

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07036 A1

(51) International Patent Classification⁷: A61K 31/195,
31/4704, A61P 19/10, C07D 239/14, 215/22

(21) International Application Number: PCT/US00/19885

(22) International Filing Date: 20 July 2000 (20.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/358,035 21 July 1999 (21.07.1999) US

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(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,
DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZW.

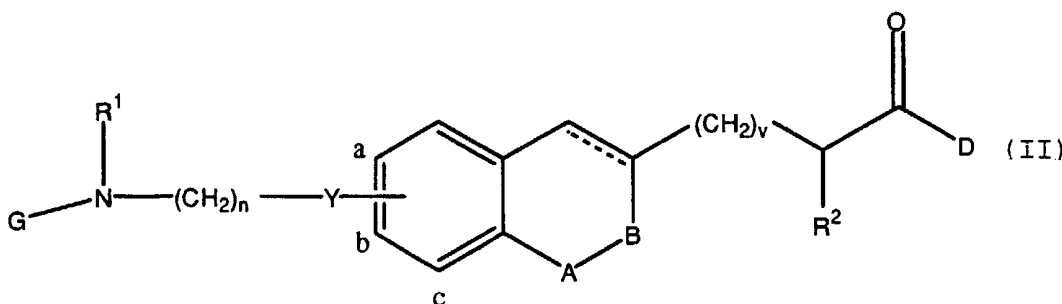
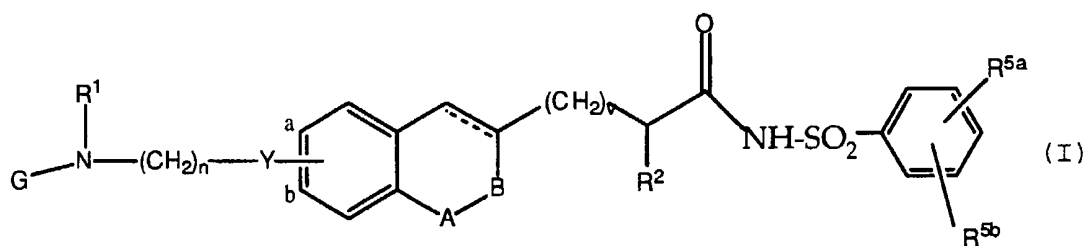
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC ANTAGONISTS SELECTIVE FOR THE $\alpha_3\beta_3$ INTEGRIN



(57) Abstract: This invention provides novel bicyclic compounds of Formula (I): wherein u, v, m, Y, G, A-B, R¹, R^{1a}, R², R⁴, R⁵, R^{5a}, and R^{5b} are defined in the specification which compounds exhibit activity as inhibitors of bone resorption and compounds of Formula (II) wherein u, v, m, Y, G, D, A-B, R¹, R^{1a}, R², R³, R⁴, R⁵, R^{5a}, and R^{5b} are defined in the specification which compounds exhibit activity as inhibitors of bone resorption.



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Title: BICYCLIC ANTAGONISTS SELECTIVE FOR THE $\alpha_v\beta_3$ INTEGRIN

FIELD OF THE INVENTION

This invention relates to a series of tetrahydro- and dihydroquinoline, tetrahydronaphthalene and tetrahydro-5H-
10 benzocycloheptene bicyclic compounds of Formulae (I) and (II) and non-toxic salts thereof, which selectively antagonize the $\alpha_v\beta_3$ integrin while minimally inhibiting platelet aggregation mediated by $\alpha_{IIb}\beta_3$ integrin and are useful as bone antiresorptive agents.

15

BACKGROUