, 1H), 7.29 (m, 1H), 7.21 (m, 2H), 6.95 (m, 2H), 6.84 (m, 1H), 4.14 (dd, $J=7.41$, 14.45 Hz, 2H), 3.66 (m, 2H), 2.82 (m, 2H), 2.43 (m, 1H), 2.01 (m, 2H), 1.88 (m, 2H), 1.26 (t, $J=7.41$, 3H.)

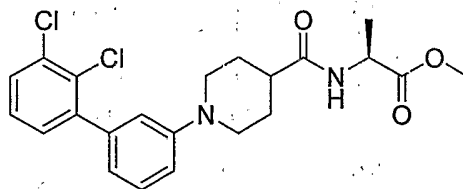
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Example 17E

2,3-Dichloro-3'-piperidine-4-carboxylic acid

Example 17D (0.350 g, 0.925 mmol) was
5 processed as in Example 1E to provide the title com-
pound (0.292 g, 90.1%) as a cream color powder.
¹H NMR (CDCl₃, 400 MHz) δ 11.36 (s, 1H), 7.45 (m,
1H), 7.32 (t, J=7.81 Hz, 1H), 7.23 (m, 2H), 7.00 (m,
2H), 6.91 (m, 1H), 3.69 (m, 2H), 2.88 (m, 2H), 2.52
10 (m, 1H), 2.08 (m, 2H), 1.94 (m, 2H).



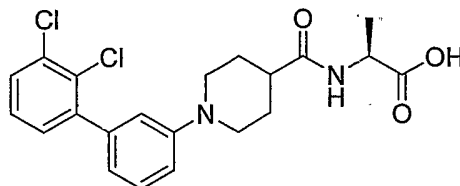
Example 17F

2,3-Dichloro-3'-2-[(piperidine-4-carbonyl)-amino]-
propionic acid methyl ester

15 Example 17E (0.150 g, 0.428 mmol) was pro-
cessed as in Example 1F to provide the title com-
pound (0.1600 g, 85.8%) as a cream color powder.
¹H NMR (CDCl₃, 400 MHz) δ 7.44 (m, 1H), 7.31 (t,
J=7.81 Hz, 1H), 7.23 (m, 2H), 6.96 (m, 2H), 6.85 (m,
20 1H), 6.27 (d, J=7.42 Hz, 1H), 4.61 (m, 1H), 3.78 (m,

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5H), 2.78 (m, 2H), 2.31 (m, 1H), 1.95 (m, 4H), 1.42 (d, $J=7.03$ Hz, 3H).



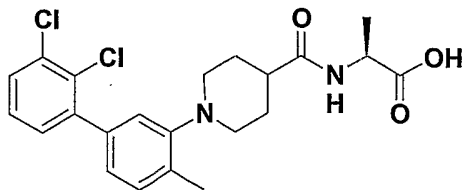
Example 17G

5 2,3-Dichloro-3'-2[(piperidine-4-carbonyl)-amino]-
propionic acid

Example 17F (0.230 g, 0.368 mmol) was processed as in Example 1G to provide the title compound (0.104 g, 67.2%) as a cream color powder.

10 ^1H NMR (CDCl_3 , 400 MHz) δ 12.45 (s, 1H), 8.18 (m, 1H), 7.71 (m, 1H), 7.48 (t, $J=7.8$ Hz, 1H), 7.44 (m, 1H), 7.44 (m, 1H), 7.35 (t, $J=7.21$ Hz, 1H), 7.07 (m, 1H), 6.98 (m, 2H), 6.85 (d, $J=7.02$ Hz, 1H), 4.25 (m, 1H), 3.82 (m, 2H), 2.78 (m, 2H), 2.41 (m, 1H), 1.82
15 (m, 4H), 1.34 (d, $J=7.41$ Hz, 3H). Analytical HPLC (Method A) $R_t=2.73$ min (100.0 area%, 220 nm). LCMS (APCI+ Method D) m/z 421.1 (M^+), $R_t=2.77$ min (220 nm, 100.0 area%).

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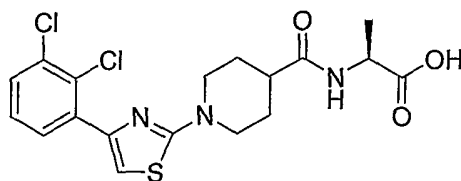


Example 18

2,3-Dichloro-4'-methyl-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid

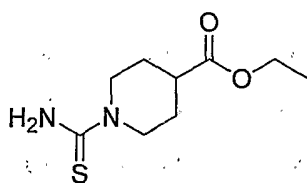
- 5 Example 18 was prepared as in Example 17
by substituting 4-methyl-3-nitro-phenylboronic acid
for 3-nitro-phenylboronic acid. The title compound
(0.090 g, 48.6%) was obtained as a cream color
powder. ¹H NMR (CDCl₃, 400 MHz) δ 12.4 (s, 1H), 8.08
10 (d, J=7.42 Hz, 1H), 7.62 (m, 1H), 7.4 (t, J=7.81 Hz,
1H), 7.35 (m, 1H), 7.22 (d, J=7.42 Hz, 54H), 6.98
(m, 2H), 4.18 (m, 1H), 3.11 (m, 2H), 2.6 (m, 2H),
2.26 (m, 3H), 1.76 (m, 4H), 1.24 (d, J=7.42 Hz, 3H).
HPLC (Method A) Rt=2.65 min (93.0 area%, 254 nm).
15 LCMS (APCI+ Method D) m/z 435.1 (M⁺), Rt=3.36 min
(254 nm, 90.6 area%).

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Example 19

2-((1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-
piperidine-4-carbonyl)-amino)-propionic acid

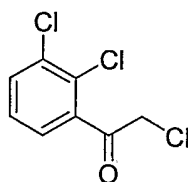


Example 19A

1-Thiocarbamoyl-piperidine-4-carboxylic acid ethyl
ester

To a flask was added trimethylsilyl-thio-
10 isocyanate (5.01 g, 38.2 mmol), 60 mL dry DCM, eth-
ylisonipeccotat (2.00 g, 12.72 mmol) and 4-dimethyl-
amino-pyridine (0.077 g, 0.636 mmol). The mixture
was stirred at 40°C for 72 h and cooled to ambient
temperature. DCM (40 mL) was added and the mixture
15 washed with 0.3 N HCl (3x30 mL). The organic layer
was separated, dried (Na₂SO₄), filtered, and concen-
trated under reduced pressure. The crude product
was purified by flash chromatography on silica gel
eluting with 15% 7 N methanolic ammonia/DCM to pro-
20 vide the title compound (1.30 g, 47.2%) as a light
yellow solid.

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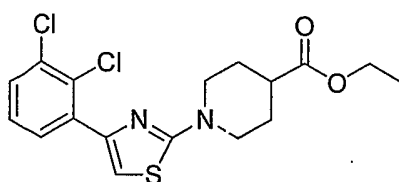


Example 19B

2-Chloro-1-(2,3-dichloro-phenyl)-ethanone

To a mixture of 2-3-dichloro-acetophenone
5 in carbon tetrachloride (9 mL) was added sulfuryl
chloride (3.93 g, 29.05 mmol). The mixture was
heated to 45°C for 48 h. The mixture was cooled to
ambient temperature and a second bolus of sulfuryl
chloride (3.93 g, 29.05 mmol) was added. The mix-
10 ture was stirred at 45°C for 72 h. The mixture was
cooled to ambient temperature and concentrated under
reduced vacuum to provide the title compound. The
light orange solid (5.80 g, 95%) was carried on
without further purification. Analytical HPLC
15 (Method A) Rt=3.07 min (7 area%, 220 nm, starting
material); Rt=3.35 min (68 area%, 220 nm, Example
19B).

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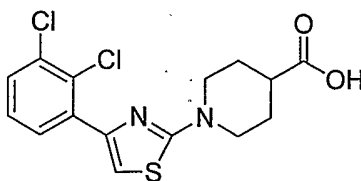


Example 19C

1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carboxylic acid ethyl ester

- 5 To a solution of 19A (1.66 g, 7.68 mmol) in 10 mL THF at 0°C was added LiHMDS (1.41 g, 8.44 mmol). The mixture was stirred for 10 min and 19B (2.40 g, 10.74 mmol) was added. The mixture was allowed to warm to ambient temperature over 3 h.
- 10 The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 1:4 EtOAc:hexane to provide the title compound (0.300 g, 10%) as a light yellow solid. Note: only pure fraction collected off column. ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (dd, *J*=1.56, 7.80, 1H), 7.39 (dd, *J*=1.56, 7.80, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 7.06 (s, 1H), 4.17 (q, *J*=7.02, 14.43 Hz, 2H), 4 (m, 2H), 3.14 (m, 2H), 2.53 (m, 1H), 2.03 (m, 2H), 1.87 (m, 2H), 1.27 (t, *J*=7.21 Hz, 3H.)

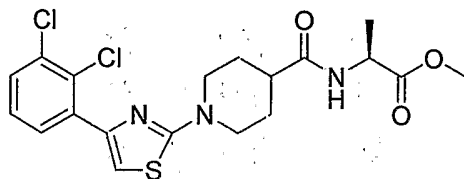
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Example 19D

1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carboxylic acid

5 Example 19D (0.30 g, 0.778 mmol) was processed as in Example 1E to provide the title compound (0.250 g, 90.0%) as a light yellow colored powder.

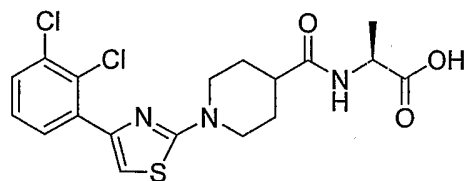


10 Example 19E

2-({1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl}-amino)-propionic acid methyl ester

15 Example 19D (0.100g, 0.280 mmol) was processed as in Example 1F to provide the title compound (0.100 g, 81.0%) as a light yellow colored powder.

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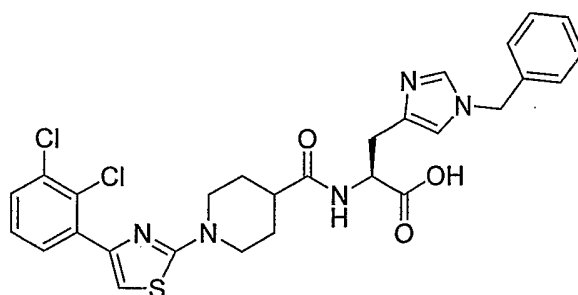


Example 19F

2-((1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl)-amino)-propionic acid

5 Example 19F (0.104 g, 67.2%) was prepared
as described in Example 1G substituting Example 19E
(0.230 g, 0.368 mmol) for Example 1D. The title
compound (0.104 g, 67.2%) was obtained as a pale
yellow powder. ¹H NMR (DMSO-d₆, 400 MHz) δ 7.79 (dd,
10 J=1.56, 7.80 Hz, 1H), 7.4 (dd, J=1.56, 7.80 Hz, 1H),
7.22 (t, J=7.8 Hz, 1H), 7.06 (s, 1H), 4.18 (q,
J=7.02, 14.40 Hz, 2H), 4.00 (m, 2H), 3.14 (m, 2H),
2.53 (m, 1H), 2.03 (m, 2H), 1.87 (m, 2H), 1.27 (t,
J=7.21 Hz, 3H). Analytical HPLC (Method A) Rt=2.953
15 min (96 area%, 220 nm). LCMS (APCI+ Method D) m/z
428.1 (M⁺), Rt=3.13 min (220 nm, 100.0 area%).

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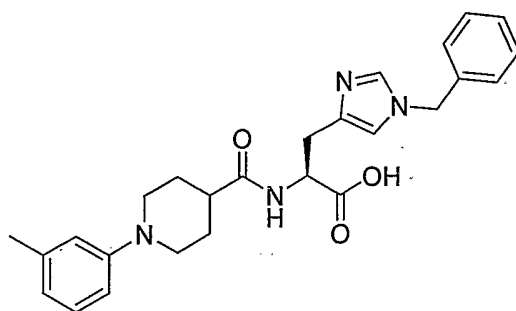


Example 20

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[4-(2,3-
 5 dichloro-phenyl)-thiazol-2-yl]-piperidine-4-
 carbonyl}-amino)-propionic acid

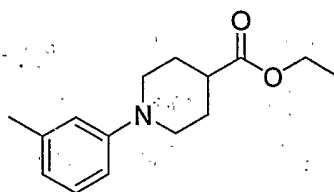
Example 19D (0.120 g, 0.336 mmol) was
 processed as in Example 19 substituting L-N¹-benzyl
 histidine methyl ester dihydrochloride for L-alanine
 methyl ester to provide the title compound (0.100 g,
 10 50.9%) as a light yellow colored powder. ¹H NMR
 (DMSO-*d*₆, 400 MHz) δ 8.05 (d, *J*=7.81 Hz, 1H), 7.76
 (dd, *J*=1.56, 8.20 Hz, 1H), 7.67 (m, 1H), 7.59 (dd,
J=1.56, 8.20 Hz, 1H), 7.37 (t, *J*=7.81 Hz, 1H), 7.3
 (m, 4H), 7.19 (d, *J*=6.64 Hz, 2H), 6.84 (s, 1H), 5.1
 15 (s, 2H), 4.37 (m, 1H), 3.82 (m, 2H), 3.01 (m, 2H),
 2.88 (s, 1H), 2.76 (s, 1H), 2.34 (s, 1H), 1.68 (s,
 1H), 1.54 (m, 2H), 1.44 (s, 1H). Analytical HPLC
 (Method A) Rt=2.64 min (93.0 area%, 220 nm). LCMS
 (APCI+ Method D) *m/z* 584.1 (M⁺), Rt=2.72 min (220 nm,
 20 100.0 area%).

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Example 21

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-m-tolyl-piperidine-4-carbonyl)-amino]-propionic acid



5

Example 21A

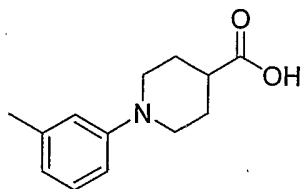
1-m-Tolyl-piperidine-4-carboxylic acid ethyl ester

A sealed tube charged with the 3-bromotoluene (159 mg, 1.325 mmol), $\text{Pd}_2(\text{dba})_3$ (30 mg, 0.0331 mmol, 2.5 mol %), (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine (Strem or Aldrich) (39 mg, 0.0994 mmol, 7.5 mol %), ethylisonipeccotatate (0.245 mL, 1.59 mmol), and powdered dried K_3PO_4 (393 mg, 1.855 mmol) in dry DME (1 mL) was purged under N_2 (3X) and heated at 90°C for 5 h under N_2 atmosphere. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (2x4 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (Biotage Flash 40 s+)

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eluting with 10% acetone/hexane to provide the title compound (300 mg, 91%) as a straw color liquid.

LCMS (APCI+; Method D) m/z 248, $(M+H)^+$.



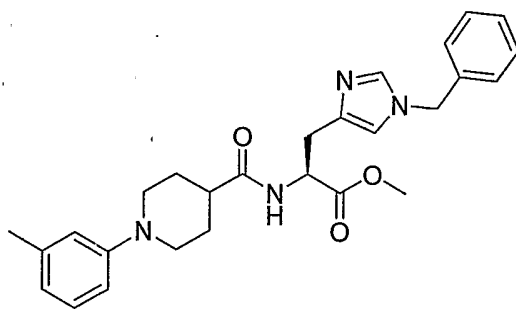
5

Example 21B

1-m-Tolyl-piperidine-4-carboxylic acid

A solution of Example 21A (298 mg, 1.205 mmol) in THF:MeOH (1:1, 6 mL) was treated with a solution of LiOH·H₂O (76 mg, 1.807 mmol) in water (2 mL) at ambient temperature for 18 h. The solvents were removed under reduced pressure. The residue dissolved in water (5 mL) and washed with EtOAc (2X5 mL) to remove organic impurities. Then the aqueous layer was made acidic with 10% aq HCl. The product formed was soluble in aqueous acidic medium and water was removed by evaporating with CH₃CN to provide the lithium salt of the title compound (159 mg, 50%). LCMS (APCI+; Method D) m/z 220, $(M+H)^+$.

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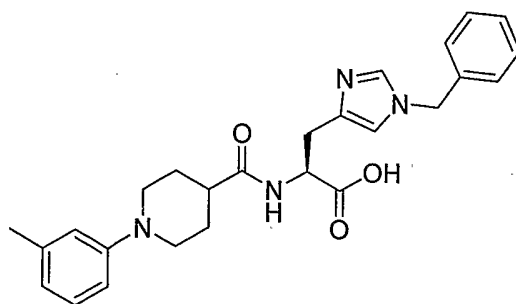


Example 21C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-m-tolyl-
piperidine-4-carbonyl)-amino]-propionic acid methyl
ester

5 A solution of Example 21B (159 mg, 0.607 mmol), HOBt·H₂O (139 mg, 0.9098 mmol), L-N¹-benzyl histidine methyl ester dihydrochloride (242 mg, 0.728 mmol), and triethylamine (0.296 mL, 2.123 mmol), in dry DMF (3 mL) was treated with EDC (174 mg, 0.9098 mmol) at ambient temperature under N₂ atmosphere for 18 h. The reaction mixture was diluted with EtOAc (10 mL), washed with water (2x5 mL), dried (MgSO₄), filtered, and evaporated to dry-
10 ness. The residue obtained was purified by flash chromatography on silica gel (Alltech SEP pack, 20 g) eluting with 2% MeOH/CH₂Cl₂ followed by 7% MeOH/-CH₂Cl₂ to provide the title compound (130 mg, 47%
15 yield) as white solid. LCMS (APCI+; Method D) m/z 461, (M+H)⁺. Analytical HPLC (Method C) Rt=1.532 min (254 nm, 100 area%).
20

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Example 21D

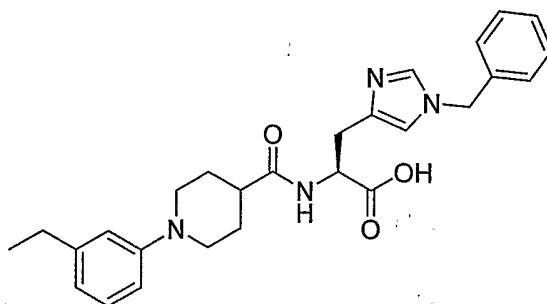
3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-m-tolyl-piperidine-4-carbonyl)-amino]-propionic acid

5 A solution of ester Example 21C (130 mg, 0.2823 mmol) in THF:MeOH (1:1 mixture, 5 mL) was treated with a solution of LiOH·H₂O (14 mg, 0.3389 mmol) in water (1 mL) at ambient temperature for 5 h. The solvents were removed, residue dissolved in
10 water (3 mL) and made acidic (pH 3-4) with formic acid. The product formed was soluble in water at this stage and the water was removed under reduced pressure. The residue was crystallized with a small amount of water (1-2 mL). The solid formed was
15 collected by filtration and dried under vacuum (oil pump) to provide the title compound (60 mg, 48%) as a white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, J=8.19 Hz, 1H), 7.67 (s, 1H), 7.36-7.29 (m, 3H), 7.23-7.21 (m, 2H), 7.07 (t, J=7.80 Hz, 1H), 6.87 (s, 1H), 6.73 (s, 1H), 6.71-6.69 (m, 1H), 6.57 (d, J=8.19 Hz, 1H), 5.13 (s, 2H), 4.41-4.36 (m, 1H), 3.66-3.58 (m, 1H), 2.91-2.86 (m, 1H), 2.80-2.74 (m, 1H), 2.64-2.54 (m, 2H), 2.68-2.19 (m, 1H), 2.24 (s, 3H), 1.70-1.65 (m, 1H), 1.62-1.46 (m, 3H). LCMS

20

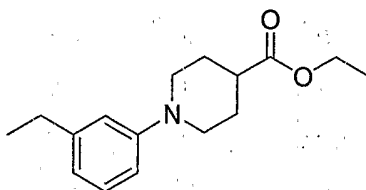
- 137 -

(APCI+; Method D) m/z 501, 503, $(M+H)^+$. Analytical HPLC (Method C) $R_t=1.763$ min. (220 nm, 100 area%).



Example 22

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3-ethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid



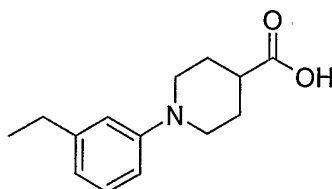
Example 22A

10 1-(3-Ethyl-phenyl)-piperidine-4-carboxylic acid ethyl ester

The title compound (275 mg, 79.4%) was prepared by the method described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3-ethyl-benzene (245 mg, 1.325 mmol). ^1H NMR (400 MHz, DMSO- d_6) δ 7.10 (t, $J=7.80$ Hz, 1H), 6.77-6.72 (m, 2H), 6.61 (d, $J=7.41$ Hz, 1H), 4.08 (q, $J=7.02$ Hz, 2H), 3.64-3.59 (m, 2H), 2.76-2.69 (m, 2H), 2.54-2.51 (m, 2H), 2.51-2.49 (m, 2H), 2.51-2.49 (m, 2H), 2.48-2.44 (m, 1H), 1.91-1.87 (m, 2H), 1.69 (1.59

- 138 -

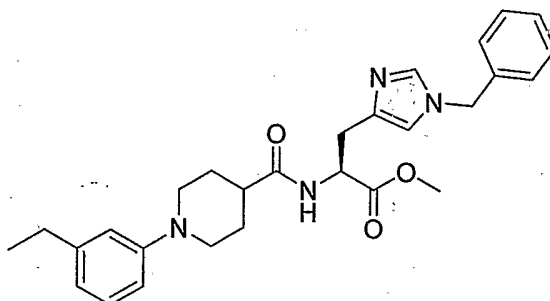
(m, 2H), 1.19 (t, $J=7.02$ Hz, 3H), 1.15 (t, $J=7.41$ Hz, 3H). LCMS (APCI+; Method D) m/z 262, (M+H)⁺.



Example 22B

5 1-(3-Ethyl-phenyl)-piperidine-4-carboxylic acid

Example 22A (190 mg, 0.727 mmol) was hydrolyzed with LiOH·H₂O (37 mg, 0.872 mmol) as described in Example 21B to provide the title compound (210 mg, 87%) as an off-white color powder. LCMS
10 (APCI+; Method D) m/z 234, (M+H)⁺.

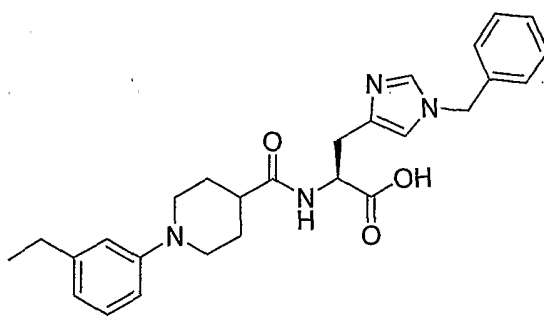


Example 22C

15 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-ethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

The title compound was prepared from Example 22B (150 mg, 0.643 mmol) as described in Example 21C. LCMS (APCI+; Method D) m/z 476, (M+H)⁺.

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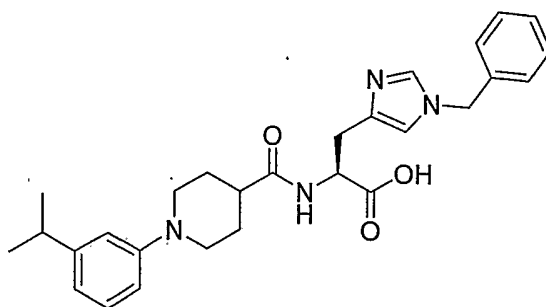


Example 22D

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-ethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

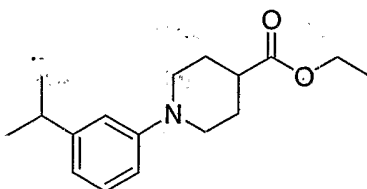
5 The title compound can be prepared according to the method described in Example 21D.

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Example 23

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-isopropyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid



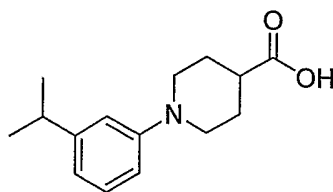
5

Example 23A

1-(3-Isopropyl-phenyl)-piperidine-4-carboxylic acid
ethyl ester

The title compound (150 mg, 40%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3-isopropyl-benzene (269 mg, 1.325 mmol). LCMS (APCI+; Method D) m/z 276, $(M+H)^+$.

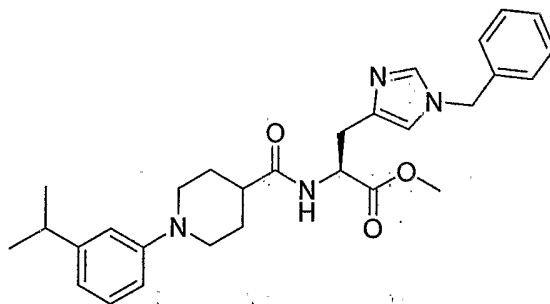
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Example 23B

1-(3-Isopropyl-phenyl)-piperidine-4-carboxylic acid

Example 23A (340 mg, 1.235 mmol) was hydrolyzed with LiOH.H₂O (78 mg, 1.852 mmol) as described in Example 21B to provide the title compound (300 mg, 84%) as a white powder. LCMS (APCI+; Method D) *m/z* 248, (M+H)⁺.

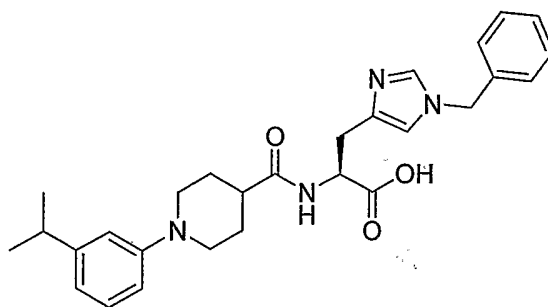


Example 23C

3-(1-Benzyl-1H-imidazol-4-yl)-2-({[1-(3-isopropyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

The title compound (220 mg, 74% yield) was prepared from Example 23B (150 mg, 0.6065 mmol) as described in Example 21C. LCMS (APCI+; Method D) *m/z* 489, (M+H)⁺. Analytical HPLC (Method C) *R*_t=1.545 min (254 nm 97 area%).

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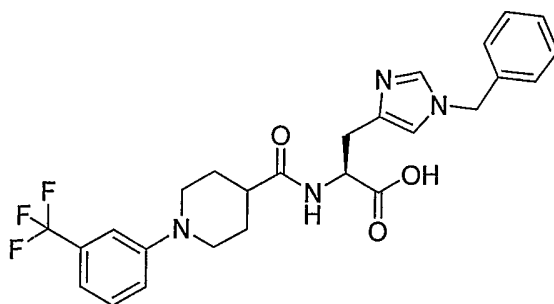


Example 23D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3-isopropyl-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid

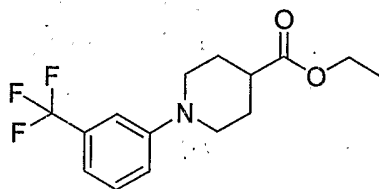
5 The title compound was prepared from Example 23C (220 mg, 0.450 mmol) as described in Example 21D. Example 23D (88 mg, 39%) was obtained as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (d, *J*=7.80 Hz, 1H), 7.67 (s, 1H), 7.37-7.29 (m, 3H),
10 7.29-7.21 (m, 2H), 7.12 (t, *J*=7.80 Hz, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.71 (dd, *J*₁=8.19 Hz, *J*₂=1.56 Hz, 1H), 6.64 (d, *J*=7.41 Hz, 1H), 5.13 (s, 2H), 4.41-
4.35 (m, 1H), 3.68-3.57 (m, 1H), 2.91-2.87 (m, 1H),
2.83-2.74 (m, 2H), 2.64-2.54 (m, 2H), 2.27-2.20 (m,
15 1H), 1.71-1.65 (m, 1H), 1.61-1.45 (m, 3H), 1.18 (d, *J*=7.02 Hz, 6H). LCMS (APCI+; Method D) *m/z* 275(M+H)⁺. Analytical HPLC (Method C) *R*_t=1.975 min (220 nm, 95 area %).

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Example 24

3-(1-Benzyl-1H-imidazol-4-yl)-2-({[1-(3-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

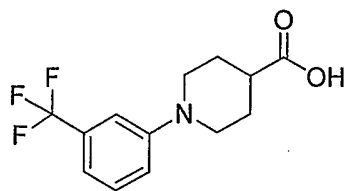


Example 24A

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carboxylic acid ethyl ester

10 The title compound (165 mg, 58%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3-trifluoromethyl-benzene (303.76 mg, 1.325 mmol). LCMS (APCI+; Method D) m/z 302, $(M+H)^+$.

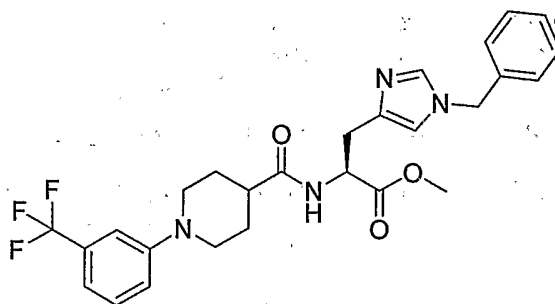
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Example 24B

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carboxylic
acid

5 Example 24A (270 mg, 0.896 mmol) was hydrolyzed with LiOH.H₂O (57 mg, 1.344 mmol) as described in Example 21B to provide the title compound (165 mg, 58%) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48-7.39 (m, 3H), 7.18 (s, 1H), 3.73-3.65 (m, 2H), 3.06-2.94 (m, 2H), 2.46 (m, 1H), 1.97-1.93 (m, 2H), 1.77-1.71 (m, 2H). LCMS (APCI+; Method D) *m/z* 274, (M+H)⁺.



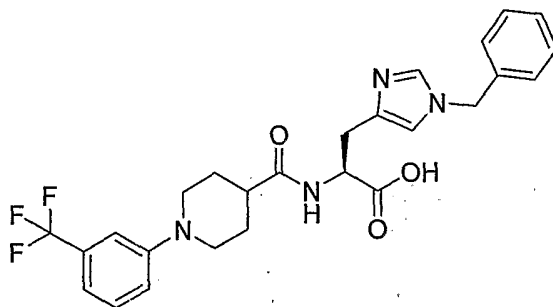
Example 24C

15 3-(1-Benzyl-1H-imidazol-4-yl)-2-({[1-(3-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

 The title compound (150 mg, 48% yield) was prepared from Example 24B (165 mg, 0.6065 mmol) as described in Example 21C. LCMS (APCI+; Method D)

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m/z 515, $(M+H)^+$. Analytical HPLC (Method C) R_t =1.452 min (220 nm, 98 area%).

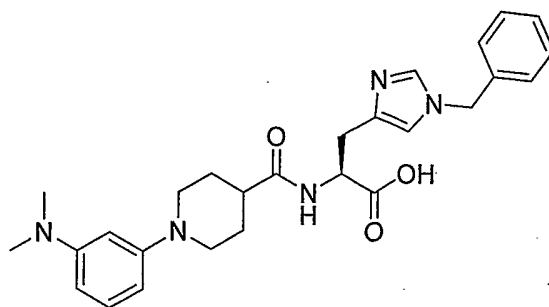


Example 24D

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

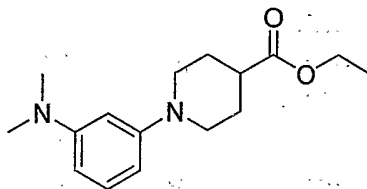
The title compound was prepared from Example 24C (150 mg, 0.292 mmol) as described in Example 10 21D. The title compound (73 mg, 50%) was obtained as a white powder. ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (d, J =7.80 Hz, 1H), 7.68 (s, 1H), 7.41 (t, J =7.80 Hz, 1H), 7.37-7.27 (m, 3H), 7.23-7.19 (m, 3H), 7.13 (s, 1H), 7.03 (d, J =7.41 Hz, 1H), 6.87 (s, 1H), 5.13 15 (s, 2H), 4.42-4.37 (m, 1H), 3.79-3.70 (m, 2H), 2.92-2.87 (m, 1H), 2.81-2.67 (m, 3H), 2.34-2.27 (m, 1H), 1.73-1.68 (m, 1H), 1.61-1.43 (m, 3H). LCMS (APCI+; Method D) m/z 502, $(M+H)^+$. Analytical HPLC (Method C) R_t =2.378 min (220 nm, 100 area %).

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Example 25.

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-
dimethylamino-phenyl)-piperidine-4-carbonyl]-amino)-
propionic acid

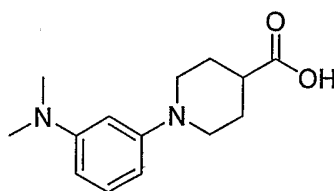


Example 25A

1-(3-Dimethylamino-phenyl)-piperidine-4-carboxylic
acid ethyl ester

The title compound was prepared by the
procedure described in Example 21A, substituting 1-
bromo-3-methyl-benzene with (3-bromo-phenyl)dimeth-
ylamine (270 mg, 1.325 mmol). LCMS (APCI+; Method
D) m/z 277, $(M+H)^+$.

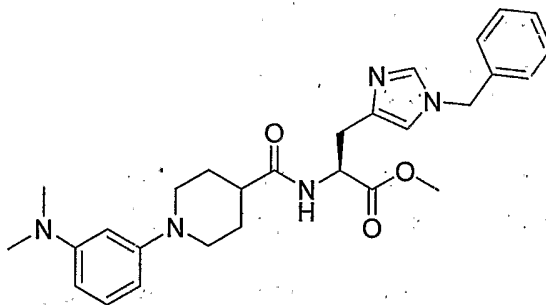
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Example 25B

1-(3-Dimethylamino-phenyl)-piperidine-4-carboxylic
acid

5 Example 25A (259 mg, 0.937 mmol) was hydrolyzed with LiOH·H₂O (59 mg, 1.406 mmol) as described in Example 21B to provide the title compound (151 mg, 55%) as a white powder. LCMS (APCI+; Method D) *m/z* 249, (M+H)⁺.



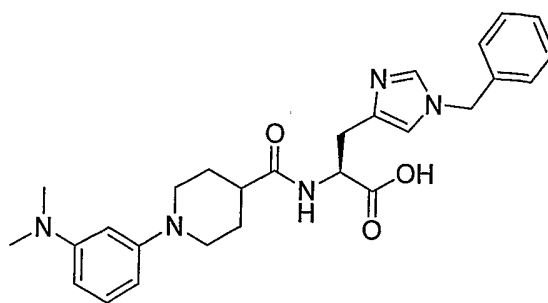
10

Example 25C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3-dimethylamino-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid methyl ester

15 The title compound (120 mg, 40.4 yield) was prepared from Example 25B (150 mg, 0.607 mmol) as described in Example 21C. LCMS (APCI+; Method D) *m/z* 490, (M+H)⁺. Analytical HPLC (Method C) *R*_t=1.562 min (220 nm, 96 area%).

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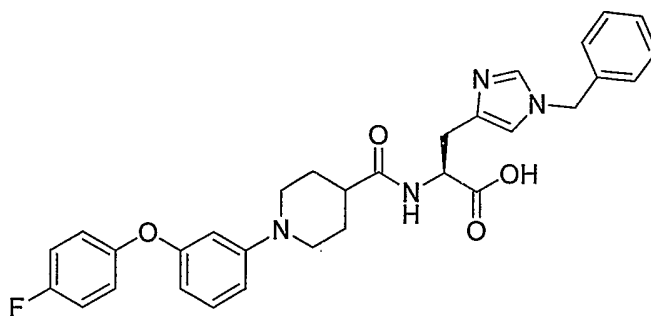


Example 25D

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3-
dimethylamino-phenyl)-piperidine-4-carbonyl]-amino}-
propionic acid

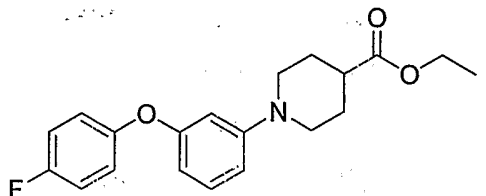
The title compound was prepared from Example 25C (120 mg, 0.245 mmol) as described in Example 21D. The title compound (50 mg, 43%) was obtained as a white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (s, 1H), 7.69 (d, J=7.80 Hz, 1H), 7.58 (s, 1H), 7.30-7.2 (m, 2H), 7.16 (d, J=6.63 Hz, 1H), 6.94 (t, J=7.80 Hz, 1H), 6.77 (s, 1H), 6.20-6.12 (m, 2H), 5.05 (s, 2H), 4.23 (m, 1H), 3.58-3.49 (m, 2H), 2.88-2.83 (m, 1H), 2.80 (s, 6H), 2.73-2.61 (m, 1H), 2.56-2.46 (m, 2H), 2.18-2.13 (m, 1H), 1.67-1.57 (m, 1H), 1.54-1.39 (m, 3H). LCMS (APCI+; Method D) m/z 476, (M+H)⁺. Analytical HPLC (Method C) Rt=1.715 min (220 nm, 100 area%).

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Example 26

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-
 5 phenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-
 propionic acid

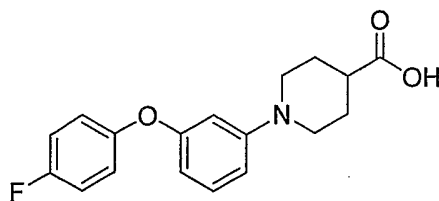


Example 26A

1-[3-(4-Fluoro-phenoxy)-phenyl]-piperidine-4-
 carboxylic acid ethyl ester

10 The title compound was prepared by the
 procedure described in Example 21A, substituting 1-
 bromo-3-methyl-benzene with 1-bromo-3-(4-fluoro-
 phenyloxy)benzene (360 mg, 1.325 mmol). LCMS
 (APCI+; Method D) m/z 344, $(M+H)^+$.

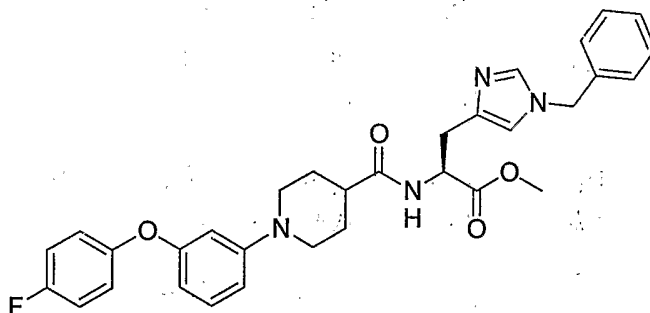
- 150 -



Example 26B

1-[3-(4-Fluoro-phenoxy)-phenyl]-piperidine-4-carboxylic acid

50 Example 26A (331 mg, 1.017 mmol) was treated with LiOH·H₂O (64 mg, 1.526 mmol) as described in Example 21B to provide the title compound (180 mg, 59%) as a white powder. LCMS (APCI+; Method D) *m/z* 316, (M+H)⁺.

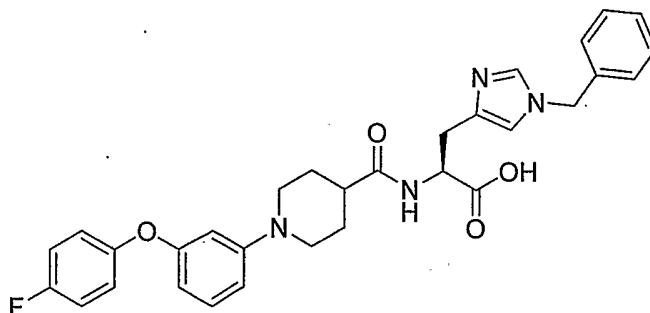


Example 26C

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-phenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid methyl ester

15 The title compound (130 mg, 40% yield) was prepared from Example 26B (191 mg, 0.607 mmol) as described in Example 21C. LCMS (APCI+; Method D) *m/z* 557, (M+H)⁺. Analytical HPLC (Method C) *R_t*=1.57 min (220 nm, 100 area%).

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Example 26D

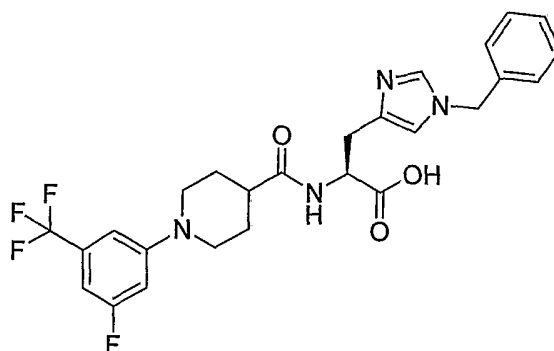
3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-
phenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-
propionic acid

5

The title compound was prepared from Example 26C (130 mg, 0.234 mmol) as described in Example 21D. Example 26D (70 mg, 55%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.03 (d, $J=8.19$ Hz, 1H), 7.68 (s, 1H), 7.34-7.31 (m, 2H), 7.27-7.15 (m, 6H), 7.06-7.02 (m, 2H), 6.86 (s, 1H), 6.69 (dd, $J_1=8.19$ Hz, $J_2=1.95$ Hz, 1H), 6.54 (m, 1H), 6.29 (dd, $J_1=7.41$ Hz, $J_2=1.56$ Hz, 1H), 5.12 (s, 2H), 4.41-4.36 (m, 1H), 3.67-3.57 (m, 2H), 2.91-2.86 (m, 1H), 2.80-2.74 (m, 1H), 2.68-2.57 (m, 2H), 2.28-2.22 (m, 1H), 1.68-1.63 (m, 1H), 1.58-1.45 (m, 3H). LCMS (APCI+; Method D) m/z 543, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $\text{Rt}=2.417$ min. (220 nm, 100 area%).

15

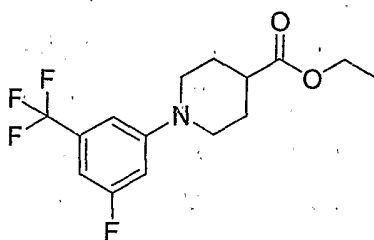
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Example 27

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3-fluoro-5-
trifluoromethyl-phenyl)-piperidine-4-carbonyl]-
amino]-propionic acid

5



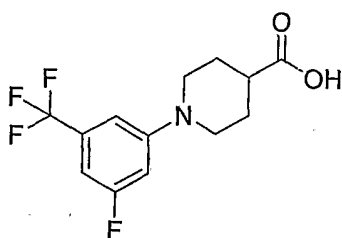
Example 27A

1-(3-Fluoro-5-trifluoromethyl-phenyl)-piperidine-4-
carboxylic acid ethyl ester

10

The title compound was prepared by the
procedure described in Example 21A, substituting 1-
bromo-3-methyl-benzene with 1-bromo-3-fluoro-5-tri-
fluoromethyl-benzene (328 mg, 1.325 mmol).

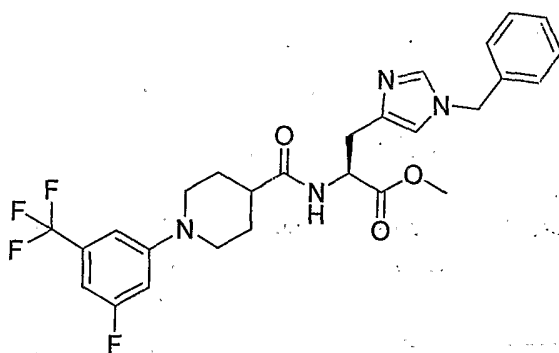
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Example 27B

1-(3-Fluoro-5-trifluoromethyl-phenyl)-piperidine-4-carboxylic acid

5 Example 27A (280 mg, 0.877 mmol) was treated with LiOH·H₂O (55 mg, 1.315 mmol) as described in Example 21B to provide the title compound (177 mg, 61%) as a white powder. LCMS (APCI+; Method D) *m/z* 292, (M+H)⁺, (92 area %).



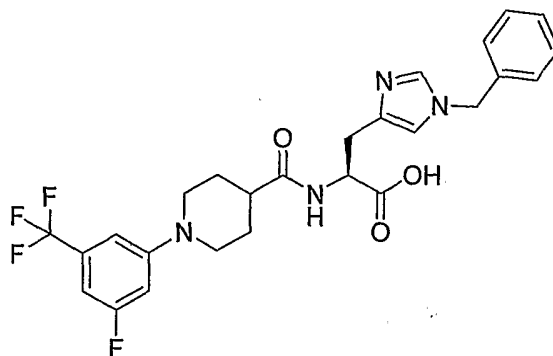
10

Example 27C

3-(1-Benzyl-1H-imidazol-4-yl)-2-({[1-(3-fluoro-5-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

15 The title compound (218 mg, 68%) was prepared from Example 27B (177 mg, 0.607 mmol) as described in Example 21C. LCMS (APCI+; Method D) *m/z* 533, (M+H)⁺.

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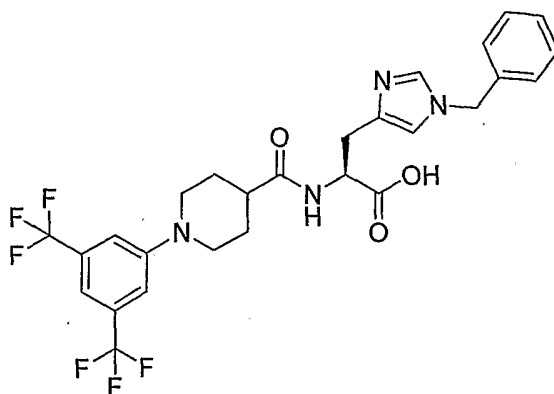


Example 27D

3-(1-Benzyl-1H-imidazol-4-yl)-2-({[1-(3-fluoro-5-
trifluoromethyl-phenyl)-piperidine-4-carbonyl]-
5 amino}-propionic acid

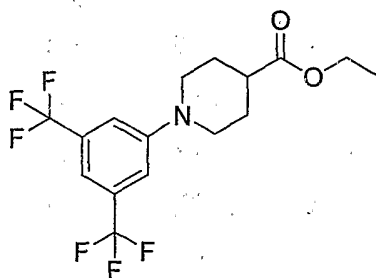
The title compound was prepared from Exam-
ple 27C (218 mg, 409 μ mol) as described in Example
21D. Example 27D (173 mg, 82%) was obtained as a
white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.07 (d,
10 $J=7.80$ Hz, 1H), 7.67 (s, 1H), 7.36-7.33 (m, 2H),
7.30-7.28 (m, 1H), 7.23-7.21 (m, 2H), 7.05-7.00 (m,
2H), 6.87-6.84 (m, 2H), 5.13 (s, 2H), 4.42-4.36 (m,
1H), 3.85-3.75 (m, 2H), 2.91-2.87 (m, 1H), 2.83-2.74
(m, 3H), 2.36-2.30 (m, 1H), 1.71-1.66 (m, 1H), 1.58-
15 1.40 (m, 3H). LCMS (APCI+; Method D) m/z 519,
($\text{M}+\text{H}$) $^+$. Analytical HPLC (Method C) $R_t=2.50$ min (220
nm, 96.3 area%).

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Example 28

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3,5-bis-
trifluoromethyl-phenyl)-piperidine-4-carbonyl]-
amino)-propionic acid



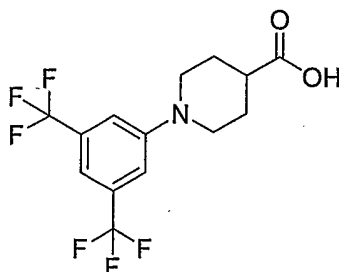
Example 28A

1-(3,5-Bis-trifluoromethyl-phenyl)-piperidine-4-
carboxylic acid ethyl ester

The title compound (386 mg, 79%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3,5-bis-trifluoromethyl-benzene (388 mg, 1.325 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 (s, 2H), 7.27 (s, 1H), 4.08 (q, J=7.02 Hz, 2H), 3.90-3.85 (m, 2H), 2.98-2.92 (m, 2H), 2.61-2.54 (m, 1H), 1.94-1.90

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(m, 2H), 1.67-1.57 (m, 2H), 1.19 (t, $J=7.02$ Hz, 3H).
LCMS (APCI+; Method D) m/z 370, (M+H)⁺.

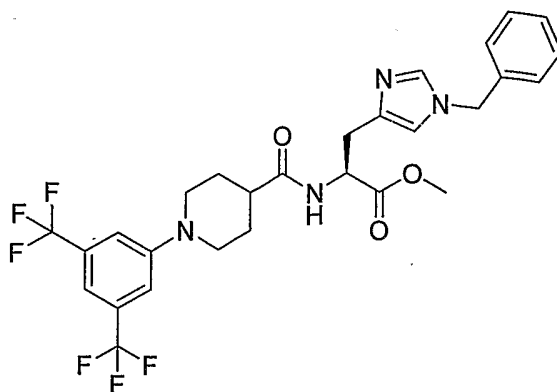


Example 28B

5 1-(3,5-Bis-trifluoromethyl-phenyl)-piperidine-4-carboxylic acid

Example 28A (380 mg, 1.029 mmol) was hydrolyzed with LiOH·H₂O (86 mg, 2.058 mmol) as described in Example 21B to provide the title compound
10 (347 mg, 98.82%) as a white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 12.31 (s, 1H), 7.46 (s, 2H), 7.27 (s, 1H), 3.89-3.85 (m, 2H), 2.98-2.91 (m, 2H), 2.47-2.44 (m, 1H), 1.94-1.89 (m, 2H), 1.66-1.56 (m, 2H). LCMS (APCI+; Method D) m/z 342, (M+H)⁺.

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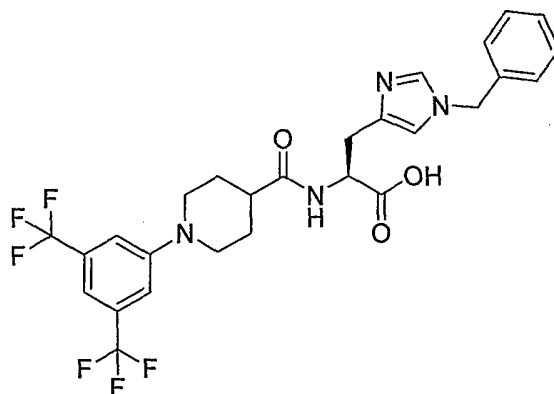


Example 28C

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3,5-bis-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

The title compound (165 mg, 74% yield) was prepared from Example 28B (130 mg, 0.383 mmol) as described in Example 21C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.21 (d, $J=7.41$, 1H), 7.67 (s, 1H), 7.44 (s, 2H), 7.36-7.33 (m, 2H), 7.28-7.20 (m, 2H), 6.88 (s, 1H), 5.13 (s, 2H), 4.47-4.42 (m, 1H), 3.93-3.85 (m, 2H), 3.55 (s, 3H), 2.89-2.78 (m, 4H), 2.39-2.33 (m, 1H), 1.75-1.70 (m, 1H), 1.64-1.59 (1H), 1.58-1.43 (m, 2H). LCMS (APCI+; Method D) m/z 583, $(\text{M}+\text{H})^+$.

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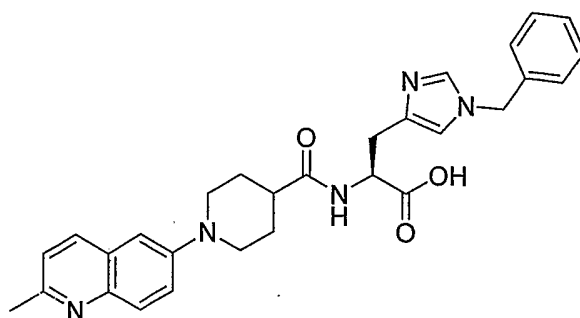


Example 28D

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3,5-bis-
trifluoromethyl-phenyl)-piperidine-4-carbonyl]-
amino}-propionic acid

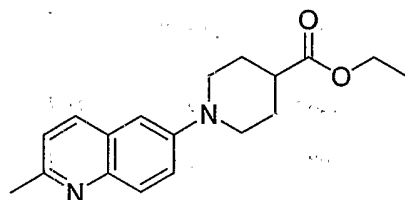
The title compound was prepared from Example 28C (160 mg, 0.275 mmol) as described in Example 21D. Example 28D (117 mg, 75%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.09 (d, $J=7.80$ Hz, 1H), 7.67 (s, 1H), 7.44 (s, 2H), 7.36-7.33 (m, 2H), 7.29-7.27 (m, 2H), 7.23-7.21 (m, 2H), 6.87 (s, 1H), 5.13 (s, 2H), 4.42-4.37 (m, 1H), 3.93-3.83 (m, 2H), 2.92-2.85 (m, 2H), 2.81-2.74 (m, 2H), 2.37-2.32 (m, 1H), 1.74-1.69 (m, 1H), 1.61-1.56 (m, 1H), 1.53-1.44 (m, 2H). LCMS (APCI+; Method D) m/z 569, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $R_t=2.704$ min (220 nm, 100 area%).

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Example 29

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(2-methyl-
quinolin-6-yl)-piperidine-4-carbonyl]-amino)-
propionic acid



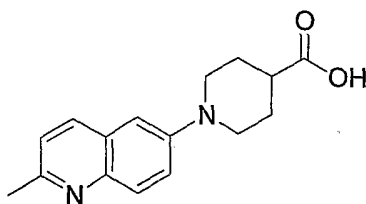
Example 29A

1-(2-Methyl-quinolin-6-yl)-piperidine-4-carboxylic
acid ethyl ester

10

The title compound was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 6-bromo-2-methyl-quinoline. Example 29A was used for the preparation of Example 29B directly.

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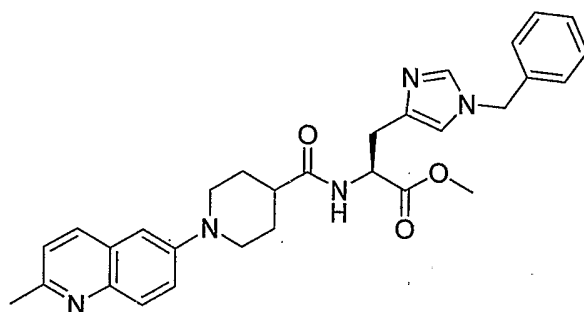


Example 29B

1-(2-Methyl-quinolin-6-yl)-piperidine-4-carboxylic acid

5 Example 29A (280 mg, 0.938 mmol) was
treated with LiOH·H₂O (59 mg, 1.408 mmol) as de-
scribed in Example 21B to provide the title compound
(164 mg, 56%) as a yellow color solid. ¹H NMR (400
10 MHz, DMSO-d₆) δ 8.73 (d, J=8.58 Hz, 1H), 8.30 (d,
J=9.36 Hz, 1H), 7.98 (d, d, J₁=22.73 Hz, J₂=9.36 Hz,
1H), 7.78 (d, J=8.56 Hz, 1H), 7.53 (d, J=2.73 Hz,
1H), 3.94-3.88 (m, 2H), 3.07-3.01 (m, 2H), 2.90 (s,
3H), 2.58-2.53 (m, 1H), 1.99-1.95 (m, 2H), 1.73-1.63
(m, 2H). LCMS (APCI+; Method D) m/z 271, (M+H)⁺.

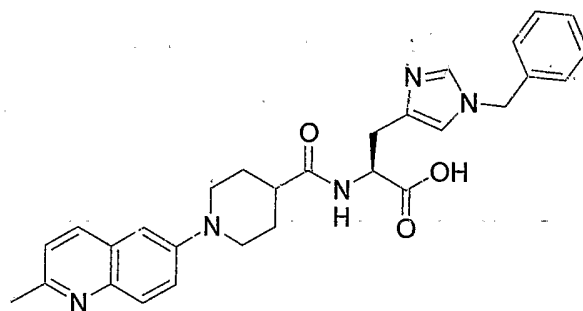
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Example 29C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(2-methyl-
quinolin-6-yl)-piperidine-4-carbonyl]-amino]-
propionic acid methyl ester

The title compound (50 mg, 16%) was prepared from Example 29B (163 mg, 0.607 mmol) as described in Example 21C. LCMS (APCI+; Method D) m/z 512, $(M+H)^+$. Analytical HPLC (Method C) $R_t=1.565$ min
(220 nm, 89 area%).



Example 29D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(2-methyl-
quinolin-6-yl)-piperidine-4-carbonyl]-amino]-
propionic acid

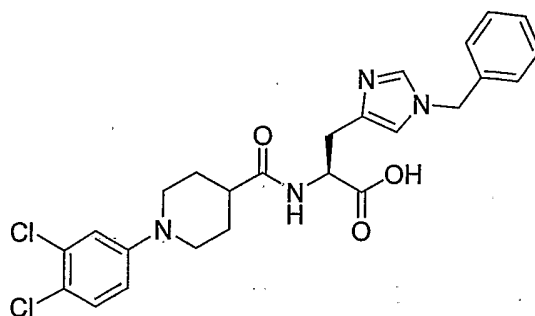
The title compound was prepared from Example 29C (50 mg, 0.098 mmol) as described in Example

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21D. The crude product obtained was purified by C-18 Reverse phase HPLC using a gradient of 5-95% CH₃CN/H₂O containing 1% TFA to provide the title compound (62 mg, 92%) as a bright yellow powder.

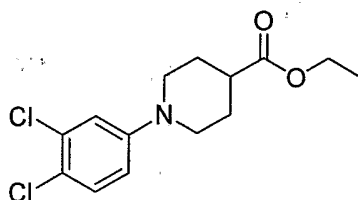
5 ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (s, 1H), 8.69 (d, J=8.58 Hz, 1H), 8.27 (d, J=8.58 Hz, 1H), 7.99 (d, J=9.36 Hz, 1H), 7.90 (d, d, J₁=2.24 Hz, J₂=9.36 Hz, 1H), 7.77 (d, J=8.58 Hz, 1H), 7.466 (m, 1H), 7.43-7.37 (m, 6H), 5.39 (s, 2H), 4.58-4.52 (m, 1H), 3.95-10 3.86 (m, 2H), 3.17-3.12 (m, 1H), 2.97-2.84 (m, 3H), 2.83 (s, 3H), 2.36-2.27 (m, 1H), 1.74-1.68 (m, 1H), 1.60-1.52 (m, 2H), 1.45-1.40 (m, 1H). LCMS (APCI+; Method D) m/z 498, (M+H)⁺, Rt=1.78 min.

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Example 30

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3,4-dichloro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

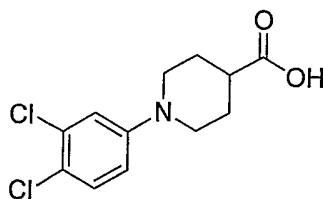


Example 30A

1-(3,4-Dichloro-phenyl)-piperidine-4-carboxylic acid
ethyl ester

The title compound (322 mg, 80.5%) was
 10 prepared by the procedure described in Example 21A,
 substituting 1-bromo-3-methyl-benzene with 4-bromo-
 1,2-dichloro-benzene (299 mg, 1,325 mmol). ¹H NMR
 (400 MHz, DMSO-*d*₆) δ 7.37 (d, *J*=8.97 Hz, 1H), 7.12
 (d, *J*=3.12 Hz, 1H), 6.93 (d, d, *J*₁=8.97 Hz, *J*₂=2.73
 15 Hz, 1H), 4.07 (q, *J*=7.02 Hz, 2H), 3.70-3.65 (m, 2H),
 2.85-2.79 (m, 2H), 2.56-2.52 (m, 1H), 1.89-1.85 (m,
 2H), 1.64-1.58 (m, 2H), 1.19 (t, *J*=7.41 Hz, 3H).
 LCMS (APCI+; Method D) *m/z* 302, 304, (M+H)⁺.

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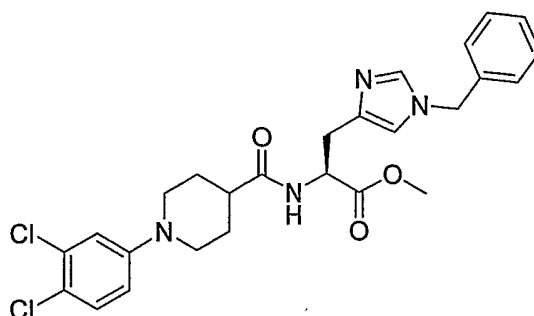


Example 30B

1-(3,4-Dichloro-phenyl)-piperidine-4-carboxylic acid

Example 30A (318 mg, 1.052 mmol) was
5 treated with LiOH.H₂O (88 mg, 2.105 mmol) as de-
scribed in Example 21B to provide the title compound
(276 mg, 96%) as a white powder. ¹H NMR (400 MHz,
DMSO-d₆) δ 12.27 (s, 1H), 7.37 (d, J=8.97 Hz, 1H),
7.12 (d, J=3.12 Hz, 1H), 6.93 (d, d, J₁=31.2 Hz,
10 J₂=8.97 Hz, 1H), 3.69-3.64 (m, 2H), 2.84-2.78 (m,
2H), 2.45-2.38 (m, 1H), 1.89-1.85 (m, 2H), 1.64-1.54
(m, 2H). LCMS (APCI+; Method D) m/z 274, 276,
(M+H)⁺.

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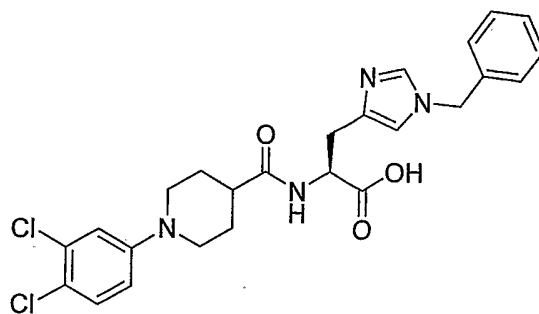


Example 30C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3,4-dichloro-
phenyl)-piperidine-4-carbonyl]-amino]-propionic acid
5 methyl ester

The title compound (130 mg, 69% yield) was
prepared from Example 30B (100 mg, 0.365 mmol) as
described in Example 21C. ¹H NMR (400 MHz, DMSO-*d*₆)
δ 8.17 (d, *J*=7.41 Hz, 1H), 7.66 (s, 1H), 7.38-7.30
10 (m, 4H), 7.22-7.19 (m, 2H), 7.10 (d, *J*=2.73 Hz, 1H),
6.91 (d, d, *J*₁=2.73 Hz, *J*₂=8.97 Hz, 1H), 6.87 (s,
1H), 5.13 (s, 2H), 4.47-4.41 (m, 1H), 3.73-3.65 (m,
2H), 3.55 (s, 3H), 2.89-2.79 (m, 2H), 2.75-2.66 (m,
2H), 2.34-2.26 (m, 1H), 1.69-1.65 (m, 1H), 1.59-1.44
15 (m, 3H). LCMS (APCI+; Method D) *m/z* 515, 517,
(*M*+H)⁺.

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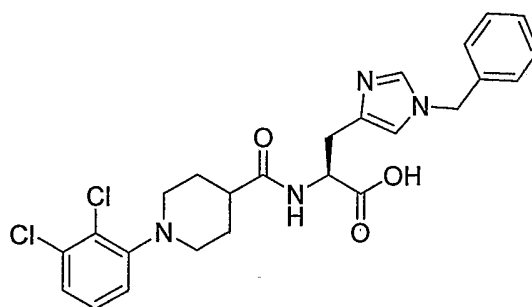


Example 30D.

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3,4-dichloro-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid

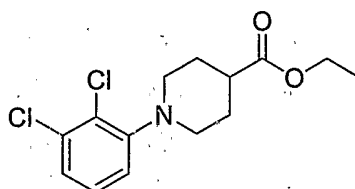
5 The title compound was prepared from Exam-
ple 30C (130 mg, 0.2522 mmol) as described in Exam-
ple 21D. Example 30D (93 mg, 73.54%) was obtained
as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.38
(br s, 1H), 8.14 (d, $J=8.19$ Hz, 1H), 7.40-7.35 (m,
10 5H), 7.29-7.28 (m, 2H), 7.13 (s, 1H), 7.09 (d,
 $J=2.73$ Hz, 1H), 6.91 (d, d, $J_1=3.12$ Hz, $J_2=8.97$ Hz,
1H), 5.25 (s, 2H), 4.49-4.43 (m, 1H), 3.73-3.63 (m,
2H), 3.03-2.98 (m, 1H), 2.88-2.82 (m, 1H), 2.73-2.63
(m, 2H), 2.29-2.28 (m, 1H), 1.67-1.61 (m, 1H), 1.55-
15 1.46 (m, 2H), 1.43-1.38 (m, 1H). LCMS (APCI+;
Method D) m/z 501, 503, $(\text{M}+\text{H})^+$. Analytical HPLC
(Method C) $R_t=2.465$ min (220 nm, 100 area%).

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Example 31

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(2,3-dichloro-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid



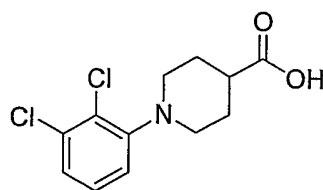
5

Example 31A

1-(2,3-Dichloro-phenyl)-piperidine-4-carboxylic acid ethyl ester

The title compound was prepared by the
 10 procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-2,3-dichloro-benzene (200 mg, 0.885 mmol). The title compound (124 mg, 46%) was obtained as a yellow color liquid.
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.30-7.29 (m, 2H), 7.14-7.11 (m, 1H), 4.09 (t, *J*=7.02 Hz, 2H), 3.25-3.20 (m, 2H), 2.75-2.69 (m, 2H), 2.48 (m, 1H), 1.96-1.92 (m, 2H), 1.79-1.69 (m, 2H), 1.20 (t, *J*=7.02 Hz, 3H).
 15 LCMS (APCI+; Method D) *m/z* 302, 304, (M+H)⁺.

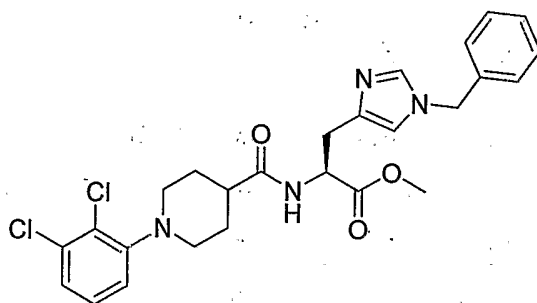
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Example 31B

1-(2,3-Dichloro-phenyl)-piperidine-4-carboxylic acid

Example 31A (120 mg, 0.397 mmol) was hydrolyzed with LiOH.H₂O (20 mg, 0.477 mmol) as described in Example 21B to provide the title compound (100 mg, 96%) as a white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 12.30 (br s, 1H), 7.30-7.28 (m, 2H), 7.14-7.12 (m, 1H), 3.24-3.19 (m, 2H), 2.74-2.68 (m, 2H), 2.44-2.56 (m, 1H), 1.95-1.91 (m, 2H), 1.77-1.68 (m, 2H). LCMS (APCI+; Method D) m/z 274, 276, (M+H)⁺.



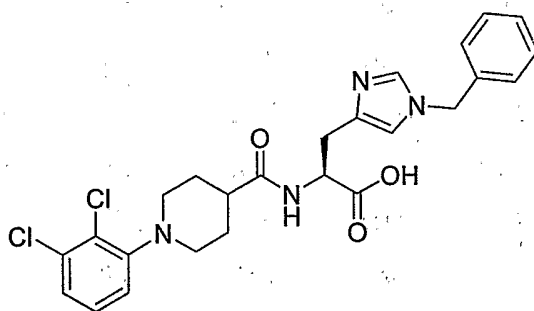
Example 31C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(2,3-dichlorophenyl)-piperidine-4-carbonyl]-amino]-propionic acid methyl ester

The title compound (135 mg, 72% yield) was prepared from Example 31B (100 mg, 0.365 mmol) as described in Example 21C. ¹H NMR (400 MHz, DMSO-d₆)

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δ 8.19 (d, $J=7.80$ Hz, 1H), 7.68 (s, 1H), 7.35-7.27 (m, 5H), 7.21-7.19 (m, 2H), 7.14-7.12 (m, 1H), 6.89 (s, 1H), 5.13 (s, 2H), 4.49-4.44 (m, 1H), 3.56 (s, 3H), 3.26-3.20 (m, 2H), 2.86-2.77 (m, 2H), 2.66-2.57 (m, 2H), 2.31-2.23 (m, 1H), 1.73-1.67 (m, 2H), 1.64-1.59 (m, 2H). LCMS (APCI+; Method D) m/z 515, 517, (M+H)⁺.

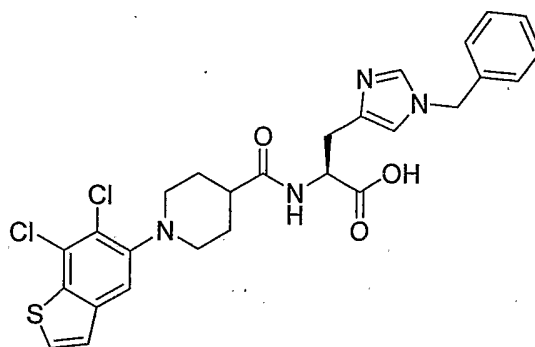


Example 31D

10 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(2,3-dichlorophenyl)-piperidine-4-carbonyl]-amino)-propionic acid

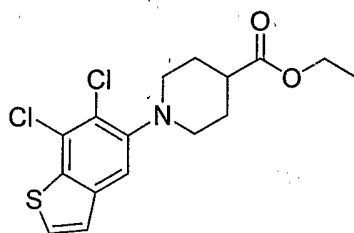
The title compound was prepared from Example 31C (130 mg, 0.2522 mmol) as described in Example 21D. Example 31D (78 mg, 62%) was obtained as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, $J=8.19$ Hz, 1H), 7.68 (s, 1H), 7.35-7.27 (m, 5H), 7.22-7.20 (m, 2H), 7.14-7.12 (m, 1H), 6.87 (s, 1H), 5.13 (s, 2H), 4.44-4.38 (m, 1H), 3.26-3.19 (m, 2H), 2.92-2.87 (m, 1H), 2.82-2.76 (m, 1H), 2.66-2.56 (m, 2H), 2.28-2.22 (m, 1H), 1.73-1.69 (m, 2H), 1.62-1.57 (m, 2H). LCMS (APCI+; Method D) m/z 510, 503, (M+H)⁺. Analytical HPLC (Method C) $R_t=2.431$ min (220 nm, 100 area%).

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Example 32

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(6,7-dichloro-
benzo[b]thiophen-5-yl)-piperidine-4-carbonyl]-
amino}-propionic acid

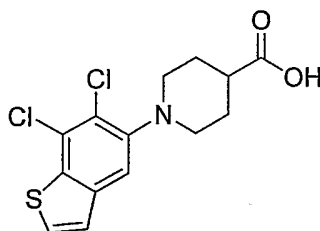


Example 32A

1-(6,7-Dichloro-benzo[b]thiophen-5-yl)-piperidine-4-
carboxylic acid ethyl ester

The title compound was prepared by the
procedure described in Example 21A, substituting 1-
bromo-3-methyl-benzene with 5-bromo-6,7-dichloro-
benzo[b]thiophene (Example 49D, 100 mg, 0.355 mmol).
The title compound (46 mg, 36%) was obtained as a
yellow color liquid. LCMS (APCI+; Method D) m/z
358, $(M+H)^+$.

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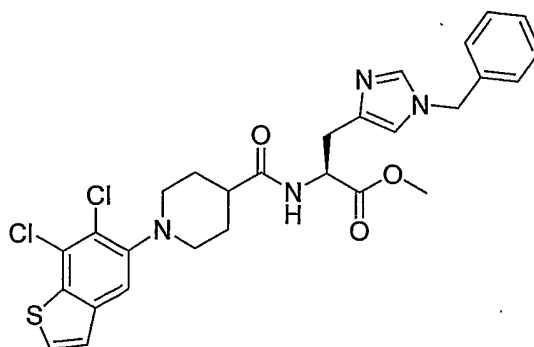
Example 32B

1-(6,7-Dichloro-benzo[b]thiophen-5-yl)-piperidine-4-carboxylic acid ethyl ester

5 Example 32A (45 mg, 126 μ mol) was hydrolyzed with LiOH $\cdot$ H₂O (6 mg, 0.151 mmol) as described in Example 21B to provide the title compound (30 mg, 72%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (d, J=5.46 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J=5.46 Hz, 1H), 3.26-3.23 (m, 2H), 2.78-2.72 (m, 2H), 2.45-2.38 (m, 1H), 1.99-1.93 (m, 2H), 1.82-1.73 (m, 2H). LCMS (APCI+; Method D) m/z 330, 332, (M+H)⁺.

10

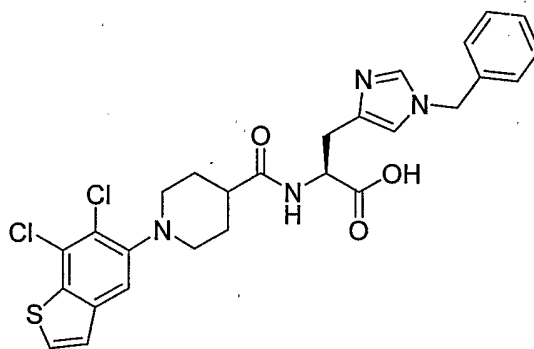
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Example 32C

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(6,7-dichloro-
benzo[b]thiophen-5-yl)-piperidine-4-carbonyl]-
5 amino)-propionic acid methyl ester.

The title compound (31 mg, 64%) was pre-
pared from Example 32B (28 mg, 0.085 mmol) as de-
scribed in Example 21C. LCMS (APCI+; Method D) m/z ,
571, 573 ($M+H$)⁺.



Example 32D

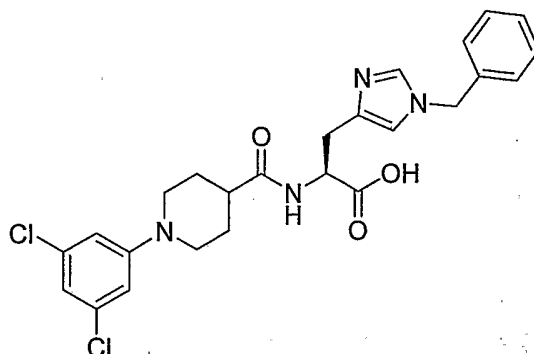
3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(6,7-dichloro-
benzo[b]thiophen-5-yl)-piperidine-4-carbonyl]-
10 amino)-propionic acid

The title compound (8 mg, 26.45%) was pre-
pared from Example 32C (31 mg, 0.0542 mmol) as de-
15

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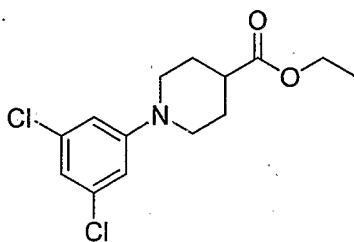
scribed in Example 21D. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ
8.09 (d, $J=7.80$ Hz, 1H), 7.88 (d, $J=5.46$ Hz, 1H),
7.68 (d, $J=8.58$ Hz, 1H), 7.67 (s, 1H), 7.50 (d,
 $J=5.46$ Hz, 1H), 7.35-7.26 (m, 3H), 7.22-7.20 (m,
5 2H), 6.89 (s, 1H), 5.13 (s, 2H), 4.46-4.40 (m, 1H),
3.29-3.23 (m, 2H), 2.94-2.89 (m, 1H), 2.83-2.77 (m,
1H), 2.71-2.59 (m, 2H), 2.33-2.25 (m, 1H), 1.77-1.72
(m, 2H), 1.68-1.62 (m, 2H). LCMS (APCI+; Method D)
 m/z 557, 559, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C)
10 $\text{Rt}=557, 559$ min (220 nm, 100 area%).

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Example 33

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3,5-dichloro-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid

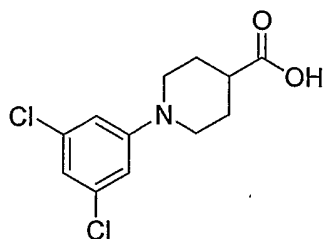


Example 33A

1-(3,5-Dichloro-phenyl)-piperidine-4-carboxylic acid ethyl ester

The title compound (263 mg, 65.75%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3,5-dichloro-benzene (299 mg, 1.325 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 6.93 (d, J=1.95 Hz, 2H), 6.82 (t, J=1.95 Hz, 1H), 4.07 (q, J=7.02 Hz, 2H), 3.75-3.70 (m, 2H), 2.89-2.83 (m, 2H), 2.58-2.52 (m, 1H), 1.89-1.84 (m, 2H), 1.63-1.53 (m, 2H), 1.19 (t, J=7.02 Hz, 3H). LCMS (APCI+; Method D) m/z 302, 304, (M+H)⁺.

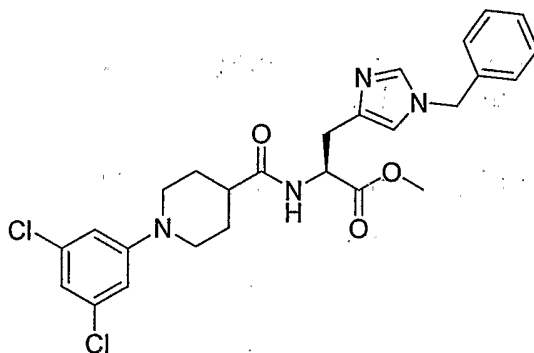
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Example 33B

1-(3,5-Dichloro-phenyl)-piperidine-4-carboxylic acid

Example 33A (260 mg, 0.704 mmol) was hydrolyzed with LiOH·H₂O (59 mg, 1.41 mmol) as described in Example 21B to provide the title compound (225 mg, 95%). ¹H NMR (400 MHz, DMSO-d₆) δ 12.28 (s, 1H), 6.92 (d, J=1.95 Hz, 2H), 6.82-6.80 (m, 1H), 3.74-3.69 (m, 2H), 2.87-2.82 (m, 2H), 2.47-2.42 (m, 1H), 1.88-1.84 (m, 2H), 1.61-1.52 (m, 2H). LCMS (APCI+; Method D) m/z 274, 276, (M+H)⁺.



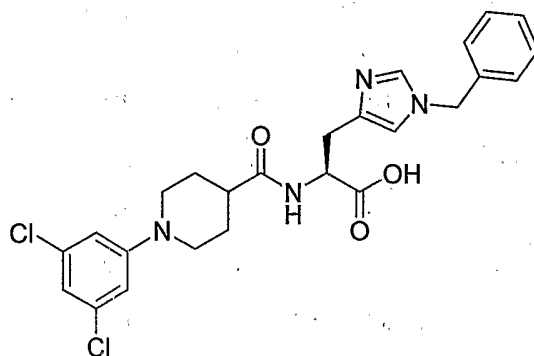
Example 33C

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3,5-dichlorophenyl)-piperidine-4-carbonyl]-amino)-propionic acid methyl ester

The title compound (156 mg, 83%) was prepared from Example 33B (100 mg, 0.365 mmol) as de-

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scribed in Example 21C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.18 (d, $J=7.41$ Hz, 1H), 7.66 (d, $J=1.56$ Hz, 1H), 7.37-7.27 (m, 3H), 7.22-7.19 (m, 2H), 6.91 (d, $J=1.56$ Hz, 2H), 6.87 (d, $J=1.17$ Hz, 1H), 6.82 (t, $J=1.56$ Hz, 1H), 5.13 (s, 2H), 4.47-4.41 (m, 1H), 3.78-3.70 (m, 2H), 3.55 (s, 3H), 2.87-2.76 (m, 3H), 2.73-2.69 (m, 1H), 2.35-2.29 (m, 1H), 1.68-1.63 (m, 2H), 1.58-1.41 (m, 3H). LCMS (APCI+; Method D) m/z 515, 517, $(\text{M}+\text{H})^+$.



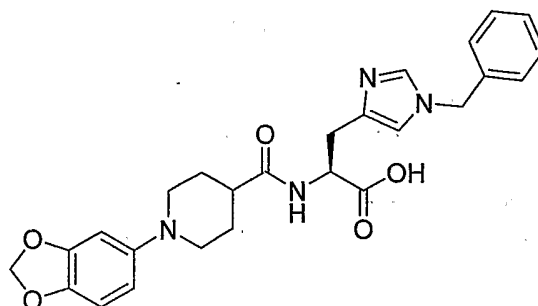
Example 33D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(3,5-dichlorophenyl)-piperidine-4-carbonyl]-amino]-propionic acid

The title compound was prepared from Example 33C (160 mg, 0.3104 mmol) as described in Example 21D. Example 33D (112 mg, 69%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.05 (d, $J=7.80$ Hz, 1H), 7.67 (s, 1H), 7.37-7.29 (m, 3H), 7.22-7.20 (m, 2H), 6.91 (s, 2H), 6.86 (s, 1H), 6.82 (s, 1H), 5.13 (s, 2H), 4.42-4.36 (m, 1H), 3.78-3.68 (m, 2H), 2.91-2.86 (m, 1H), 2.86-2.72 (m, 3H), 2.34-2.28 (m, 1H), 1.68-1.63 (m, 1H), 1.56-1.40 (m, 3H). LCMS (APCI+; Method D) m/z 501, 503, $(\text{M}+\text{H})^+$.

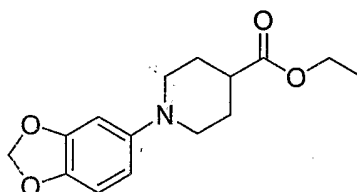
- 177 -

Analytical HPLC (Method C) Rt=2.553 min (220 nm, 95 area%).



Example 34

5 2-[(1-Benzo[1,3]dioxol-5-yl-piperidine-4-carbonyl)-amino]-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid



Example 34A

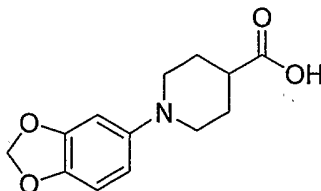
10 1-Benzo[1,3]dioxol-5-yl-piperidine-4-carboxylic acid ethyl ester

The title compound was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 5-bromo-benzo [1,3]dioxole (500 mg, 2.487 mmol). The title compound (516 mg, 75%) was obtained as a yellow color solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.74 (d, *J*=8.58 Hz, 1H), 6.66 (d, *J*=2.34 Hz, 1H), 6.33 (d, d, *J*₁=2.34Hz, *J*₂=8.58 Hz, 1H), 5.90 (s, 2H), 4.07 (q, *J*=7.21 Hz, 2H), 3.45-3.40 (m, 2H), 2.67-2.61 (m, 2H), 2.46-2.39

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(m, 1H), 1.90-1.85 (m, 2H), 1.70-1.61 (m, 2H), 1.19 (t, $J=7.21$ Hz, 3H). LCMS (APCI+; Method D) m/z 278.2, (M+H)⁺.



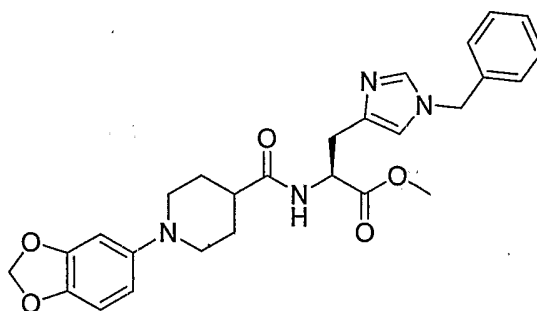
5

Example 34B

1-Benzo[1,3]dioxol-5-yl-piperidine-4-carboxylic acid

Example 34A (500 mg, 1.803 mmol) was hydrolyzed with LiOH·H₂O (91 mg, 2.164 mmol) as described in Example 21B to provide the title compound (438 mg, 97%) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.86 (br s, 1H), 7.51-7.28 (m, 2H), 7.05 (m, 1H), 6.11 (s, 2H), 3.49 (m, 4H), 2.67-2.59 (m, 1H), 2.23-2.04 (m, 4H). LCMS (APCI+; Method D) m/z 250, (M+H)⁺.

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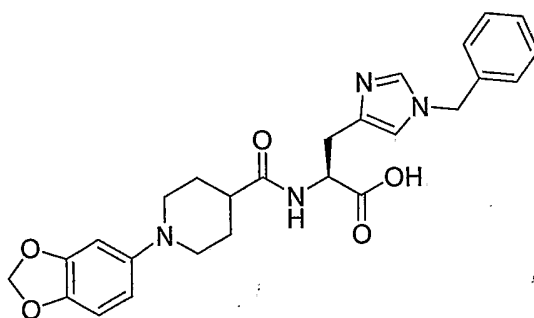


Example 34C

2-[(1-Benzo[1,3]dioxol-5-yl)piperidine-4-carbonyl]-
amino]-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid
5 methyl ester

The title compound (80 mg, 41%) was prepared from Example 34B (100 mg, 0.401 mmol) as described in Example 21C. ¹H NMR (400 MHz, DMSO-d₆) δ
8.25 (d, J=7.80 Hz, 1H), 7.67 (d, J=1.56 Hz, 1H),
10 7.37-7.27 (m, 3H), 7.22-7.19 (m, 2H), 6.87 (d,
J=1.17 Hz, 1H), 6.75 (d, J=8.58 Hz, 1H), 6.65 (d,
J=2.34 Hz, 1H), 6.33 (d, d, J₁=2.34 Hz, J₂=8.58 Hz,
1H), 5.90 (s, 2H), 5.12 (s, 2H), 4.457-4.42 (m, 1H),
3.55 (s, 3H), 3.45-3.40 (m, 2H), 2.89-2.76 (m, 2H),
15 2.57-2.40 (m, 2H), 2.23-2.17 (m, 1H), 1.70-1.62 (m,
1H), 1.60-1.50 (m, 3H). LCMS (APCI+; Method D) m/z
491, (M+H)⁺.

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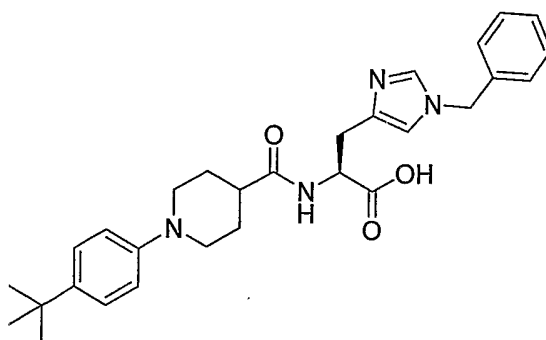


Example 34D

2-[(1-Benzo[1,3]dioxol-5-yl-piperidine-4-carbonyl)-amino]-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid

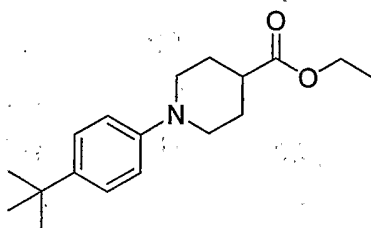
5 The title compound was prepared from Example 34C (80 mg, 163 μ mol) as described in Example 29D. Example 34D (45 mg, 41%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.17 (s, 1H), 8.26 (m, 1H), 7.46 (s, 1H), 7.42-7.37 (m, 5H), 6.85 (m, 2H), 6.55 (m, 1H), 5.97 (s, 2H), 5.38 (s, 2H), 4.59-4.52 (m, 1H), 3.51-3.39 (m, 2H), 3.16-3.12 (m, 1H), 2.97-2.90 (m, 1H), 2.80-2.66 (m, 1H), 2.26-2.14 (m, 2H), 1.72-1.62 (m, 2H), 1.56-1.48 (m, 2H). LCMS (APCI+; Method D) m/z 477, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) R_t =1.682 min (220 nm, 100 area%).

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Example 35

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(4-tert-butyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

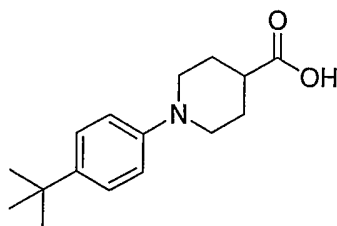


Example 35A

1-(4-tert-Butyl-phenyl)-piperidine-4-carboxylic acid ethyl ester

Example 35A was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-4-tert-butyl-benzene (250 mg, 1.173 mmol). The title compound (194 mg, 57%) was obtained as a yellow color solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.20 (d, *J*=8.97 Hz, 2H), 6.86 (d, *J*=8.97 Hz, 2H), 4.08 (q, *J*=7.02 Hz, 2H), 3.59-3.54 (m, 2H), 2.73-2.67 (m, 2H), 2.47-2.41 (m, 1H), 1.91-1.86 (m, 2H), 1.69-1.59 (m, 2H), 1.23 (s, 9H), 1.19 (t, *J*=7.02 Hz, 3H). LCMS (APCI+; Method D) *m/z* 290, (M+H)⁺.

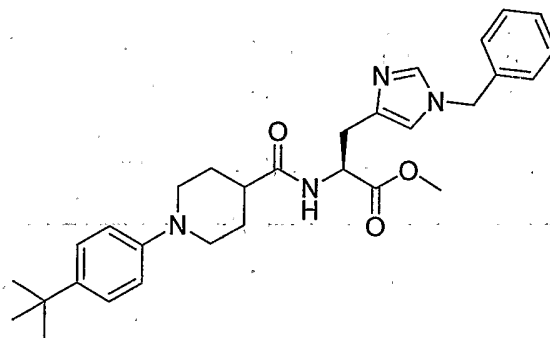
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Example 35B

1-(4-tert-Butyl-phenyl)-piperidine-4-carboxylic acid

Example 35A (190 mg, 0.657 mmol) was hydrolyzed with LiOH.H₂O (33 mg, 0.7878 mmol) as described in Example 21B to provide the title compound (127 mg, 74%). ¹H NMR (400 MHz, DMSO-d₆) δ 12.23 (s, 1H), 7.21 (d, J=8.58 Hz, 1H), 6.85 (d, J=8.58 Hz, 1H), 3.58-3.54 (m, 2H), 2.72-2.65 (m, 2H), 2.39-2.32 (m, 1H), 1.90-1.86 (m, 2H), 1.68-1.58 (m, 2H), 1.23 (s, 9H). LCMS (APCI+; Method D) m/z 262, (M+H)⁺.



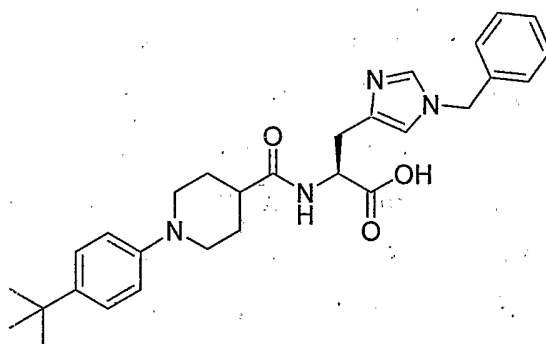
Example 35C

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(4-tert-butyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

The title compound (185 mg, 77%) was prepared from Example 35B (125 mg, 0.4783 mmol) as de-

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scribed in Example 21C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.15 (d, $J=7.80$ Hz, 1H), 7.66 (d, $J=1.56$ Hz, 1H), 7.36-7.29 (m, 3H), 7.23-7.20 (m, 4H), 6.87-6.83 (m, 3H), 5.12 (s, 2H), 4.47-4.41 (m, 1H), 3.64-3.57 (m, 2H), 3.55 (s, 3H), 2.89-2.73 (m, 2H), 2.62-2.52 (m, 2H), 2.28-2.20 (m, 1H), 1.70-1.64 (m, 1H), 1.62-1.49 (m, 3H). LCMS (APCI+; Method D) m/z 503, $(\text{M}+\text{H})^+$.

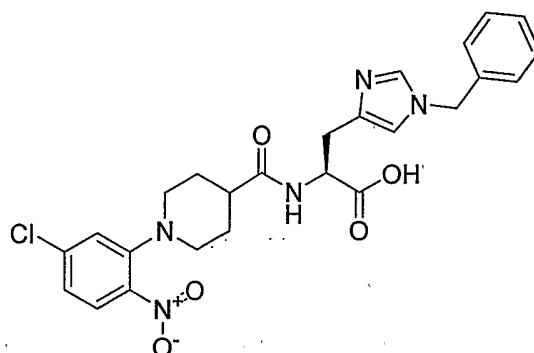


Example 35D

10 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(4-tert-butylphenyl)-piperidine-4-carbonyl]-amino)-propionic acid

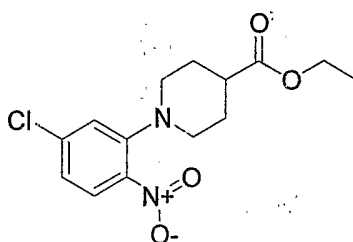
The title compound was prepared from Example 35C (175 mg, 0.3482 mmol) as described in Example 21D. Example 35D (55 mg, 32%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.03 (d, $J=7.80$ Hz, 1H), 7.68 (d, $J=1.17$ Hz, 1H), 7.36-7.30 (m, 3H), 7.22-7.20 (m, 4H), 6.87-6.83 (m, 3H), 5.13 (s, 2H), 4.42-4.36 (m, 1H), 3.63-3.54 (m, 2H), 2.91-2.86 (m, 1H), 2.80-2.74 (m, 1H), 2.61-2.52 (m, 2H), 2.26-2.19 (m, 1H), 1.71-1.62 (m, 1H), 1.59-1.47 (m, 3H), 1.24 (s, 9H). LCMS (APCI+; Method D) m/z 489, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $R_t=2.068$ min (220 nm, 100 area%).

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Example 36

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(5-chloro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid



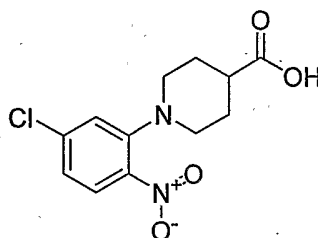
Example 36A

1-(5-Chloro-2-nitro-phenyl)-piperidine-4-carboxylic acid ethyl ester

10 A solution of 4-chloro 2-fluoronitrobenzene (5.00 g, 28.48 mmol) in dry DMF (30 mL) containing CsF (4.33 g, 28.48 mmol) was treated with ethyl isonipecotate (4.82 mL, 31.33 mmol) under N₂ atmosphere at 0°C for 1 h and then at ambient temperature for 4 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (2x50 mL). The organic layer was separated, dried (MgSO₄), filtered and evaporated to dryness to provide the title compound (9.31 g, 105% crude yield) as a yellow

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color liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.86 (d, $J=8.58$ Hz, 1H), 7.32 (d, $J=2.34$ Hz, 1H), 7.11 (d, d, $J_1=2.34$ Hz, $J_2=8.58$ Hz, 1H), 4.09 (q, $J=7.02$ Hz, 2H), 3.22-3.17 (m, 2H), 2.93-2.87 (m, 2H), 2.54-2.52 (m, 1H), 1.91-1.87 (m, 2H), 1.71-1.61 (m, 2H), 1.19 (t, $J=7.02$ Hz, 3H). LCMS (APCI+; Method D) m/z 313, $(\text{M}+\text{H})^+$. Analytical HPLC (Method E) $R_t=3.656$ min (220 nm, 100 area%).



10

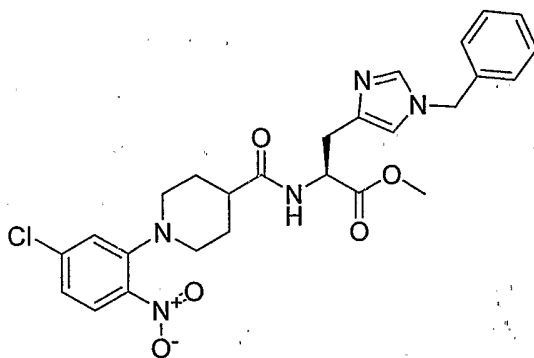
Example 36B

1-(5-Chloro-2-nitro-phenyl)-piperidine-4-carboxylic acid

A solution of ester Example 36A (150 mg, 0.4796 mmol) in THF:MeOH (1:1, 5 mL) was treated with a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (30 mg, 0.719 mmol) in water (2 mL) at ambient temperature for 1 h. The solvents were removed, residue dissolved in water (5 mL) and adjusted to pH 3.5 with formic acid. The bright yellow precipitate formed was filtered, washed with water (3x5 mL), and dried under vacuum (oil pump) for 2 h to provide the title compound (140 mg, 102% yield) as yellow color powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.33 (s, 1H), 7.86 (d, $J=8.58$ Hz, 1H), 7.32 (d, $J=2.34$ Hz, 1H), 7.10 (d, d, $J_1=2.34$ Hz, $J_2=8.58$ Hz, 1H), 3.21-3.17 (m, 2H), 2.92-2.86 (m,

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2H), 2.45-2.37 (m, 1H), 1.91-1.85 (m, 2H), 1.69-1.59 (m, 2H). LCMS (APCI+; Method D) m/z 285, 287, (M+H)⁺.



5

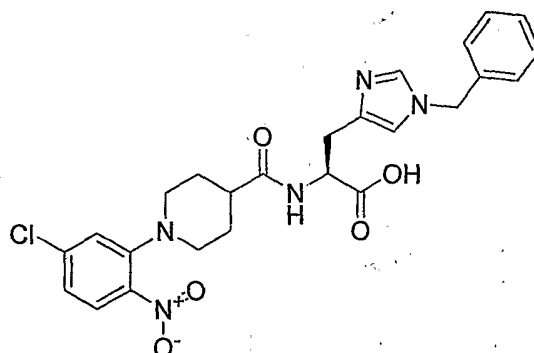
Example 36C

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-chloro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid methyl ester

A solution of acid Example 36B (130 mg, 0.457 mmol), HOBt.H₂O (105 mg, 0.685 mmol), L-N¹-benzyl histidine methyl ester dihydrochloride (182 mg, 0.548 mmol), and triethylamine (0.223 mL, 1.598 mmol), in dry DMF (3 mL) was treated with EDC (131 mg, 0.685 mmol) at ambient temperature under N₂ atmosphere for 18 h. The reaction mixture was diluted with EtOAc (10 mL), washed with water (2x5 mL), dried (MgSO₄), filtered, and evaporated to dryness. The residue obtained was purified by flash chromatography on silica gel (Biotage 40+S) eluting with 5% methanol and CH₂Cl₂ to provide the title compound (238 mg, 99%) as a bright yellow powder. ¹H NMR (400 MHz, DMSO-d₆) δ 8.20 (d, J=7.80 Hz, 1H), 7.86 (d, J=7.58 Hz, 1H), 7.66 (d, J=1.56 Hz, 1H),

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7.35-7.27 (m, 4H), 7.22-7.20 (m, 2H), 7.09 (d, d, $J_1=2.24$ Hz, $J_2=8.58$ Hz, 1H), 6.86 (s, 1H), 5.12 (s, 2H), 4.48-4.42 (m, 1H), 3.56 (s, 3H), 3.22-3.12 (m, 2H), 2.88-2.75 (m, 4H), 2.31-2.55 (m, 1H), 1.69-1.61 (m, 2H), 1.58-1.50 (m, 2H). LCMS (APCI+; Method D) m/z 526, (M+H)⁺.



Example 36D

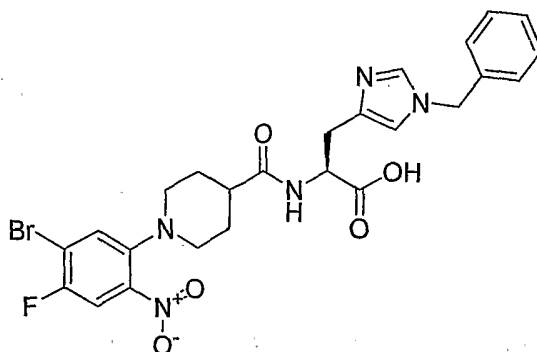
3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(5-chloro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

A solution of Example 36C (210 mg, 0.3993 mmol) in THF:MeOH (1:1, 5 mL) was treated with a solution of LiOH·H₂O (20 mg, 0.4791 mmol) in water (15 mL) at ambient temperature for 6 h. The solvents were removed, the residue dissolved in water (6 mL) and washed with EtOAc (2x3 mL) to remove a minor impurity. The aqueous layer was made acidic (pH 4) with formic acid. The precipitate formed was collected by filtration. The solid was washed with water (2x5 mL) and dried under vacuum (oil pump) to provide the title compound (195 mg, 94.87%) as a yellow color solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.07

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(d, $J=7.80$ Hz, 1H), 7.86 (d, $J=8.97$ Hz, 1H), 7.67
(d, $J=1.17$ Hz, 1H), 7.35-7.26 (m, 4H), 7.22-7.20 (m,
2H), 7.09 (d, d, $J_1=2.34$ Hz, $J_2=8.97$ Hz, 1H), 6.86
(d, $J=1.17$ Hz, 1H), 5.12 (s, 2H), 4.42-4.37 (m, 1H),
5 3.22-3.11 (m, 2H), 2.92-2.85 (m, 1H), 2.82-2.74 (m,
3H), 2.32-2.22 (m, 1H), 1.709-1.58 (m, 2H), 1.54-
1.48 (m, 2H). LCMS (APCI+; Method D) m/z 512, 514,
(M+H)⁺. Analytical HPLC (Method C) $R_t=2.330$ min (220
nm, 99.44%, area%).

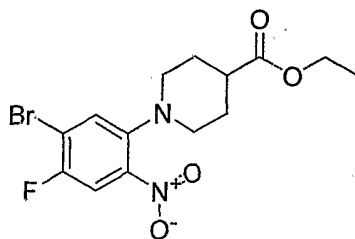
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Example 37

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

5



Example 37A

1-(5-Bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carboxylic acid ethyl ester

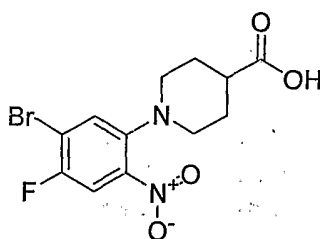
10

A solution of 4-bromo 2,5-difluoronitrobenzene (5.00 g, 21.01 mmol) in dry DMF (30 mL) containing CsF (3.19 g, 21.01 mmol) was treated with ethyl isonipecotatate (3.56 mL, 23.11 mmol) under N₂ atmosphere at ambient temperature for 18 h. The bright orange color suspension was diluted with EtOAc (150 mL) and washed with water (3x50 mL). The organic layer was separated, dried (using MgSO₄), filtered, and evaporated to dryness to provide the crude title compound (8.02 g, 101.74 %) as a bright

15

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red liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.01 (d, $J=8.19$ Hz, 1H), 7.68 (d, $J=6.24$ Hz, 1H), 4.09 (q, $J=7.02$ Hz, 2H), 3.15-3.10 (m, 2H), 2.89-2.83 (m, 2H), 2.48-2.44 (m, 1H), 1.91-1.87 (m, 2H), 1.70-1.60 (m, 2H), 1.19 (t, $J=7.02$ Hz, 3H). LCMS (APCI+; Method D) m/z 375; 377, $(\text{M}+\text{H})^+$.

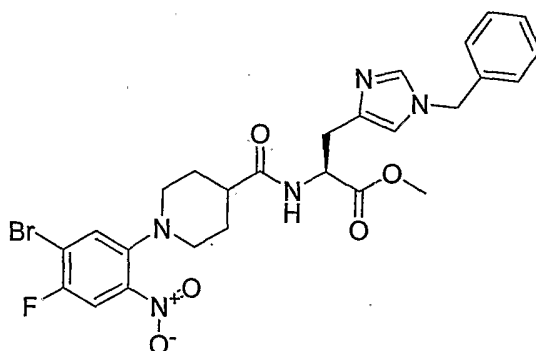


Example 37B

10 1-(5-Bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carboxylic acid

The title compound was prepared from Example 37A (150 mg, 0.4 mmol) as described in Example 36B. Example 37B (137 mg, 99%) was obtained as a bright orange powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.31 (s, 1H), 8.02 (d, $J=8.19$ Hz, 1H), 7.68 (d, $J=6.24$ Hz, 1H), 3.14-3.09 (m, 2H), 2.88-2.83 (m, 2H), 2.42-2.34 (m, 1H), 1.91-1.86 (m, 2H), 1.68-1.58 (m, 2H). LCMS (APCI+; Method D) m/z 347, $(\text{M}+\text{H})^+$.

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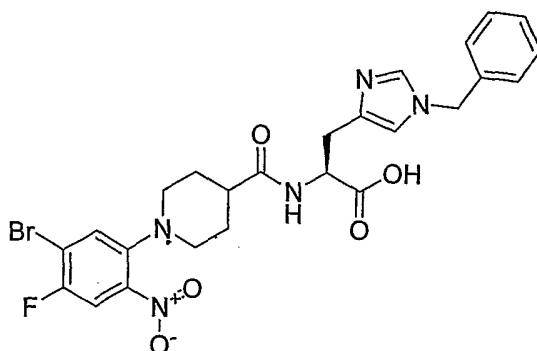


Example 37C

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carbonyl]-
 5 amino}-propionic acid methyl ester

Example 37B (135 mg, 0.389 mmol) was treated with L-N¹-benzyl histidine methyl ester dihydrochloride (155 mg, 0.467 mmol) as described in Example 36C to provide the title compound (215 mg,
 10 94%) as a bright yellow liquid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.20 (d, J=7.80 Hz, 1H), 8.12 (d, J=8.19 Hz, 1H), 7.68-7.66 (m, 2H), 7.35-7.27 (m, 3H), 7.21-7.19 (m, 2H), 6.87 (d, J=1.17 Hz, 1H), 5.13 (s, 2H), 4.48-4.42 (m, 1H), 3.56 (s, 3H), 3.15-3.04 (m, 2H),
 15 2.86-2.75 (m, 4H), 2.89-2.21 (m, 1H), 1.68-1.61 (m, 2H), 1.57-1.48 (m, 2H). LCMS (APCI+; Method D) m/z 588, 589, (M+H)⁺.

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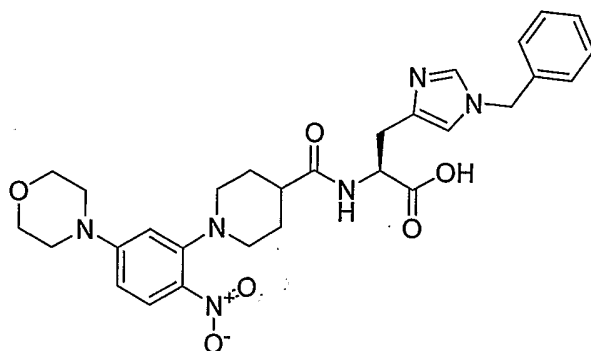


Example 37D:

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

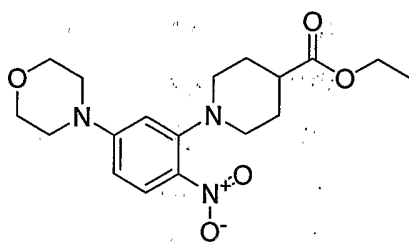
The title compound was prepared from Example 37C (210 mg, 0.399 mmol) as described in Example 36D. Example 37D (195 mg, 94.87%) was obtained as a yellow color solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.07 (d, J=8.19 Hz, 1H), 8.01 (d, J=8.58 Hz, 1H), 7.66 (m, 2H), 7.35-7.26 (m, 3H), 7.22-7.20 (m, 2H), 6.86 (s, 1H), 5.12 (s, 2H), 4.42-4.37 (m, 1H), 3.15-3.04 (m, 2H), 2.92-2.87 (m, 1H), 2.83-2.74 (m, 2H), 2.27-2.19 (m, 1H), 1.69-1.61 (m, 1H), 1.58-1.47 (m, 2H). LCMS (APCI+; Method D) m/z 512, 514, (M+H)⁺ Analytical HPLC (Method C) Rt=2.425 min (220 nm, 99.44 area%).

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Example 38

3-(1-Benzyl-1H-imidazol-4-yl)-2-[[1-(5-morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carbonyl]-amino]-propionic acid



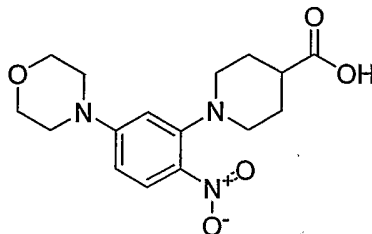
Example 38A

1-(5-Morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carboxylic acid ethyl ester

10 A sealed tube containing a solution of
 Example 36A (500 mg, 1.599 mmol) and morpholine (2
 mL, 23 mmol) was heated at 100°C for 15 h. The re-
 action mixture was directly purified by silica gel
 flash chromatography (Biotage 40+M) eluting with 10%
 15 acetone/hexane to provide the title compound (400
 mg, 69%) as a yellow powder. ¹H NMR (400 MHz, DMSO-
 d₆) δ 7.92 (d, J=9.36 Hz, 1H), 6.61 (d, d, J₁=2.24
 Hz, J₂=9.36 Hz, 1H), 6.41 (d, J=2.73 Hz, 1H), 4.09
 (q, J=7.02 Hz, 2H), 3.70-3.70 (m, 4H), 3.36-3.34 (m,

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4H), 3.23-3.17 (m, 2H), 2.86-2.79 (m, 2H), 2.48 (m, 1H), 1.92-1.87 (m, 2H), 1.78-1.68 (m, 2H), 1.20 (t, $J=7.02$ Hz, 3H). LCMS (APCI+; Method D) m/z 364, (M+H).



5

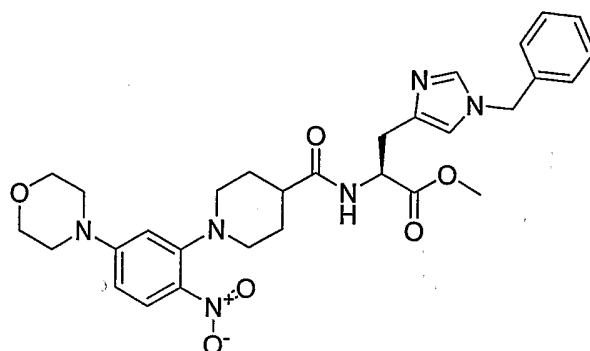
Example 38B

1-(5-Morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carboxylic acid

A solution of Example 38A (150 mg, 0.4128 mmol) in THF:MeOH (1:1, 5 mL) was treated with a solution of LiOH.H₂O (21 mg, 0.4953 mmol) in water (1 mL) at ambient temperature for 5 h. The solvents were removed, residue dissolved in water (6 mL) and washed with EtOAc (2x3 mL) to remove a minor impurity. The aqueous layer was made acidic (pH 4) with formic acid. The precipitate formed was filtered, washed with water (2x5 mL), and dried under vacuum (oil pump) to provide the title compound (115 mg, 83.08%) as a yellow color solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.30 (s, 1H), 7.91 (d, $J=9.36$ Hz, 1H), 6.60- (d, d, $J_1=2.73$ Hz, $J_2=9.36$ Hz, 1H), 6.41 (d, $J=2.73$ Hz, 1H), 3.72-3.69 (m, 4H), 3.36-3.33 (m, 4H), 3.22-3.18 (m, 2H), 2.85-2.88 (m, 2H), 2.42-2.36 (m, 1H), 1.92-1.87 (m, 2H), 1.77-1.68 (m, 2H).

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LCMS (APCI+; Method D) m/z 336, $(M+H)^+$. Analytical HPLC (Method C) $R_t=2.356$ min (220 nm, 100 area%).

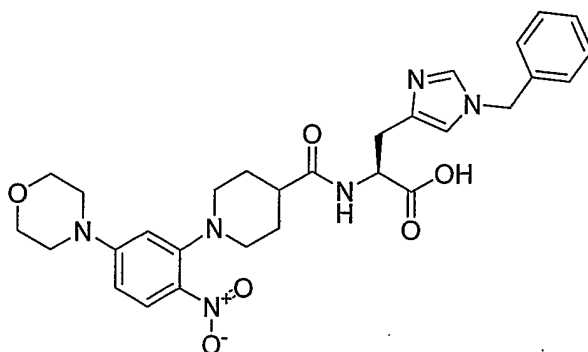


Example 38C

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid methyl ester

The title compound was prepared according to the procedure described in Example 36C substituting Example 36B with Example 38B (110 mg, 0.328 mmol). Example 38C (130 mg, 67.64%) was obtained as a bright yellow powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.19 (d, $J=7.41$ Hz, 1H), 7.91 (d, $J=9.75$ Hz, 1H), 7.66 (d, $J=1.17$ Hz, 1H), 7.35-7.31 (m, 2H), 7.28-7.25 (m, 1H), 7.21-7.19 (m, 2H), 6.87 (d, $J=1.17$ Hz, 1H), 6.50 (d, d, $J_1=2.73$ Hz, $J_2=9.36$ Hz, 1H), 6.40 (d, $J=2.73$ Hz, 1H), 5.12 (s, 2H), 4.48-4.43 (m, 1H), 3.73-3.70 (m, 4H), 3.56 (s, 3H), 3.36-3.33 (m, 4H), 3.26-3.14 (m, 2H), 2.86-2.75 (m, 4H), 2.33-2.24 (m, 1H), 1.73-1.65 (m, 2H), 1.61-1.57 (m, 2H). LCMS (APCI+; Method D) m/z 577, $(M+H)^+$. Analytical HPLC (Method C) $R_t=2.185$ min (220 nm, 98.42 area%).

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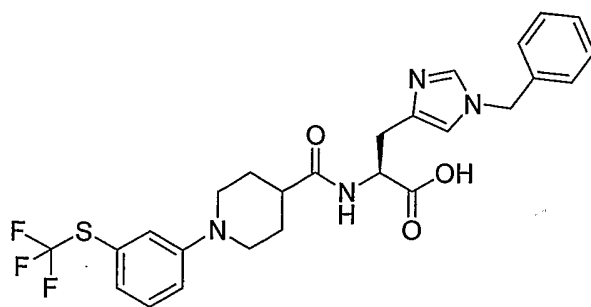
Example 38D

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(5-morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

The title compound was prepared from Example 38C (126 mg, 0.219 mol) as described in Example 36D. Example 38D (110 mg, 89.48%) was obtained as a bright yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ

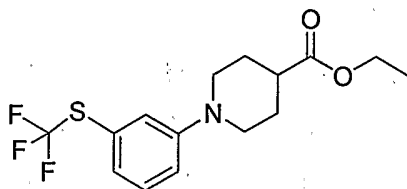
8.07 (d, *J*=7.80 Hz, 1H), 7.91 (d, *J*=9.36 Hz, 1H), 7.68 (s, 1H), 7.34-7.31 (m, 2H), 7.27-7.25 (m, 1H), 7.22-7.20 (m, 2H), 6.87 (s, 1H), 6.60 (d, d, *J*₁=2.24 Hz, *J*₂=9.36 Hz, 1H), 6.39 (d, *J*=2.24 Hz, 1H), 5.13 (s, 2H), 4.43-4.38 (m, 1H), 3.73-3.70 (m, 4H), 3.36-3.34 (m, 4H), 3.26-3.13 (m, 2H), 2.91-2.87 (m, 1H), 2.82-2.69 (m, 3H), 2.30-2.22 (m, 1H) 1.71-1.66 (m, 2H), 1.62-1.53 (m, 2H). LCMS (APCI+; Method D) *m/z* 563, (M+H)⁺. Analytical HPLC (Method C) *R*_t=2.105 min (220 nm, 100 area%).

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Example 39

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3-trifluoromethylsulfanyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid



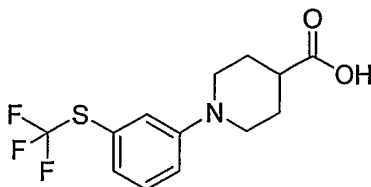
Example 39A

1-(3-Trifluoromethylsulfanyl-phenyl)-piperidine-4-carboxylic acid ethyl ester

10 The title compound (355 mg, 79.2%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-3-trifluoromethyl-sulfanyl-benzene (341 mg, 1.325 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.36-7.32 (m, 1H), 7.19-7.15 (m, 2H), 7.04 (d, *J*=7.41 Hz, 1H), 4.08 (q, *J*=7.02 Hz, 2H), 3.72-3.67 (m, 2H), 2.87-2.79 (m, 2H), 2.56-2.51 (m, 1H), 1.93-1.88 (m, 2H), 1.68-1.58 (m, 2H), 1.19 (t, *J*=7.02 Hz, 3H). LCMS (APCI+): (M+H)⁺=563. Analytical HPLC purity=100%,
 15 retention time 2.105 min. LCMS (APCI+; Method D)

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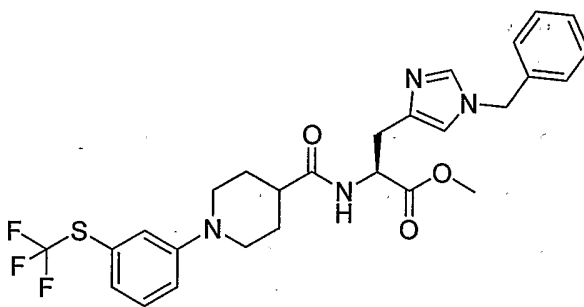
m/z 334, $(M+H)^+$. Analytical HPLC (Method C) $R_t=3.988$ min (220 nm, 98.57 area%).



Example 39B

5 1-(3-Trifluoromethylsulfanyl-phenyl)-piperidine-4-carboxylic acid

Example 39A (350 mg, 0.1.050 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (53 mg, 1.26 mmol) as described in Example 21B to provide the title compound
10 (210 mg, 65.5%) as a cream color solid. LCMS (APCI+; Method D) m/z 306, $(M+H)^+$.



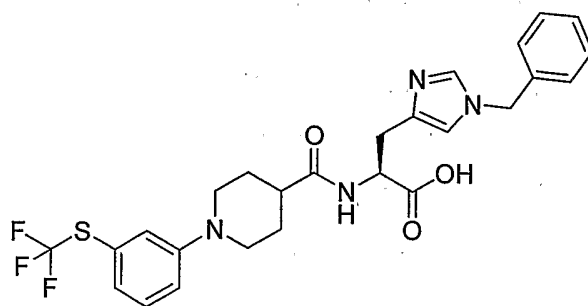
Example 39C

15 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethylsulfanyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid methyl ester

The title compound (228 mg, 76.6%) was prepared from Example 39B (197 mg, 0.645 mmol) as described in Example 21C. Example 39C was obtained

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as a cream color solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.16 (d, $J=7.41$ Hz, 1H), 7.66 (s, 1H), 7.37-7.28 (m, 2H), 7.22-7.20 (m, 2H), 7.16-7.13 (m, 2H), 7.05-7.03 (m, 1H), 6.87 (s, 1H), 5.13 (s, 2H), 4.47-4.42 (m, 1H), 3.76-3.67 (m, 2H), 3.55 (s, 3H), 2.89-2.79 (m, 2H), 2.76-2.66 (m, 2H), 2.34-2.28 (m, 1H), 1.73-1.66 (m, 1H), 1.61-1.43 (m, 3H). LCMS (APCI+; Method D) m/z 547, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $R_t=2.639$ min (220 nm, 93.83 area%).



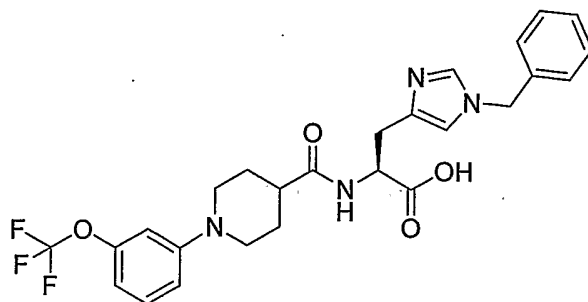
Example 39D

3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethylsulfanyl-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid

The title compound was prepared from Example 39C (282 mg, 0.516 mmol) as described in Example 21D. Example 39D (258 mg, 91.31%) was obtained as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.03 (d, $J=7.81$ Hz, 1H), 7.67 (s, 1H), 7.36-7.29 (m, 4H), 7.23-7.21 (m, 2H), 7.16-7.13 (m, 2H), 7.04 (d, $J=7.42$ Hz, 1H), 6.86 (s, 1H), 5.13 (s, 2H), 4.42-4.37 (m, 1H), 3.76-3.65 (m, 2H), 2.91-2.87 (m, 1H), 2.81-2.65 (m, 3H), 2.33-2.26 (m, 1H), 1.72-1.67 (m, 1H), 1.61-1.44 (m, 3H). LCMS (APCI+; Method D) m/z

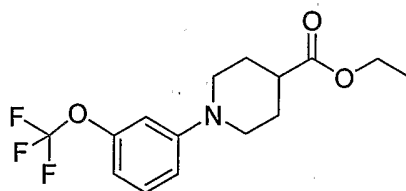
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533, (M+H)⁺. Analytical HPLC (Method C) Rt=2.525 min (220 nm, 97.24 area%).



Example 40

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-([1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino)-propionic acid



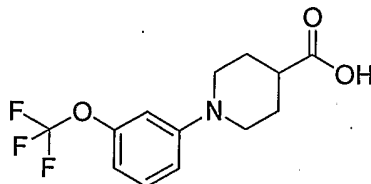
Example 40A

10 1-(3-Trifluoromethoxy-phenyl)-piperidine-4-carboxylic acid ethyl ester

The title compound (331 mg, 73.78%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 1-bromo-
 15 3-trifluoromethoxy-benzene (0.197 mL, 1.325 mmol).
¹H NMR (400 MHz, DMSO-d₆) δ 7.29 (t, J=8.19 Hz, 1H), 6.94 (d, d, J₁=3.12 Hz, J =8.58 Hz, 1H), 6.83 (s, 1H), 6.68 (d, J=8.19 Hz, 1H), 4.08 (q, J=7.02 Hz, 2H), 3.72-3.67 (m, 2H), 2.86-2.79 (m, 2H), 2.58-2.53
 20 (m, 1H), 1.91-1.87 (m, 2H), 1.678-1.56 (m, 2H), 1.19

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(t, $J=7.02$ Hz, 3H). LCMS (APCI+; Method D) m/z 318, $(M+H)^+$. Analytical HPLC (Method C) $R_t=3.792$ min (220 nm, 97.24 area%).



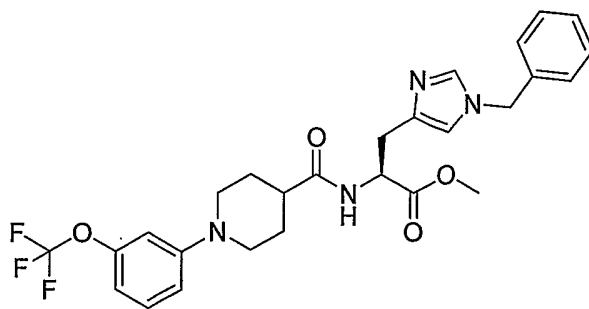
5

Example 40B

1-(3-Trifluoromethoxy-phenyl)-piperidine-4-carboxylic acid

Example 40A (325 mg, 1.024 mmol) was hydrolyzed with LiOH.H₂O (52 mg, 1.229 mmol) as described in Example 21B to provide the title compound (289 mg, 96.62%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.28 (t, $J=8.19$ Hz, 1H), 6.95 (d, d, $J_1=1.95$ Hz, $J_2=8.19$ Hz, 1H), 6.23 (m, 1H), 6.67 (m, 1H), 3.71-3.66 (m, 2H), 2.84-2.77 (m, 2H), 2.44-2.37 (m, 1H), 1.91-1.85 (m, 2H), 1.65-1.55 (m, 2H). LCMS (APCI+; Method D) m/z 290, $(M+H)^+$.

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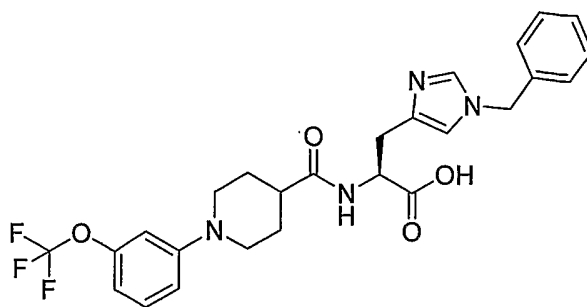


Example 40C

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3-
trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-
amino}-propionic acid methyl ester

The title compound (120 mg, 82%) was prepared from Example 40B (80 mg, 0.277 mmol) as described in Example 21C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.16 (d, $J=7.80$ Hz, 1H), 7.66 (s, 1H), 7.37-7.27 (m, 4H), 7.21 (d, $J=8.19$ Hz, 2H), 6.93 (dd, $J_1=8.19$ Hz, $J_2=2.24$ Hz, 1H), 6.87 (s, 1H), 6.81 (s, 1H), 6.67 (d, $J=8.19$ Hz, 1H), 5.13 (s, 2H), 4.47-4.42 (m, 1H), 3.75-3.64 (m, 2H), 3.55 (s, 3H), 2.89-2.78 (m, 2H), 2.75-2.66 (m, 2H), 2.35-2.26 (m, 1H), 1.78-1.66 (m, 1H), 1.60-1.45 (m, 3H). LCMS (APCI+; Method D) m/z 531, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $R_t=2.525$ min (220 nm, 100 area%).

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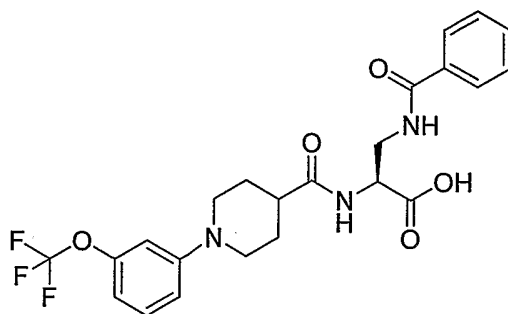


Example 40D

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

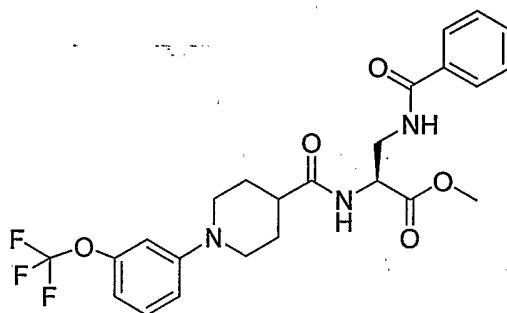
The title compound was prepared from Example 40C (107 mg, 0.202 mmol) as described in Example 21D. Example 40D (65 mg, 62.4%) was obtained as a white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (d, J=7.81 Hz, 1H), 7.67 (s, 1H), 7.37-7.27 (m, 4H), 7.22 (d, J=8.20 Hz, 1H), 6.94 (m, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 6.66 (d, J=8.20 Hz, 1H), 5.13 (s, 2H), 4.42-4.37 (m, 1H), 3.75-3.65 (m, 2H), 2.91-2.86 (m, 1H), 2.81-2.65 (m, 3H), 2.33-2.56 (m, 1H), 1.72-1.66 (m, 1H), 1.58-1.44 (m, 3H). LCMS (APCI+; Method D) m/z 517, (M+H)⁺. Analytical HPLC (Method C) Rt=2.44 min (220 nm, 100 area%).

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Example 41

3-Benzoylamino-2-([1-(3-trifluoromethoxy-phenyl)-
piperidine-4-carbonyl]-amino)-propionic acid



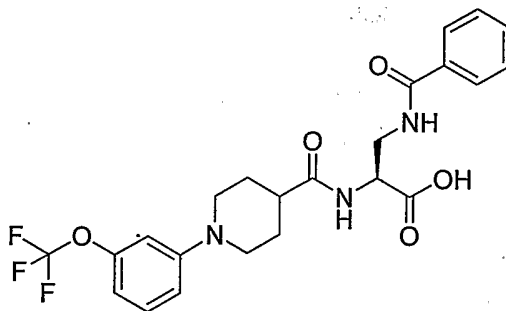
Example 41A

3-Benzoylamino-2-([1-(3-trifluoromethoxy-phenyl)-
piperidine-4-carbonyl]-amino)-propionic acid methyl
ester

10 The title compound (130 mg, 86%) was pre-
pared from Example 40B (80 mg, 277 μ mol) and methyl-
2-amino-3-benzoylamino-propionate HCl salt (202 mg,
0.553 mmol) as described in Example 21C. Example
41A was obtained as a cream color solid. ^1H NMR
15 (400 MHz, $\text{DMSO}-d_6$) δ 8.55 (t, $J=5.85$ Hz, 1H), 8.27
(d, $J=7.80$ Hz, 1H), 7.86 (d, $J=8.19$ Hz, 1H), 7.81-
7.78 (m, 2H), 7.54-7.45 (m, 5H), 7.28 (t, $J=8.19$ Hz,
1H), 6.93 (d, d, $J_1=8.19$ Hz, $J_2=1.95$ Hz, 1H), 6.81

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(s, 1H), 6.66 (d, $J=8.17$ Hz, 1H), 4.4 (q, $J=7.02$ Hz, 1H), 3.80-3.70 (m, 2H), 3.64-3.59 (m, 5H), 2.79-2.71 (m, 2H), 2.44-2.37 (m, 1H), 1.78-1.73 (m, 2H), 1.65-1.55 (m, 2H). LCMS (APCI+; Method D) m/z 494, (M+H)⁺. Analytical HPLC (Method C) $R_t=3.072$ min (220 nm, 90.5 area%).

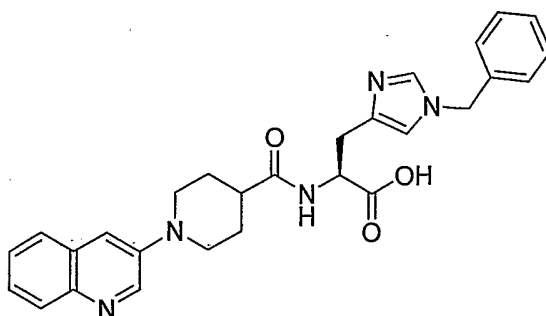


Example 41B

3-Benzoylamino-2-{[1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid

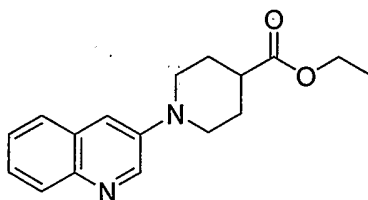
The title compound was prepared from Example 41A (125 mg, 0.253 mmol) as described in Example 21D. Example 41B (101 mg, 83%) was obtained as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.68 (br s, 1H), 8.51 (d, $J=5.86$ Hz, 1H), 8.13 (d, $J=7.81$ Hz, 1H), 7.80-7.78 (m, 2H), 7.53-7.52 (m, 1H), 7.48-7.45 (m, 2H), 7.27 (t, $J=8.20$ Hz, 1H), 6.93 (d, d, $J_1=8.59$ Hz, $J_2=2.34$ Hz, 1H), 6.81 (s, 1H), 6.66 (d, $J=7.81$ Hz, 1H), 4.48-4.43 (m, 1H), 3.77-3.71 (m, 2H), 3.62-3.58 (m, 2H), 2.79-2.70 (m, 2H), 2.41-2.36 (m, 1H), 1.78-1.40 (m, 2H), 1.65-1.55 (m, 2H). LCMS (APCI+; Method D) m/z 480, (M+H)⁺. Analytical HPLC (Method C) $R_t=2.811$ min (220 nm, 94.96 area%).

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Example 42

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid



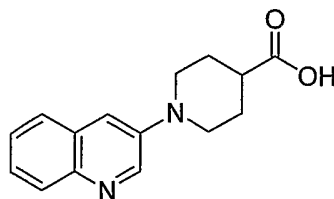
5

Example 42A

1-Quinolin-3-yl-piperidine-4-carboxylic acid ethyl ester

The title compound (325 mg, 86.25%) was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 3-bromo-quinoline (276 mg, 1.325 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.86 (d, *J*=3.12 Hz, 1H), 7.86 (d, d, *J*₁=3.51Hz, *J*₂=6.24 Hz, 1H), 7.78 (d, d, *J*₁=3.51 Hz, *J*₂=5.85 Hz, 1H), 7.55 (d, *J*=2.73 Hz, 1H), 7.49-7.45 (m, 2H), 4.10 (q, *J*=7.02 Hz, 2H), 3.84-3.79 (m, 2H), 2.94-2.88 (m, 2H), 2.61-2.53 (m, 1H), 2.01-1.95 (m, 2H), 1.79-1.69 (m, 2H), 1.20 (t, *J*=7.02Hz, 3H). LCMS (APCI+; Method D) *m/z* 285, (M+H)⁺. Analytical HPLC (Method C) *R*_t=2.247 min (220 nm, 97.83 area%).

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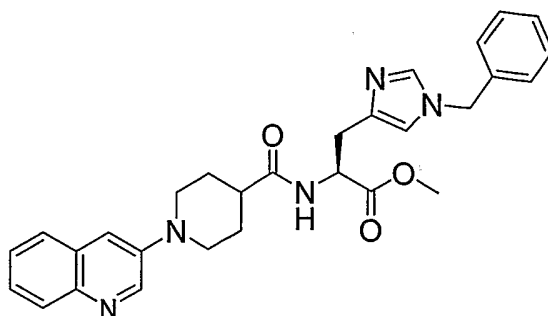


Example 42B

1-Quinolin-3-yl-piperidine-4-carboxylic acid

Example 42A (320 mg, 1.125 mmol) was hydrolyzed with LiOH.H₂O (57 mg, 1.35 mmol) as described in Example 21B to provide the title compound (285 mg, 98.3%). ¹H NMR (400 MHz, DMSO-d₆) δ 12.30 (s, 1H), 8.56 (d, J=2.73 Hz, 1H), 7.86-7.84 (m, 1H), 7.79-7.77 (m, 1H), 7.55 (d, J=2.73 Hz, 1H), 7.49-7.45 (m, 2H), 3.83-3.79 (m, 2H), 2.93-2.87 (m, 2H), 2.48-2.43 (m, 1H), 1.98-1.93 (m, 2H), 1.77-1.67 (m, 2H). LCMS (APCI+; Method D) m/z 257, (M+H)⁺. Analytical HPLC (Method C) Rt=99.48 min (220 nm, 99.48 area%).

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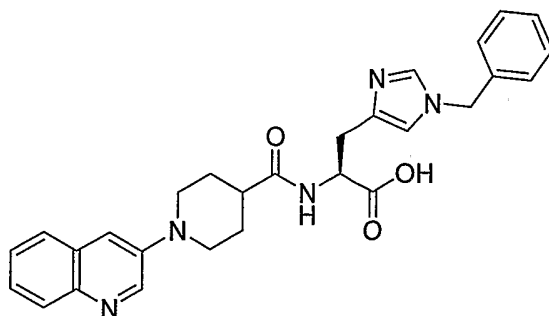
Example 42C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-quinolin-3-yl-
piperidine-4-carbonyl)-amino]-propionic acid methyl
ester

The title compound (100 mg, 64.39%) was prepared from Example 42B (80 mg, 0.312 mmol) as described in Example 21C. Example 42C was obtained as a cream color powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ

8.85 (d, *J*=3.12 Hz, 1H), 8.21 (d, *J*=7.80 Hz, 1H),
7.87-7.84 (m, 1H), 7.80-7.72 (m, 1H), 7.67 (s, 1H),
7.53 (d, *J*=2.73 Hz, 1H), 7.49 (s, 1H), 7.48-7.46 (m, 2H),
7.38-7.27 (m, 3H), 7.23-7.20 (m, 2H), 6.89 (s, 2H),
5.13 (s, 2H), 4.49-4.43 (m, 1H), 3.87-3.81 (m, 2H),
3.56 (s, 3H), 2.89-2.74 (m, 4H), 2.39-2.31 (m, 1H),
1.79-1.74 (m, 1H), 1.69-1.58 (m, 2H). LCMS (APCI+; Method D) *m/z* 498, (M+H)⁺. Analytical HPLC (Method C) *R*_t=1.863 min (220 nm, 100 area%).

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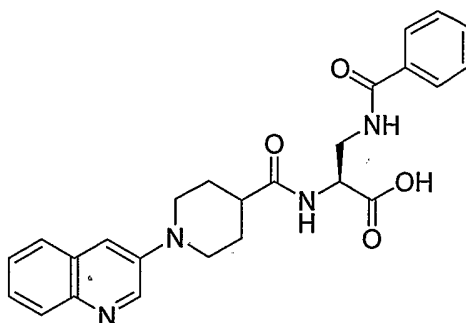


Example 42D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid

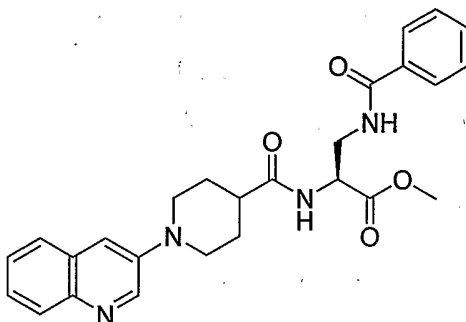
5 The title compound was prepared from Example 42C (95 mg, 0.191 mmol) as described in Example 21D. Example 42D (54 mg, 58.5%) was obtained as a cream color solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (d, J=2.73 Hz, 1H), 8.05 (d, J=7.80 Hz, 1H), 7.87-7.84 (m, 1H), 7.80-7.77 (m, 1H), 7.67 (s, 1H), 7.53 (d, J=2.73 Hz, 1H), 7.48-7.46 (m, 2H), 7.36-7.29 (m, 3H), 7.23-7.20 (m, 2H), 6.88 (s, 1H), 5.13 (s, 2H), 4.44-4.38 (m, 1H), 3.87-3.79 (m, 2H), 3.36 (m, 1H), 2.93-2.88 (m, 2H), 2.82-2.74 (m, 3H), 2.37-2.31 (m, 1H), 1.80-1.71 (m, 1H), 1.68-1.57 (m, 4H). LCMS (APCI+; Method D) m/z 484, (M+H)⁺. Analytical HPLC (Method C) Rt=1.758 min (220 nm, 100 area%).

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Example 43

3-Benzoylamino-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid



5

Example 43A

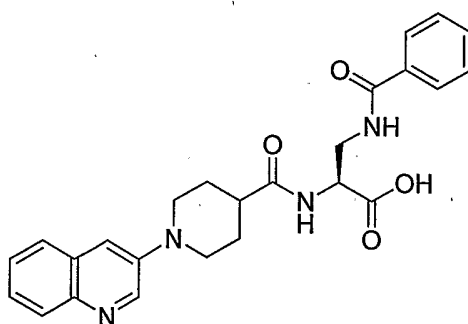
3-Benzoylamino-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid methyl ester

Example 43A was prepared from Example 42B
10 (80 mg, 312 μ mol) and methyl-2-amino-3-benzoylamino-propionate HCl salt (231 mg, 0.624 μ mol) as described in Example 21C. The title compound (110 mg, 76.5%) was obtained as a cream color solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.85 (d, $J=2.73$ Hz, 1H), 8.57 (d, $J=5.85$ Hz, 1H), 8.30 (d, $J=8.00$ Hz, 1H), 7.86-7.56 (m, 4H), 7.56-7.52 (m, 2H), 7.50-7.45 (m, 4H), 4.50 (q, $J=6.63$ Hz, 1H), 3.93-3.85 (m, 2H), 3.65 (m,

15

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1H), 3.62 (s, 3H), 3.60 (m, 1H), 2.88-2.79 (m, 2H),
2.48-2.39 (m, 1H), 1.89-1.81 (m, 2H), 1.77-1.69 (m,
2H). LCMS (APCI+; Method D) m/z 461, (M+H)⁺.
Analytical HPLC (Method C) R_t =1.99 min (220 nm,
5 96.78 area%).

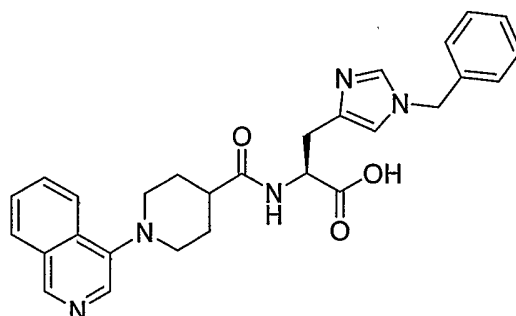


Example 43B

3-Benzoylamino-2-[(1-quinolin-3-yl-piperidine-4-
carbonyl)-amino]-propionic acid

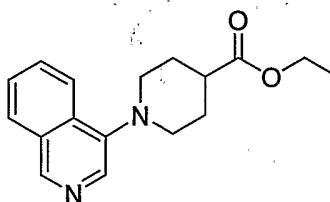
10 The title compound was prepared from Exam-
ple 43A (105 mg, 0.228 mmol) as described in Example
21D. Example 43B (76 mg, 75%) was obtained as a
cream color powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ
12.68 (s, 1H), 8.84 (d, J =2.73 Hz, 1H), 8.53 (t,
15 J =5.85, 1H), 8.16 (d, J =7.80 Hz, 1H), 7.86-7.56 (m,
4H), 7.53-7.51 (m, 2H), 7.48-4.46 (m, 4H), 4.50-4.44
(m, 1H), 3.91-3.84 (m, 1H), 3.63-3.60 (m, 2H), 2.87-
2.79 (m, 2H), 2.45-2.40 (m, 1H), 1.86-1.81 (m, 2H),
1.76-1.67 (m, 2H). LCMS (APCI+; Method D) m/z 447,
20 (M+H)⁺. Analytical HPLC (Method C) R_t =1.831 min (220
nm, 100 area%).

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Example 44

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid



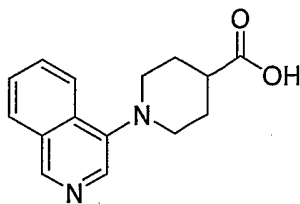
5

Example 44A

1-Isoquinolin-4-yl-piperidine-4-carboxylic acid
ethyl ester

Example 44A was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with 4-bromo-isoquinoline (276 mg, 1.325 mmol). The title compound (230 mg, 59.4%) was obtained as a yellow color solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.99 (s, 1H), 8.16 (s, 1H), 8.10-8.04 (m, 2H), 7.81-7.77 (m, 1H), 7.69-7.65 (m, 1H), 4.13 (q, J=7.02 Hz, 2H), 3.38-3.34 (m, 2H), 2.91-2.85 (m, 2H), 2.61-2.53 (m, 1H), 2.05-2.01 (m, 2H), 1.96-1.87 (m, 2H), 1.23 (t, J=7.02 Hz, 3H). LCMS (APCI+; Method D) m/z 285, (M+H)⁺. Analytical HPLC (Method C) Rt=2.041 min (220 nm, 97.29 area%).

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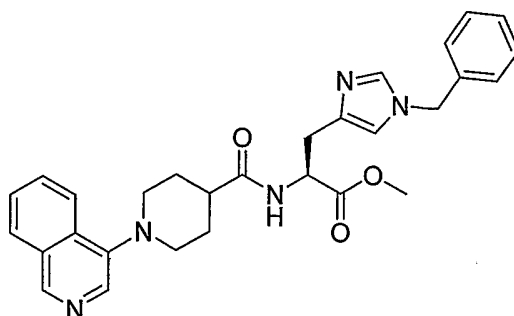


Example 44B

1-Isoquinolin-4-yl-piperidine-4-carboxylic acid

Example 44A (220 mg, 0.774 mmol) was hydrolyzed with LiOH.H₂O (39 mg, 0.928 mmol) as described in Example 21B to provide the title compound (189 mg, 98.44%) as a cream color solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.35 (s, 1H), 8.99 (s, 1H), 8.16 (s, 1H), 8.09 (d, *J*=8.18 Hz, 1H), 8.05 (d, *J*=7.41 Hz, 1H), 7.81-7.77 (m, 1H), 7.69-7.65 (m, 1H), 3.39-3.36 (m, 2H), 2.91-2.84 (m, 2H), 2.49-2.43 (m, 1H), 2.04-2.00 (m, 2H), 1.94-1.85 (m, 2H). LCMS (APCI+; Method D) *m/z* 257, (M+H)⁺. Analytical HPLC (Method C) Rt=1.620 min (220 nm, 98.44 area%).

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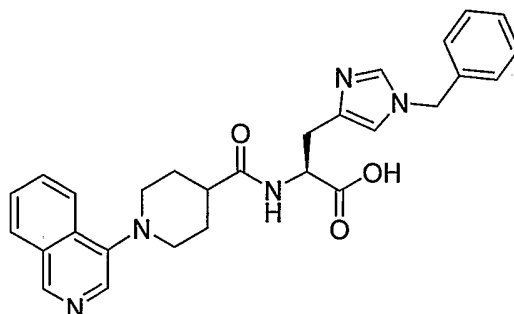


Example 44C

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid
5 methyl ester

Example 44C was prepared from Example 44B (80 mg, 0.312 mmol) as described in Example 21C. The title compound (75 mg, 48%) was obtained as a cream color solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.99 (s, 1H), 8.23 (d, $J=7.41$ Hz, 1H), 8.16 (s, 1H), 8.094 (d, $J=7.798$ Hz, 1H), 8.023 (d, $J=8.58$ Hz, 1H), 7.82-7.78 (m, 1H), 7.70-7.66 (m, 2H), 7.35-7.30 (m, 2H), 7.26-7.20 (m, 3H), 6.90 (s, 1H), 5.14 (s, 2H), 4.53-4.47 (m, 1H), 3.58 (s, 3H), 2.93-2.74 (m, 4H), 2.39-2.31 (m, 1H), 1.91-1.76 (m, 3H), 1.72-1.67 (m, 1H). LCMS (APCI+; Method D) m/z 498, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $R_t=1.863$ min (220 nm, 100 area%).

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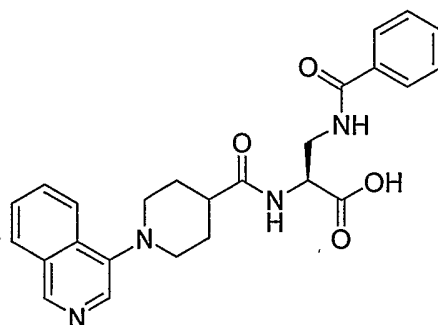


Example 44D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid

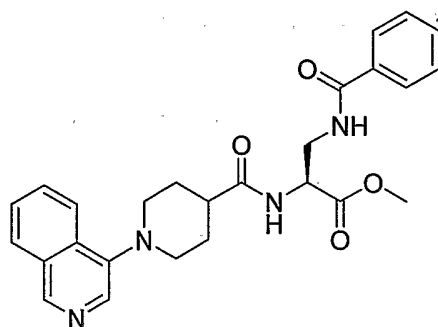
5 The title compound was prepared from Example 44C (70 mg, 0.141 mmol) as described in Example 21D. Example 44D (50 mg, 73.5%) was obtained as a cream color solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.99 (s, 1H), 8.40 (s, 1H), 8.144 (s, 1H), 8.09(d, $J=8.19$ Hz, 1H), 8.02 (d, $J=8.58$ Hz, 1H), 7.79 (t, $J=7.02$ Hz, 1H), 7.69-7.65 (m, 2H), 7.33-7.30 (m, 2H), 7.24-7.20 (m, 3H), 6.84 (s, 1H), 5.12 (s, 2H), 4.25-4.21 (m, 1H), 3.38-3.29 (m, 2H), 2.97-2.92 (m, 1H), 2.82-2.71 (m, 3H), 2.36-2.28 (m, 1H), 1.87-1.73 (m, 3H), 1.67-1.62 (m, 1H). LCMS (APCI+; Method D) m/z 484, $(\text{M}+\text{H})^+$. Analytical HPLC (Method C) $\text{Rt}=1.82$ min (220 nm, 100 area%).

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Example 45

3-Benzoylamino-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid



5

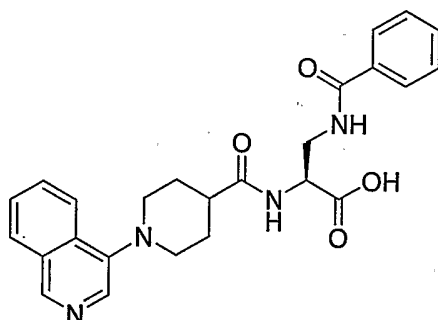
Example 45A

3-Benzoylamino-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid methyl ester

Example 45A was prepared from Example 44B (80 mg, 312 μ mol) and methyl-2-amino-3-benzoylamino-propionate HCl salt (231 mg, 0.624 μ mol) as described in Example 21C. The title compound (120 mg, 83.5%) was obtained as a yellow color solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.58 (t, $J=5.85$ Hz, 1H), 8.32 (d, $J=8.00$ Hz, 1H), 8.16 (s, 1H), 8.08 (d, $J=7.80$ Hz, 1H), 8.02 (d, $J=8.19$ Hz, 1H), 7.83-7.77 (m, 3H), 7.69-7.65 (m, 1H), 7.56-7.46 (m, 3H),

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4.54 (q, $J=6.63$, 1H), 3.65 (m, 1H), 3.63 (s, 3H),
3.62 (m, 1H), 3.42-3.36 (m, 1H), 2.67-2.79 (m, 2H),
2.46-2.40 (m, 1H), 1.93-1.86 (m, 3H), 1.25 (m, 1H),
0.86 (m, 1H). LCMS (APCI+; Method D) m/z 461,
5 (M+H)⁺. Analytical HPLC (Method C) $R_t=1.877$ min (220
nm, 100 area%).

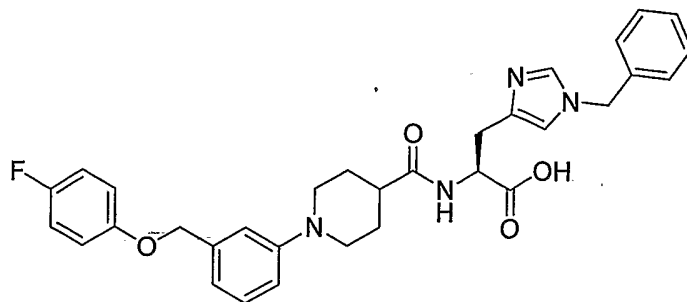


Example 45B

10 3-Benzoylamino-2-[(1-isoquinolin-4-yl-piperidine-4-
carbonyl)-amino]-propionic acid

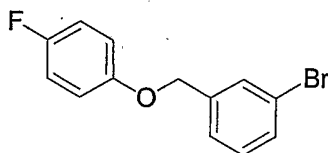
The title compound was prepared from Exam-
ple 45A (115 mg, 0.250 mmol) as described in Example
21D. Example 45B (80 mg, 71.75%) was obtained as a
cream color powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ
15 12.70 (s, 1H), 8.99 (s, 1H), 8.54 (t, $J=5.85$ Hz,
1H), 8.18 (d, $J=7.80$ Hz, 1H), 8.16 (s, 1H), 8.08 (d,
 $J=8.19$ Hz, 1H), 8.02 (d, $J=8.19$ Hz, 1H), 7.84-7.80
(m, 2H), 7.89-7.76 (m, 1H), 7.69-7.65 (m, 1H), 7.54-
7.50 (m, 1H), 7.49-7.46 (m, 2H), 4.54-4.49 (m, 1H),
20 3.65-3.62 (m, 2H), 3.41-3.34 (m, 2H), 2.86-2.76 (m,
2H), 2.45-2.40 (m, 1H), 1.92-1.87 (m, 4H). LCMS
(APCI+; Method D) m/z 447, (M+H)⁺. Analytical HPLC
(Method C) $R_t=1.739$ min (220 nm, 100 area%).

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Example 46

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-
 5 phenoxymethyl)-phenyl]-piperidine-4-carbonyl}-
 amino)-propionic acid



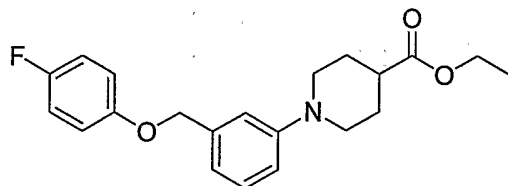
Example 46A

3-(4-Fluoro-phenoxy) benzyl bromide

A solution of 3-bromobenzylalcohol (161
 10 mL, 1.337 mmol), Ph_3P (427 mg, 1.626 mmol), and Et_3N
 (0.413 mL, 2.962 mmol) in anhydrous THF (5 mL) was
 treated with 4-fluoro phenol (180 mg, 1.604 mmol)
 and DEAD (0.253 mL, 1.604 mmol) and stirred under N_2
 atmosphere at ambient temperature for 18 h. The re-
 15 action mixture was diluted with EtOAc (25 mL) and
 washed with water (1x 10 mL), 1N NaOH (2x10 mL), and
 brine (2x10 mL). The organic layer was separated,
 dried (Na_2SO_4), filtered, and evaporated to dryness
 to provide a colorless oil. This was crystallized
 20 upon standing at room temperature for 1 h. The
 product formed was triturated with hexane and the

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filtrate collected was evaporated to dryness. The residue obtained was purified by flash chromatography on silica gel (Biotage 40+ S) eluting with 5% EtOAc/hexane to provide the title compound (210 mg, 53.67%) as a colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (m, 1H), 7.55 (m, 1H), 7.46-7.44 (m, 1H), 7.38-7.34 (m, 1H), 7.18-7.11 (m, 2H), 7.04-7.01 (m, 2H), 5.09 (s, 2H).



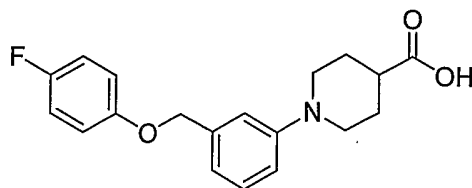
10

Example 46B

1-[3-(4-Fluoro-phenoxy-methyl)-phenyl]-piperidine-4-carboxylic acid ethyl ester

Example 46B was prepared by the procedure described in Example 21A, substituting 1-bromo-3-methyl-benzene with Example 46A (205 mg, 0.729 mmol). The title compound (230 mg, 103%) was obtained as a colorless oil. LCMS (APCI+; Method D) *m/z* 358, (M+H)⁺. Analytical HPLC (Method C) *R*_t=3.114 min (220 nm, 92 area%).

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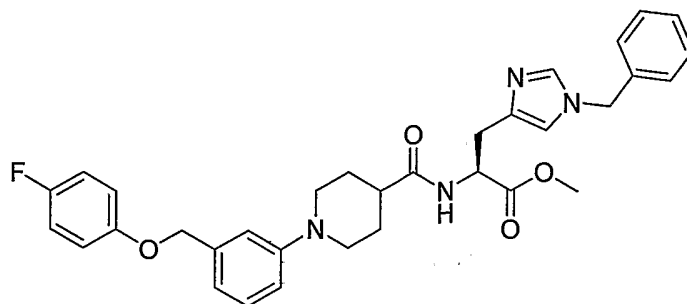


Example 46C

1-[3-(4-Fluoro-phenoxy-methyl)-phenyl]-piperidine-4-carboxylic acid

5 Example 46B (60 mg, 0.168 mmol) was hydrolyzed with LiOH.H₂O (8.5 mg, 0.201 mmol) as described in Example 21B to provide the title compound (54 mg, 97.67%) as a white powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (s, 1H), 7.20 (t, *J*=7.81 Hz, 1H),
10 7.13 -7.09 (m, 2H), 7.02-6.99 (m, 3H), 6.88 (d, d, *J*₁=8.20 Hz, *J*₂=2.34 Hz, 1H), 6.81 (d, *J*=7.42 Hz, 1H), 5.00 (s, 2H), 3.66-3.61 (m, 2H), 2.79-2.72 (m, 2H), 2.43-2.36 (m, 1H), 1.91-1.86 (m, 2H), 1.67-1.57 (m, 2H). LCMS (APCI+; Method D) *m/z* 330, (M+H)⁺.

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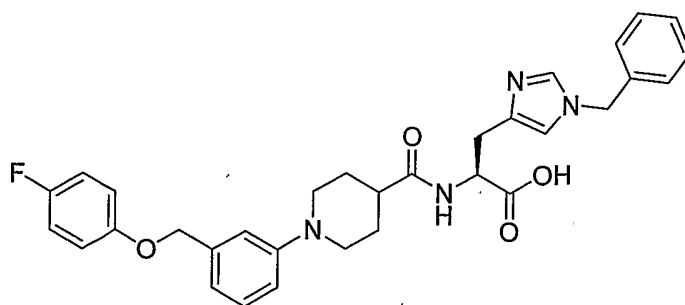


Example 46D

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-
phenoxy-methyl)-phenyl]-piperidine-4-carbonyl}-
amino)-propionic acid methyl ester

Example 46D (70 mg, 75%) was prepared from
Example 46C (50 mg, 0.152 mmol) as described in
Example 21C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.14 (d,
 $J=7.81$ Hz, 1H), 7.66 (s, 1H), 7.36-7.28 (m, 3H),
10 7.22-7.19 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.99 (m,
3H), 6.89-6.87 (m, 2H), 6.82 (d, $J=7.42$ Hz, 1H),
5.12 (s, 2H), 5.00 (s, 2H), 4.48-4.42 (m, 1H), 3.69-
3.63 (m, 2H), 3.55 (s, 3H), 2.85-2.76 (m, 2H), 2.69-
22.59 (m, 2H), 2.30-2.25 (m, 1H), 1.71-1.64 (m, 1H),
15 1.59-1.48 (m, 3H). LCMS (APCI+; Method D) m/z 571,
($\text{M}+\text{H}$) $^+$. Analytical HPLC (Method C) $R_t=2.401$ min (220
nm, 92.78 area%).

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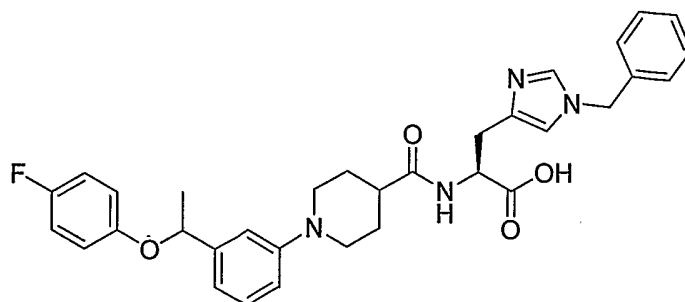


Example 46E

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluoro-
5 phenoxymethyl)-phenyl]-piperidine-4-carbonyl}-
amino)-propionic acid

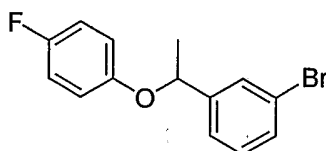
The title compound was prepared from Exam-
ple 46D (65 mg, 0.114 mmol) as described in Example
21D. Example 46E (45 mg, 71%) was obtained as a
white powder. ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d,
10 J=7.81 Hz, 1H), 7.67 (s, 1H), 7.36-7.28 (m, 3H),
7.24-7.19 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.98 (m,
3H), 6.89-6.86 (m, 2H), 6.82-6.81 (m, 1H), 5.12 (s,
1H), 5.01 (s, 2H), 4.42-4.37 (m, 1H), 3.70-3.59 (m,
2H), 2.91-2.86 (m, 1H), 2.81-2.75 (m, 1H), 2.68-2.58
15 (m, 2H), 2.29-2.23 (m, 1H), 1.73-1.65 (m, 1H), 1.62-
1.47 (m, 3H). LCMS (APCI+): (M+H)⁺=557. LCMS
(APCI+; Method D) m/z 557, (M+H)⁺. Analytical HPLC
(Method C) Rt=2.319 min (220 nm, 92.94 area%).

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Example 47

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-{3-[1-(4-fluoro-
 5 phenoxy)-ethyl]-phenyl}-piperidine-4-carbonyl)-
 amino]-propionic acid

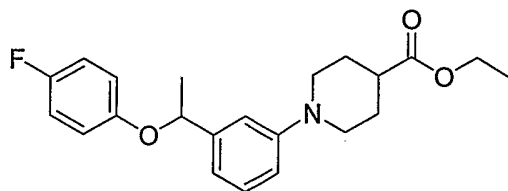


Example 47A

3-(4-Fluoro-phenoxy) α -methylbenzyl bromide

Example 47A was prepared by the procedure
 10 described in Example 46A, substituting 3-bromobenzyl
 alcohol with 1-(3-bromo-phenyl)-ethanol (250 mg,
 1.243 mmol). The title compound (230 mg, 50%) was
 obtained as a colorless liquid. ^1H NMR (400 MHz,
 DMSO- d_6) δ 7.59 (m, 1H), 7.47-7.44 (m, 1H), 7.42-7.39
 15 (m, 1H), 7.33-7.29 (m, 1H), 7.07-7.03 (m, 2H), 6.93-
 6.89 (m, 2H), 5.50 (q, $J=6.23$ Hz, 1H), 1.52 (d,
 $J=6.24$ Hz, 3H). LCMS (APCI+; Method D) m/z 295,
 (M+H) $^+$.

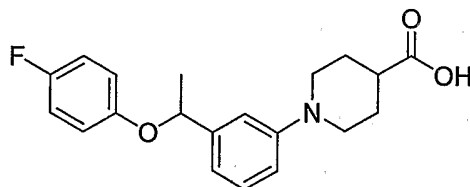
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Example 47B

1-{3-[1-(4-Fluorophenoxy)ethyl]-phenyl}-
piperidine-4-carboxylic acid ethyl ester

5 Example 47B was prepared by the procedure
described in Example 21A, substituting 1-bromo-3-
methyl-benzene with Example 47A (225 mg, 0.762
mmol). The title compound (140 mg, 58%) was obtained
as a colorless oil. LCMS (APCI+; Method D) m/z 372,
10 (M+H)⁺. Analytical HPLC (Method C) R_t =3.375 min (220
nm, 98 area%).



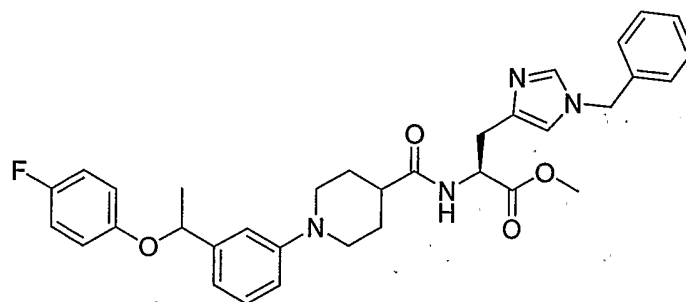
Example 47C

15 1-{3-[1-(4-Fluorophenoxy)ethyl]-phenyl}-
piperidine-4-carboxylic acid

Example 47B (135 mg, 0.363 mmol) was hy-
drolyzed with LiOH.H₂O (18 mg, 0.436 mmol) as de-
scribed in Example 21B to provide the title compound
(80 mg, 49%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.14 (t,
20 J =7.80 Hz, 1H), 7.04 -6.99 (m, 2H), 6.96 (s, 1H),
6.91-6.87 (m, 2H), 6.816.75 (m, 2H), 5.35 (q, J =6.25

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Hz, 1H), 3.61-3.58 (m, 2H), 2.75-2.67 (m, 2H), 2.36-2.29 (m, 1H), 1.89 (m, 2H), 1.66-1.57 (m, 2H), 1.51 (d, $J=6.64$ Hz, 3H). LCMS (APCI+; Method D) m/z 344 (M+H)⁺.

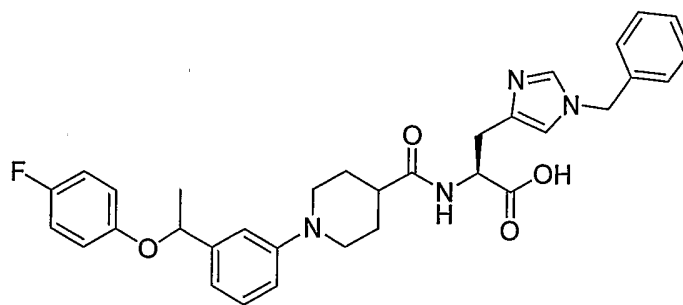


Example 47D

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-{3-[1-(4-fluorophenoxy)-ethyl]-phenyl}-piperidin-4-carbonyl)-amino]-propionic acid methyl ester

Example 47D was prepared from Example 47C (70 mg, 0.204 mmol) as described in Example 21C. The title compound (70 mg, 51%) was obtained as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 (d, $J=7.42$ Hz, 1H), 7.66 (s, 1H), 7.36-7.32 (m, 2H), 7.30-7.28 (m, 1H), 7.22-7.20 (m, 2H), 7.17-7.12 (m, 1H), 7.04-7.00 (m, 2H), 6.95 (m, 1H), 6.91-6.87 (m, 3H), 6.80-6.76 (m, 2H), 5.34 (q, $J=6.25$ Hz, 1H), 5.12 (s, 2H), 4.47-4.42 (m, 1H), 3.65-3.52 (m, 2H), 3.55 (s, 3H), 2.85-2.76 (m, 2H), 2.63-2.55 (m, 2H), 2.29-2.23 (m, 1H), 1.71-1.66 (m, 1H), 1.61-1.54 (m, 3H), 1.52 (d, $J=6.25$ Hz, 3H). LCMS (APCI+; Method D) m/z 585, (M+H)⁺. Analytical HPLC (Method C) $R_t=2.467$ min (220 nm, 86.94 area%).

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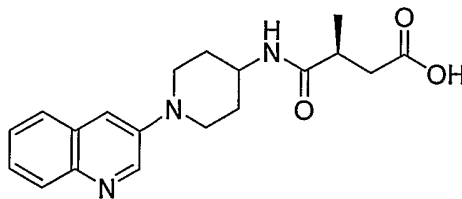


Example 47E

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-{3-[1-(4-fluoro-
5 phenoxy)-ethyl]-phenyl}-piperidine-4-carbonyl)-
amino]-propionic acid

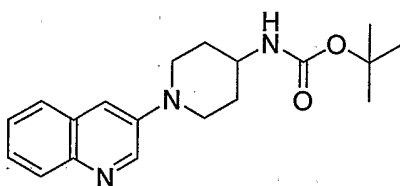
The title compound was prepared from Exam-
ple 47D (65 mg, 0.111 mmol) as described in Example
21D. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (d, *J*=7.42 Hz,
1H), 7.67 (s, 1H), 7.36-7.21 (m, 1H), 7.17-7.13 (m,
10 2H), 7.056-7.00 (m, 3H), 6.94-6.86 (m, 3H), 6.80-
6.76 (m, 2H), 5.35 (q, *J*=6.23 Hz, 1H), 5.12 (s, 2H),
4.43-4.46 (m, 1H), 3.67-3.55 (m, 2H), 2.91-2.87 (m,
1H), 2.81-2.75 (m, 1H), 2.65-2.54 (m, 2H), 2.27-2.19
15 (m, 1H), 1.92-1.86 (m, 1H), 1.71-1.56 (m, 3H), 1.52
(d, *J*=6.23 Hz, 3H). LCMS (APCI+; Method D) *m/z* 571,
(*M*+*H*)⁺. Analytical HPLC (Method C) *R*_t=2.372 min (220
nm, 83 area%).

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Example 48

3-Methyl-N-(1-quinolin-3-yl-piperidin-4-yl)-
succinamic acid



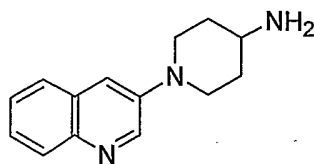
5

Example 48A

(1-Quinolin-3-yl-piperidin-4-yl)-carbamic acid tert-
butyl ester

The title compound was prepared by the
10 procedure described in Example 21A, substituting 1-
bromo-3-methyl-benzene with 3-bromo-quinoline (416
mg, 2.00 mmol) and ethyl isonipecotate with piper-
idin-4-yl-carbamic acid tert-butyl ester (481 mg,
2.4 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (d,
15 J=2.73 Hz, 1H), 7.86-7.83 (m, 1H), 7.80-7.76 (m,
1H), 7.53 (d, J=2.34 Hz, 1H), 7.48-7.45 (m, 2H),
6.89 (br d, J=7.81 Hz, 1H), 3.83 (m, 2H), 3.50-3.42
(m, 1H), 2.91-2.84 (m, 2H), 1.88-1.84 (m, 2H), 1.59-
1.50 (m, 2H), 1.40 (s, 9H). LCMS (APCI+; Method D)
20 m/z 328, (M+H)⁺, major peak 228 [(M-^tBuCO₂)+H]⁺.
Analytical HPLC (Method C) Rt=2.312 min (220 nm,
92.7 area%).

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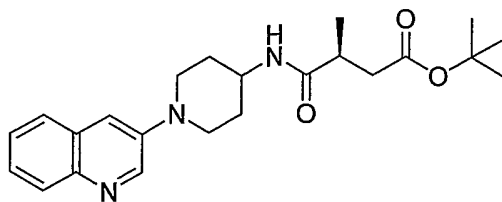


Example 48B

1-Quinolin-3-yl-piperidin-4-ylamine.HCl

A suspension of Example 48A (350 mg, 1.07 mmol) in CH₂Cl₂ was treated with 4N HCl in dioxane (6 mL) at 0°C under N₂ atmosphere for 30 min and allowed to stir at ambient temperature. After 2 hours the solvent was removed under reduced pressure and the residue obtained was dried under vacuum for 5 h to provide the title compound (325 mg, 95%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.23 (d, J=2.73 Hz, 1H), 8.42 (m, 1H), 8.36 (m, 2H), 8.25 (d, J=9.76 Hz, 1H), 8.07 (d, J=9.76 Hz, 1H), 7.80-7.76 (m, 2H), 4.09 (d, J=13.28 Hz, 2H), 3.35-3.27 (m, 1H), 3.08 (t, J=11.71 Hz, 2H), 2.09 (m, 2H), 1.78-1.68 (m, 2H). LCMS (APCI+; Method D) m/z 228, (M+H)⁺. Analytical HPLC (Method C) Rt=1.493 min (220 nm, 94.03 area%).

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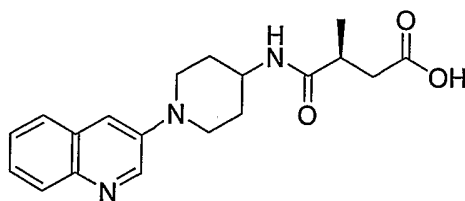


Example 48C

3-Methyl-N-(1-quinolin-3-yl-piperidin-4-yl)-
succinamic acid tert-butyl ester

5 The title compound was prepared from
Example 48B (150 mg, 0.500 mmol) and Example 15G
(103 mg, 0.550 mmol) as described in Example 21C.
Example 48C (121 mg, 61%) was obtained as a yellow
solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.86 (d, J=2.73
10 Hz, 1H), 7.86-7.82 (m, 2H), 7.78-7.76 (m, 1H), 7.55
(d, J=3.12 Hz, 1H), 7.48-7.45 (m, 2H), 3.86-3.79 (m,
2H), 3.77-3.71 (m, 1H), 2.97-2.90 (m, 2H), 2.64-2.59
(m, 1H), 2.45 (dd, J₁=15.62 Hz, J₂=8.59 Hz, 1H), 2.18
(d, d, J₁=16.00 Hz, J₂=6.25 Hz, 1H), 1.87 (m, 2H),
15 1.60-1.50 (m, 2H), 1.38 (s, 9H), 1.02 (d, J=7.03 Hz,
3H). LCMS (APCI+; Method D) m/z 398, (M+H)⁺.
Analytical HPLC (Method C) Rt=2.208 min (220 nm, 100
area%).

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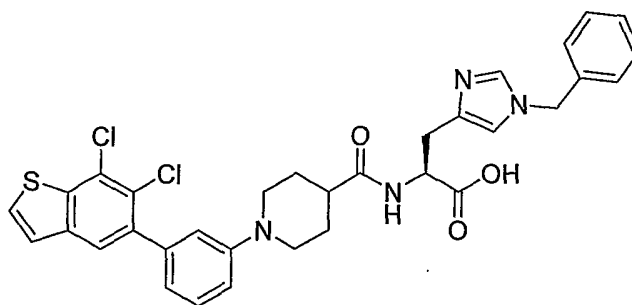


Example 48D

3-Methyl-N-(1-quinolin-3-yl-piperidin-4-yl)-
succinamic acid. HCl salt.

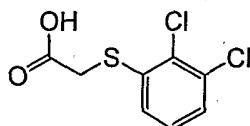
5 A solution of Example 48C (110 mg, 0.268
mmol) in CH₂Cl₂ (2 mL) was treated with TFA (0.320
mL, 4.151 mmol) under N₂ atmosphere at ambient tem-
perature for 3 h. The reaction was monitored by TLC
and by HPLC at 1 h intervals. After 3 h solvents
10 were removed and the residue obtained was evaporated
with CH₂Cl₂ (3X5 mL), followed by ether (2 mL) and
dried under vacuum to provide the title compound
(100 mg, 96.72%) as a bright yellow powder. ¹H NMR
(400 MHz, DMSO-*d*₆) δ 9.05 (d, *J*=2.73 Hz, 1H), 8.02
15 (s, 1H), 7.98-7.92 (m, 2H), 7.85 (d, *J*=7.42 Hz, 1H),
7.65-7.62 (m, 2H), 3.93-3.85 (m, 2H), 3.82-3.75 (m,
1H), 3.08-3.01 (m, 2H), 2.65-2.60 (m, 1H), 2.51-2.47
(m, 1H), 2.23-2.17 (d, d, *J*₁=6.25 Hz, *J*₂=16.14 Hz,
1H), 1.89-1.85 (m, 2H), 1.60-1.51 (m, 2H), 1.04 (d,
20 *J*=6.64 Hz, 3H). LCMS (APCI+; Method D) *m/z* 342,
(*M*+H)⁺. Analytical HPLC (Method C) *R*_t=1.660 min (220
nm, 98.7 area%).

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Example 49

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(6,7-dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid



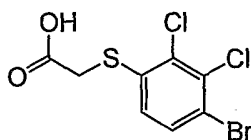
Example 49A

(2,3-Dichloro-phenylsulfanyl)-acetic acid

A 2 L, 3-neck flask, with a mechanical stir shaft, was charged with 2,3-dichlorothiophenol (50.0 g, 279 mmol) and bromoacetic acid (40.7 g, 293 mmol). The mixture was suspended in water (300 mL) and 3 M aqueous NaOH (300 mL, 900 mmol) was added. A reflux condenser was attached and a thermocouple was placed in the remaining port. The mixture was heated to 95°C internal temperature. The mixture was refluxed 15 h and then cooled to room temperature. Once the mixture had cooled, 4 M aqueous HCl (400 mL, 1.6 mol) was added and the mixture was extracted with ethyl acetate (2x1.25 L). The combined organic layers were dried (MgSO₄), filtered, and

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concentrated to an off-white solid. To the solids were added hexanes (150 mL) and the mixture heated to reflux with stirring for 15 min. The mixture was cooled to room temperature and the solid formed was collected by filtration and washed with additional hexanes (100 mL). The solid was dried under vacuum to provide the title compound (55.6 g, 84%) as a white solid. ^1H NMR (acetone- d_6 , 400 MHz) δ 7.39-7.43 (m, 2H), 7.31-7.37 (m, 1H), 3.96 (s, 2H).



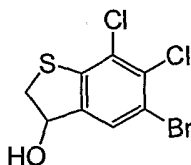
Example 49B

(4-Bromo-2,3-dichloro-phenylsulfanyl)-Acetic acid

To a solution of Example 49A (58.0 g, 245 mmol) in acetic acid (250 mL) was added iron chips (3.5 g, 63 mmol). The mixture was gently heated to dissolve Example 49A. The mixture was cooled to room temperature and bromine (25 mL, 490 mmol) was added over 20 min by addition funnel. The reaction was stirred for 4 h, then more bromine (10 mL) was added in one portion and stirring continued for 5 h. Next, a third bolus of bromine (10 mL) was added and the mixture stirred 12 h. The mixture was then quenched by careful addition of a saturated solution of NaHSO_3 and stirred for 45 min. A white precipitate formed was collected by filtration and washed with water. The solid was dried under vacuum for

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two days in a desiccator followed by six hours in a vacuum oven at 70°C to provide the title compound (76.7 g, 99%) containing 90% bromination at the 4-position. ¹H NMR (acetone-*d*₆, 400 MHz) δ 7.70 (d, *J*=8.98 Hz, 1H), 7.35 (d, *J*=8.59 Hz, 1H), 4.00 (s, 2H).



Example 49C

10 5-Bromo-6, 7-dichloro-2, 3-dihydro-benzo[b]thiophen-3-ol

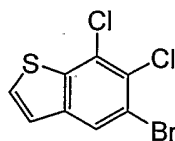
To a suspension of Example 49B (50.0 g, 158 mmol) in THF (160 mL) was added 3 drops of DMF followed by oxalyl chloride (21.1 g, 166.1 mmol) over a 15 min period. The mixture was heated to 50°C for 3 h. Next, the mixture was cooled to room temperature and concentrated *in vacuo* to obtain an intermediate acid chloride (51.3 g) as a dark yellow oil that was used in the next step without purification. A 1 L flask was charged with AlCl₃ (179 g, 1.35 mol) and methylene chloride (250 mL), and then cooled to -78°C (dry ice/acetone). A solution of the acid chloride (prepared above) in methylene chloride (150 mL) was added dropwise over 20 min. When addition was completed, the dry ice bath was removed and the reaction was allowed to warm to room temperature and stirred for an additional 1 h. The

15
20
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mixture was quenched by slowly pouring onto ice (2 L). The mixture was extracted with ethyl acetate (2x1 L), and the combined organic phases were washed with brine (500 mL). The red organic layer was
5 dried (MgSO_4), filtered, and concentrated to an orange solid. The solid was dried under high vacuum for 14 h to give an intermediate ketone, which was used in the next step without purification. The ketone was resuspended in ethanol (500 mL, absolute)
10 and NaBH_4 (12 g, 316 mmol) was added portionwise while cooling on an ice bath. The reaction was warmed to room temperature after addition was complete. After 2 h, the reaction mixture was transferred to a 4 L Erlenmeyer flask and quenched with 4
15 M aqueous HCl (caution, vigorous gas evolution). The mixture was concentrated *in vacuo*, diluted with water (200 mL), and extracted with ethyl acetate (2x500 mL). The combined organic phases were washed with brine (250 mL), dried (MgSO_4), filtered, and
20 concentrated to give a dark brown oil (45 g). This was purified by chromatography on silica gel (Bio-tage Flash 75 L) eluting with 10% ethyl acetate in hexanes followed by 20% ethyl acetate in hexanes to provide the title compound (23.0g, 48% for 3 steps)
25 as a red oil that solidified upon standing. ^1H NMR (CDCl_3 , 400 MHz) δ 7.53 (d, $J=0.78$ Hz, 1H), 5.44 (m, 1H), 3.66 (dd, $J=12.1$, 6.63 Hz, 1H), 3.35 (dd, $J=12.1$, 4.68 Hz, 1H), 2.23 (d, $J=8.19$ Hz, 1H).

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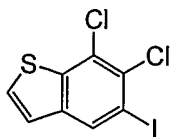
Example 49D

5-Bromo-6,7-dichloro-benzo[b]Thiophene

To a 1L flask was added Example 49C (23.0g, 76.7 mmol) and acetic acid (230 mL). The mixture was sonicated for 30 min. $\text{BF}_3\text{-Et}_2\text{O}$ (15 mL, 115 mmol) was added dropwise over 1 min at room temperature. After 15 min the homogeneous mixture was diluted with water (500 mL) and a white precipitate formed. After stirring for an additional 15 min, the solid was collected by filtration and washed with water (200 mL). The solid was dissolved in ethyl acetate (500 mL) and washed with a saturated solution of NaHCO_3 (200 mL) followed by brine (200 mL). The organic phase was dried (MgSO_4), filtered, and concentrated. The resulting pink solid was recrystallized from boiling hexanes (200 mL). The crystals (14.3 g) formed had a dark red color. The mother liquor was concentrated to give a tan solid (6.6 g) which was combined with the first crop to provide the title compound (20.9 g, 97%).

^1H NMR (CDCl_3 , 400 MHz) δ 7.97 (s, 1H), 7.51 (d, $J=5.47$ Hz, 1H), 7.24 (d, $J=5.47$ Hz, 1H).

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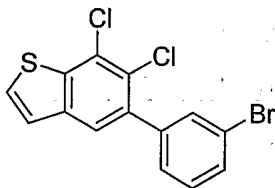


Example 49E

5-Iodo-6,7-dichloro-benzo[b]Thiophene

To a 250 mL flask was added 49D (5.00g, 17.7 mmol), copper iodide (0.170 g, 0.887 mmol), toluene (13.5 mL,) diglyme (3.5 mL,) and 1,3-diaminopropane (0.22 mL, 2.66 mmol). The mixture was heated under N₂ at 130°C for 10 days. The mixture was cooled to rt, diluted with toluene (50 mL) and washed with NH₄Cl/ brine (3x100 mL). The organic layer was concentrated to dryness to provide the title compound (5.10 g, 89%) as a 3:1 mixture of aryl iodine and aryl bromide as an orange solid.

¹H NMR (CDCl₃, 400 MHz) δ 8.24 (s, 1H), 7.51 (d, J=5.47 Hz, 1H), 7.25 (d, J=5.86 Hz, 1H.)



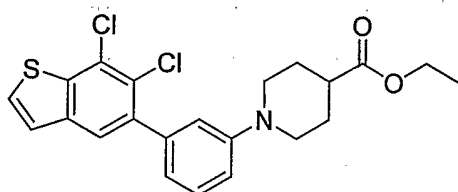
Example 49F

5-(3-Bromo-phenyl)-6,7-dichloro-benzo[b]thiophene

A solution of 49D (1.00 g, 3.55 mmol) in 14 mL DME was treated with 3-bromo-phenylboronic acid (0.855 g, 4.26 mmol) and K₂CO₃ (0.735 g, 0.532 mmol). The mixture was purged with N₂ for 15 min and

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Pd(PPh₃)₄ (0.123 g, 0.106 mmol) was added. The mixture was heated to 85°C for 72 h and cooled to ambient temperature, and concentrated *in vacuo*. The residual oil was partitioned with EtOAc (50 mL) and washed with dilute brine solution (3x25 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting white solid was purified by flash chromatography on silica gel eluting with 100% hexanes to provide the title compound (0.428 g, 33.8%) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (s, 1H), 7.59 (t, *J*=1.76 Hz, 1H), 7.53 (m, 2H), 7.38 (m, 1H), 7.33 (m, 2H).



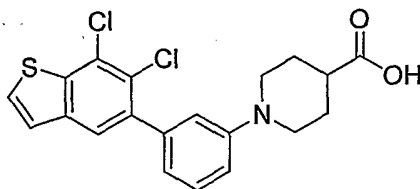
Example 49G

1-[3-(6,7-Dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carboxylic acid ethyl ester

To a solution of 49F (0.072 g, 0.20 mmol) in 0.4 mL DME was added K₂PO₃ (0.076 g, 0.362 mmol) and ethyl isonipecotate (0.047 g, 0.302 mmol). The mixture was purged with N₂ for 5 min and (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine (0.0063 g, 0.0161 mmol) and Pd₂(dba)₃ (0.0074 g, 0.008 mmol) was added and the mixture heated to 90 °C for 18 h. After cooling to ambient temperature, the mixture was partitioned between dilute brine (10 mL) and EtOAc (10 mL). The organic layer

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was washed (3X5 mL) with dilute brine and concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel eluting with EtOAc/Hexane 1:2 to give the title compound (0.034 g, 39%) as a light colored oil which solidified upon standing. ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (s, 1H), 7.51 (d, *J*=5.85 Hz, 1H), 7.32 (m, 2H), 6.98 (m, 2H), 6.91 (s, 1H), 4.17 (q, *J*=7.41, 14.2 Hz, 2H), 3.7 (m, 2H), 2.84 (m, 2H), 2.44 (m, 1H), 2.04 (m, 2H), 1.9 (m, 2H), 1.27 (t, *J*=7.02 Hz, 3H).

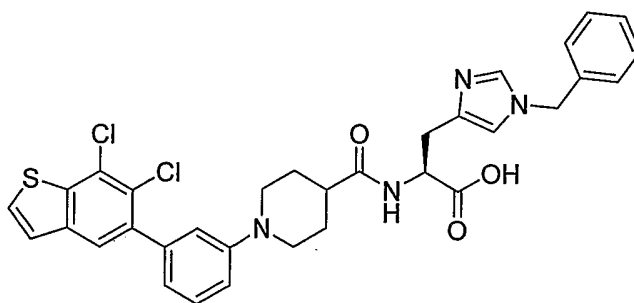


Example 49H

1-[3-(6,7-Dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carboxylic acid

Example 49G (0.034 g, 0.078 mmol) was processed as in Example 17E substituting 49F for 17D to provide the title compound (0.028 g, 90%) as an off-white powder.

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Example 49I

5 3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(6,7-dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid

Example 49H (0.034 g, 0.078 mmol) was processed as in Example 17G substituting 49H for 17E to provide the title compound (0.0075 g, 45.8%) as an off-white powder. HPLC (Method C) Rt=2.83 min (85.0
10 area%, 220 nm). LCMS (APCI+ Method D) m/z 633.2 (M^+), Rt=3.41 min (254 nm, 83.1 area%).

The following Methods may be used to test compounds of this invention. Unless otherwise indicated, the reagents used in the following examples
15 are commercially available and may be purchased from Sigma-Aldrich Company, Inc. (Milwaukee, WI, USA) or Alfa Aesar (Ward Hill, MA, USA).

Example A

Inhibition of soluble VLA-1 binding to Collagen IV

20 Generation of sVLA-1-LZ:

A soluble form of the $\alpha 1\beta 1$ heterodimer (sVLA-1-LZ) was generated by truncating each chain

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of the heterodimer at the beginning of the trans-membrane region and adding an acidic and basic leucine zipper sequence to the $\alpha 1$ and $\beta 1$ chains, respectively. The $\alpha 1$ chain (described in U.S. Patent Application Publication No. US2003/0088061) was truncated after residue P1141 of the pro-peptide and the 47 amino acid acidic leucine zipper cassette was added. The $\beta 1$ chain (Genbank accession no. P05556) was truncated after residue D728 of the pro-peptide and the 47 amino acid basic leucine zipper cassette was added. Both constructs were then expressed in CHO DG44 cells, and the heterodimer was purified from the culture supernatant using an antibody affinity column specific for the leucine zipper sequences, followed by size-exclusion chromatography on an S200 sizing column (Pharmacia, now Pfizer Inc., New York, NY USA) using methods standard to the art. (See also, U.S. Patent Application Publication No. US2003/0088061). The purified protein was stored at -70°C .

Briefly, an $\alpha 1$ -LZ construct was generated which has the extracellular domain of $\alpha 1$ fused to a C-terminal leucine zipper sequence. The extracellular domain of $\alpha 1$ was amplified using standard PCR methods and reagents in order to add restriction sites for the subcloning. The sequences of the primers used in the PCR reaction were:

5' primer: $\alpha 1$ -01: ATT CTC GAG ACC GCC ACC ATG GTC
CCC AGG CGT CC (SEQ. ID. 1)
3' primer: $\alpha 1$ -04: ATT ACG CGT TGG CAC TCT GCC CGG
TAG (SEQ. ID. 2)

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The primers above were used in a PCR reaction with an $\alpha 1$ cDNA clone (described previously, U.S. Patent Application Publication No. US2003/0088061). The resulting PCR product was subcloned 5' to the acidic leucine zipper sequence in the mammalian expression vector pDEF38 (described in U.S. Patent Application Publication No. US2003/0088061). The resulting plasmid was verified by sequencing.

10 The extracellular domain of $\beta 1$ was likewise was amplified using standard PCR methods and reagents in order to add restriction sites for the subcloning. The sequences of the primers used in the PCR reaction were:

15 5' primer: $\beta 1$ -02: ATT CTC GAG ACC GCC ACC ATG AAT
TTA CAA CCA ATT TTC TGG (SEQ. ID. 3)
3' primer: $\beta 1$ -03: GTT CCA TTC ACC CCG TTC TTG C
(SEQ. ID. 4)

In order to generate a $\beta 1$ leucine zipper soluble molecule, the 5' end of the β -1 insert was generated by PCR from a $\beta 1$ cDNA and subcloned 5' to the basic leucine zipper sequence in the mammalian expression vector pNEF38 (described in U.S. Patent Application Publication No. US2003/0088061). The
25 resulting plasmid was verified by sequencing.

Alpha 1 Leucine Zipper (Acidic) construct protein sequence:

MVPRRPASLE VTVACIWLLT VILGFCVSFN VDVKNSMTFS GPVEDMFGYT
VQQYENEEGK WVLIGSPLVG QPKNRTGDVY KCPVGRGESL PCVKLDLPVN
30 TSIPNVTEVK ENMTFGSTLV TNPNGGFLAC GPLYAYRCGH LHYTTGICSD

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VSPTFQVVNS IAPVQECSTQ LDIVIVLDGS NSIYPWDSVT AFLNDLLERM
 DIGPKQTQVG IVQYGENVTH EFNLNKYSST EEVLVAAKKI VQRGGRQTM
 ALGTDATARKE AFTEARGARR GVKKVMVIVT DGESHDNHRL KKVIQDCED
 NIQRFSIAIL GSYNRGNLST EKFEVEIKSI ASEPTEKHFF NVSDELALVT
 5 IVKTLGERIF ALEATADQSA ASFEMEMSQT GFSAHYSQDW VMLGAVGAYD
 WNGTVVMQKA SQIIIPRNTT FNVESTKKNE PLASYLGYTV NSATASSGDV
 LYIAGQPRYN HTGQVVIYRM EDGNIKILQT LSGEQIGSYF GSILTTTDDID
 KDSNTDILLV GAPMYMGTEK EEQGVVYVYA LNQTRFEYQM SLEPIKQTC
 SSRQHNSCTT ENKNEPCGAR FGTAIAAVKD LNLDFGNDIV IGAPLEDDHG
 10 GAVYIYHSG KTIKEYAQR IPSGGDGKTL KFFGQSIHGE MDLNGDGLTD
 VTIGGLGGAA LFWSRDVAVV KVTMNFEPNK VNIQKKNCHM EGKETVCINA
 TVCFDVKLKS KEDTIYEADL QYRVTLSLR QISRSFFSGT QERKVQRNIT
 VRKSECTKHS FYMLDKHDFQ DSVRITLDFN LTDPENGPVL DDSLPSNVHE
 YIPFAKDCGN KEKCISDL SL HVATTEKDLL IVRSQNDKFN VSLTVKNTKD
 15 SAYNTRTIVH YSPNLVFSGI EAIQKDSCE NHNITCKVGY PFLRRGEMVT
 FKILFQFNTS YLMENVTIYL SATSDSEEP ETLSDNVUNI SIPVKYEVGL
 QFYSSASEYH ISIAANETVP EVINSTEDIG NEINIFYLIR KSGSFPMP
 KLSISFPNMT SNGYPVLYPT GLSSSENANC RPHIFEDPFS INSGKKMTS
 TDHLKRGITL DCNTCKFATI TCNLTSSDIS QVNVSLILWK PTFIKSYFSS
 20 LNLRTIRGELR SENASLVLS SNQKRELAIQ ISKDGLPGRV PTRSSADLVP
RGSTTAPSAQ LEKELQALEK ENAQLEWELQ ALEKELAQ (SEQ. ID. 5)

Beta 1 Leucine Zipper (basic) construct protein sequence:

MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN
 25 STFLQEGMPT
 SARCDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAELKLPED
 IHQIQPQQLV
 LRLRSGEPQT FTLKFKRAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM
 NEMRRITSDF
 30 RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTTPFSYK NVLSLTNKGE
 VFNELVGKQR
 ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL
 GGIVLPNDGQ
 CHLENNMYTM SHYYDPSIA HLQKLSENN IQTIFAVTEE FQPVYKELKN
 35 LIPKSAVGTL

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SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVITISYKSY CKNGVNVTGE
 NGRKCSNISI
 GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG
 IPESPKCHEG
 5 NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE
 CVCGQCVCRK
 RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSAC
 DCSLDTSTCE
 ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR
 10 AFNKGEKKDT
 CTQECSYFNI TKVESRDKLP QPVQDPVSH CKEKDVDDCW FYFTYSVNGN
 NEVMVHVVEN
 PECPTGPDTS SADLVPRGST TAPSAQLKKK LQALKKKNAQ LKWKLOALKK KLAQ
 (SEQ. ID. 6)
 15 Signal Sequences are shown in *italics*
 Mature polypeptides are shown in plain text
 Acidic and Basic Leucine Zippers are underlined and
 bold

20 **Screening Assay for Measuring sVLA-1-LZ Binding to Collagen IV:**

A biochemical assay for measuring binding of sVLA-1-LZ to Collagen IV using time-resolved fluorescence, suitable for high-throughput screening, was developed. Briefly, 96-well Immulon-4
 25 ELISA plates were coated with sVLA-1-LZ at 2 µg/mL in 50mM NaHCO₃, pH 9.2, and incubated overnight at 4°C. The plates then were washed two times with 300 µL/well Wash Buffer (TBS; 0.1% Tween-20; 2mM MgCl₂), and blocked for 1 hour with 200 µL/well Blocking
 30 Buffer (2% BSA; CMF-PBS; 2mM MgCl₂) at room temperature. Compounds of this invention were prepared in DMSO at 200X the desired final assay concentration.

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Final concentrations were selected from a range between 0.01 nM-100 μ M. DMSO inhibitor stocks were then diluted to 2X final concentration in Dilution Buffer (TBS; 0.01% BSA; 2mM MgCl_2). Fifty μ L/well

5 Dilution Buffer, alone or in combination with, anti- α 1 mAb (Immunodiagnostic, #8149a, 2.5 μ g/mL), 10 mM EDTA, DMSO or DMSO+2X inhibitor was added to the wells of the plate, followed by 50 μ L/well Collagen

10 IV-biotin at 2 μ g/mL in Dilution buffer. Collagen IV-biotin was generated by biotinylating human Collagen IV (Sigma-Aldrich, Milwaukee, WI, USA) using a biotin labeling kit (Pierce Biotechnology, Rockford, IL, USA) following the manufacturer's protocol. The

15 plates were incubated for 1 hour at room temperature, and washed four times with Wash Buffer (300 μ L/well). The plates were then incubated with 100 μ L/well of 1:1000 diluted (with H_2O) Streptavidin-Europium (PerkinElmer, Boston, MA, USA) for 30 min. at room temperature. The plates were then washed

20 four times with Wash Buffer (300 μ L/well). One hundred μ L/well of Delphia Enhancement Solution (PerkinElmer; diluted 1:1 with dH_2O) was added, and the plates were shaken for 5 minutes. Binding was then analyzed by time resolve fluorescence (TRF)

25 using a Victor Plate-reader (PerkinElmer). Results were analyzed using the equations below. The percent of inhibition was plotted versus the log concentration of inhibitor across a twelve point titration, and a linear regression trend-line was drawn.

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Specific binding = TRF signal (Collagen-IV-biotin
in Dilution Buffer plus Ab,
DMSO only or DMSO + inhibitor) -
TRF signal (Collagen-IV-biotin
with EDTA)

5

$$\left[1 - \left(\frac{\text{specific binding of Collagen-IV-biotin with inhibitor in DMSO}}{\text{specific binding of Collagen-IV-biotin with DMSO only}} \right) \right] \times 100$$

As a variation in the assay, the effect of
serum protein in the assay was determined by substi-
tuted Collagen IV-biotin at 2µg/mL in FBS, instead
of Dilution buffer, resulting in a final serum con-
centration of 50% in the assay. The percent inhibi-
tion in the presence and absence of 50% FBS was then
compared.

15

Example B

Inhibition of VLA-1 dependent K562-α1 cell adhesion to Collagen IV

Generation of K562-α1 cells

The α1 cDNA was subcloned into the mammal-
ian expression vector pMH-neo (Hahn et al. (1993)
Gene 127:267). The resulting clone α1/pMHneo/40 was
verified by sequencing. The α1/pMHneo/40 construct
was introduced into K562 cells by electroporation.
The transfected cells were initially maintained in
complete RPMI with 10% FBS. Two days after the
transfection, the cells were spun down and resus-

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pended in complete RPMI with 10% FBS and 0.5mg/mL G418 (Sigma-Aldrich) to select for the neomycin resistance conferred by the pMHneo plasmid. Transfectants with functional $\alpha 1$ expression were selected
5 by panning the cells for binding to Type IV collagen (an $\alpha 1$ ligand). In panning experiments, K562 transfectants were stimulated with 20ng/mL of PMA and allowed to adhere to plate-bound Type IV collagen. After a 30-60 min incubation at 37°C, the unbound
10 cells were washed away and the adherent cells were recovered with versene. Cellular expression of VLA-1 was verified by FACS analysis with an $\alpha 1$ mAb.

K562- $\alpha 1$ cell adhesion assay to Collagen IV

The day prior to the assay, the K562- $\alpha 1$
15 cells were split 1:2 into fresh culture media (RPMI-1640, 10% FBS) and cultured at 37°C in CO₂. Ninety-six well Immulon-4 plates were coated with either 1.25 μ g/mL collagen IV (Sigma) in CMF-PBS or the $\alpha 1$ mAb at 5 μ g/mL in Coating Buffer (50 mM sodium
20 carbonate, 50 mM sodium bicarbonate, pH 9.6), and incubated overnight at 4°C. On the day of the assay, the plates were washed with D-PBS and then blocked with 1% BSA/D-PBS for 1.5-2.0 hours at room temperature. Compounds of this invention were prepared in
25 DMSO at 66.67X the desired final assay concentration. Final concentrations were selected from a range between 1 nM-100 μ M. Deep-well blocks (96-Square well titer plates, Beckman) were prepared with 700 μ L RPMI/well. DMSO solutions of diluted

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compound were then added to the deep-well block (10.5µL diluted compound/700µL RPMI) to generate 1.5X solutions. After blocking, the Immulon-4 plates were aspirated and 200µL RPMI only, RPMI + 5 1.5X DMSO/RPMI Solution, or RPMI + 1.5X compound in DMSO/RPMI solution was added to each well. The plates were then incubated at 37°C in 5% CO₂ for 10-30 min. K562-α1 cells were counted, spun down, washed once with RPMI and resuspended in RPMI+60ng/- 10 mL PMA at a density of 1.0X10⁶ cells/mL. One hundred µL cell suspension was then added to each well and incubated at 37°C in 5% CO₂ for 30 min. Adherent cells were then fixed to the plate with 14% glutaraldehyde/D-PBS for 1.5 hours. Plates were washed 15 with water and the cells were stained with 5% crystal violet for 5 min. at room temperature. The plates were washed with water again, and the crystal violet dye was extracted from the cells with 200 µL/well 70% ethanol. The plates were read on a 20 plate reader at A_{570nm} and A_{410nm}. Results were analyzed using the equations below. The percent inhibition was plotted versus the log concentration of inhibitor across an eight point titration, and a linear regression trend-line was drawn. As a 25 variation in the assay, the effect of serum protein in the assay was determined by substituting RPMI+50% FBS instead of RPMI. The percent inhibition in the presence and absence of 50% FBS was then compared.

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$$\text{Percent cells binding} = \left(\frac{\text{A570-A410(binding to Collagen IV)}}{\text{A570-A410(binding to Alpha1 antibody)}} \right) \times 100$$

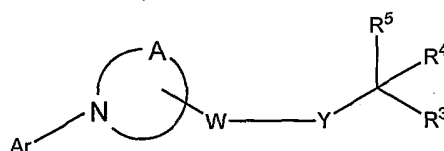
$$\text{Percent Inhibition} = \left[1 - \left(\frac{\% \text{ cells binding with inhibitor}}{\% \text{ cells binding with DMSO}} \right) \right] \times 100$$

All of the compounds of this invention that were tested exhibited at least fifty percent inhibition in one or more of the above assays when tested at a concentration of 50 μ M.

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WHAT IS CLAIMED IS:

1. A compound having a structural formula:



wherein Ar is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

A, together with the nitrogen atom bound thereto, forms a 4-8 membered nitrogen containing heterocyclic group containing 1 to 2 nitrogen atoms, wherein said heterocyclic group may be optionally substituted with 1 to 3 additional substituents each independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, hydroxy, alkoxy, thioalkyl, and halo,

wherein the one or more alkyl and substituted alkyl substituents, if present, may be attached to either a carbon or a nitrogen atom in said heterocyclic group,

wherein the one or more hydroxy and alkoxy substituents, if present, may be attached to a carbon atom in said heterocyclic group,

wherein the one or more thioalkyl and the one or more halo substituents, if present, may not

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be attached to a nitrogen atom in said heterocyclic group,

and wherein the one or more halo, thio-alkyl, and the one or more hydroxy substituents, if present, may not be attached to a carbon atom which is adjacent to a nitrogen atom in said heterocyclic group;

W is selected from the group consisting of -C(X)-NH- and -NH-C(X)-, wherein X is oxygen or sulfur,

Y is selected from the group consisting of a bond, alkylene, and substituted alkylene;

R³ and R⁴ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, amino, substituted amino, aminocarbonyloxy, oxycarbonyl-amino, aminoacyl, acylamino, aminocarbonylamino, aminosulfonylamino, aminosulfonyl, sulfonylamino, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkoxy, substituted alkoxy, carboxyl, and carboxyl esters; or R³-C-R⁴ forms a cycloalkyl, substituted cycloalkyl, heterocyclic, or substituted heterocyclic group;

R⁵ is selected from the group consisting of CR^aR^aCO₂R^a, COCO₂R^a, carboxyl, carboxyl esters, -CO-NR^aOR^a, -CONR^aSO₂R^a, heterocyclic, cyano, and hydroxy-alkyl; wherein R^a is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, heterocyclic, and substituted heterocyclic;

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with the proviso that when Y is a bond and W is C(O)NH, then R³ and/or R⁴ are not amino, substituted amino, hydroxy, or alkoxy;

and a pharmaceutically acceptable salt, a prodrug, or a tautomer thereof.

2. The compound of claim 1 wherein A together with the nitrogen atom bound thereto form a piperidine ring.

3. The compound of claim 1 wherein W is -C(O)-NH-.

4. The compound of claim 1 wherein W is -NH-C(O)-.

5. The compound of claim 1 wherein Y is a bond.

6. The compound of claim 1 wherein Y is methylene.

7. The compound of claim 1 wherein R⁴ is hydrogen.

8. The compound of claim 1 wherein R⁵ is -CO₂H.

9. The compound of claim 1 wherein R³ is alkyl or substituted alkyl.

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10. The compound of claim 9 wherein R^3 is selected from the group consisting of:

methyl;

N-benzylimidazol-4-ylmethylene' and

phenylacetamidomethylene.

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11. The compound of claim 1 wherein Ar is selected from the group consisting of:

5-(2,3-dichlorophenyl)pyridin-3-yl;
4-(2,3-dichlorophenyl)pyridin-2-yl;
5-(2,3-dichlorophenyl)pyridin-2-yl;
3-methyl-5-(2,3-dichlorophenyl)pyridin-2-yl;
3-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl;
5-methyl-4-(2,3-dichlorophenyl)pyridin-2-yl;
5-(2,3-dichlorophenyl)pyridin-2-yl;
6-methyl-3-(2,3-dichlorophenyl)phenyl;
4-(2,3-dichlorophenyl)thiazol-2-yl;
5-bromo-pyridin-3-yl;
pyridin-3-yl;
3-(2,3-dichlorophenyl)phenyl;
6-methyl-3-(2,3-dichlorophenyl)phenyl;
3-methylphenyl;
3-ethylphenyl;
3-isopropylphenyl;
3-trifluoromethylphenyl;
3-dimethylaminophenyl;
3-(4-fluorophenoxy)phenyl;
3-fluoro-5-trifluoromethylphenyl;
3,5-trifluoromethylphenyl;
2-methylquinolin-6-yl;
3,4-dichlorophenyl;
2,3-dichlorophenyl;
6,7-dichlorobenzo[b]thiophen-5-yl;

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3,5-dichlorophenyl;
benzo[1,3]dioxol-6-yl;
4-t-butylphenyl;
3-chloro-6-nitrophenyl;
5-bromo-4-fluoro-2-nitrophenyl;
5-(N-morpholino)-2-nitrophenyl;
3-(trifluoromethylthio)phenyl;
3-(trifluoromethoxy)phenyl;
3-(trifluoromethoxy)phenyl;
quinolin-3-yl;
quinolin-3-yl;
isoquinolin-3-yl;
isoquinolin-3-yl;
(4-fluorophenyloxy)benz-3-yl;
3-(4-fluorophenyloxy)ethylphenyl;
quinolin-3-yl; and
phenyl.

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12. A compound selected from the group consisting of:

2-{[4'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[4'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[6'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[6'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[4'-(2,3-Dichloro-phenyl)-3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid/2-{[4'-(2,3-Dichloro-phenyl)-5'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-{[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{[5'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

3-Benzoylamino-2-{[5'-(2,3-dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-propionic acid;

2-[(5'-Bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

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3-Benzoylamino-2-[(5'-bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(5'-bromo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl)-amino]-propionic acid;

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic acid;

N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-3-methyl-succinamic/N-[5'-(2,3-Dichloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl]-2-methyl-succinamic acid;

2,3-Dichloro-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid;

2,3-Dichloro-4'-methyl-3'-2[(piperidine-4-carbonyl)-amino]-propionic acid;

2-({1-[4-(2,3-Dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl}-amino)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[4-(2,3-dichloro-phenyl)-thiazol-2-yl]-piperidine-4-carbonyl}-amino)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-m-tolyl-piperidine-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-(3-ethyl-phenyl)-piperidine-4-carbonyl}-amino)-propionic acid;

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3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3-isopropyl-phenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3-trifluoromethyl-phenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3-dimethyl-amino-phenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluorophenoxy)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3-fluoro-5-trifluoromethyl-phenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3,5-bis-trifluoromethyl-phenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(2-methylquinolin-6-yl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(3,4-dichlorophenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(2,3-dichlorophenyl)-piperidine-4-carbonyl}-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{1-(6,7-dichlorobenzo[b]thiophen-5-yl)-piperidine-4-carbonyl}-amino}-propionic acid;

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3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(3,5-dichloro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

2-[(1-Benzo[1,3]dioxol-5-yl-piperidine-4-carbonyl)-amino]-3-(1-benzyl-1H-imidazol-4-yl)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(4-tert-butyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(5-chloro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(5-bromo-4-fluoro-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(5-morpholin-4-yl-2-nitro-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(3-trifluoromethylsulfanyl-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-{{[1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-Benzoylamino-2-{{[1-(3-trifluoromethoxy-phenyl)-piperidine-4-carbonyl]-amino}-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid;

3-Benzoylamino-2-[(1-quinolin-3-yl-piperidine-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid;

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3-Benzoylamino-2-[(1-isoquinolin-4-yl-piperidine-4-carbonyl)-amino]-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(4-fluorophenoxymethyl)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid;

3-(1-Benzyl-1H-imidazol-4-yl)-2-[(1-{3-[1-(4-fluorophenoxy)-ethyl]-phenyl}-piperidine-4-carbonyl)-amino]-propionic acid;

3-{[5'-(1-Methyl-1H-indol-5-yl)-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carbonyl]-amino}-butyric acid;

3-Methyl-N-(1-quinolin-3-yl-piperidin-4-yl)-succinamic acid; and

3-(1-Benzyl-1H-imidazol-4-yl)-2-({1-[3-(6,7-dichloro-benzo[b]thiophen-5-yl)-phenyl]-piperidine-4-carbonyl}-amino)-propionic acid.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

14. A method of assaying a biological sample from a mammalian patient suspected of having a disease, condition, or disorder mediated, at least in part, by VLA-1, said method comprising obtaining a biological sample from said patient and assaying said sample for the presence of VLA-1.

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15. A method of inhibiting adhesion of mammalian cells to the extracellular matrix mediated, at least in part, by VLA-1, said method comprising contacting said cells with a compound of claim 1.

16. A method of treating a disease, disorder, or condition, whose progression is regulated, at least in part, by VLA-1 expression or activity in a mammalian patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of claim 1.

17. The method of claim 16 wherein said disease, disorder, or condition is selected from the group consisting of asthma, trachoma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, tumor migration, and/or tumor growth, proliferation of fibroblasts in cancer, solid tumors, meningitis, encephalitis, stroke, cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia, acute leukocyte-mediated lung injury, and fibrotic diseases.

18. The method of claim 17 wherein said disease, disorder, or condition is a fibrotic disease.

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19. The method of claim 18 wherein said fibrotic disease is selected from the group consisting of systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, and myositis.

20. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic vascular intimal hypertrophy, and is selected from the group consisting of vasculitis, polyarteritis nodosa, and temporal arteritis.

21. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic hypertrophy of skin and/or muscle tissue, and is selected from the group consisting of scleroderma, eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus, and surgical adhesions.

22. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic hypertrophy of nerve tissue, and is selected from the group consisting of cerebro sclerosis, annular sclerosis, diffuse sclerosis, and lobar sclerosis.

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23. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of lung tissue, and is selected from the group consisting of pulmonary fibrosis, idiopathic pulmonary fibrosis, the fibrotic element of pneumoconiosis, pulmonary sarcoidosis, fibrosing alveolitis, the fibrotic or hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, and emphysema.

24. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of prostate, liver, the pleura or pancreas, and is selected from the group consisting of benign prostatic hypertrophy (BPH), nonalcoholic steato hepatitis, and fibrosis of the liver.

25. The method according to claim 18 wherein said fibrotic disease has a manifestation of fibrotic hypertrophy or fibrosis of the kidney and is selected from the group consisting of chronic renal failure, lupus nephritis, alport syndrome, glomerulonephritis, and diabetic nephritis.

26. The method according to claim 16 wherein said disease, disorder, or condition is cancer.

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27. The method according to claim 26 wherein said cancer is a tumor or a neoplasm selected from the group consisting of carcinomas, adenocarcinomas, and sarcomas.

28. The method according to claim 26 wherein said cancer is selected from the group consisting of growth of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, human soft tissue carcinoma, cancer metastases, squamous cell carcinoma, esophageal squamous cell carcinoma, oral carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, non-small cell cancers, breast cancer, gastrointestinal cancers, urological cancers, malignancies of the female genital tract, malignancies of the male genital tract, kidney cancer, brain cancer, bone cancers, skin cancers, thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

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29. The method according to claim 26 wherein said cancer is a cell proliferative disorders, and is selected from the group consisting of angiogenesis-mediated diseases, benign tumors, acoustic neuromas, neurofibromas, pyogenic granulomas, biliary tract cancer, choriocarcinoma, esophageal cancer, gastric cancer, intraepithelial neoplasms, lung cancer, and neuroblastomas.

30. The method according to claim 26 wherein said administration is selected from the group consisting of orally, intravenously, parenterally, transdermally, topically, rectally, and intranasally.

31. The method according to claim 26 wherein said mammal is selected from the group consisting of humans, primates, pet or companion animals, laboratory animals, and farm animals.

32. The compound of claim 1 wherein the compound exhibits a biological activity of at least fifty percent inhibition when tested at a concentration of 50 μ M.

SEQUENCE LISTING

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Gly Ser Pro Leu Val Gly Gln Pro Lys Asn Arg Thr Gly Asp Val Tyr
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Lys Cys Pro Val Gly Arg Gly Glu Ser Leu Pro Cys Val Lys Leu Asp
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Leu Pro Val Asn Thr Ser Ile Pro Asn Val Thr Glu Val Lys Glu Asn
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Val Gly Ile Val Gln Tyr Gly Glu Asn Val Thr His Glu Phe Asn Leu
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Asn Lys Tyr Ser Ser Thr Glu Glu Val Leu Val Ala Ala Lys Lys Ile
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Ala Arg Lys Glu Ala Phe Thr Glu Ala Arg Gly Ala Arg Arg Gly Val
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Lys Lys Val Met Val Ile Val Thr Asp Gly Glu Ser His Asp Asn His
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Phe Ser Ile Ala Ile Leu Gly Ser Tyr Asn Arg Gly Asn Leu Ser Thr
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Lys Thr Leu Gly Glu Arg Ile Phe Ala Leu Glu Ala Thr Ala Asp Gln
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Thr Met Asn Phe Glu Pro Asn Lys Val Asn Ile Gln Lys Lys Asn Cys
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785 790 795 800

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Lys Tyr Glu Val Gly Leu Gln Phe Tyr Ser Ser Ala Ser Glu Tyr His
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Ile Ser Ile Ala Ala Asn Glu Thr Val Pro Glu Val Ile Asn Ser Thr
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Glu Asp Ile Gly Asn Glu Ile Asn Ile Phe Tyr Leu Ile Arg Lys Ser
980 985 990

Gly Ser Phe Pro Met Pro Glu Leu Lys Leu Ser Ile Ser Phe Pro Asn
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Thr Ile Thr Cys Asn Leu Thr Ser Ser Asp Ile Ser Gln Val Asn
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Val Ser Leu Ile Leu Trp Lys Pro Thr Phe Ile Lys Ser Tyr Phe
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 Ile Ser Gly Asn Leu Asp Ser Pro Glu Gly Gly Phe Asp Ala Ile Met
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 Gln Val Ala Val Cys Gly Ser Leu Ile Gly Trp Arg Asn Val Thr Arg
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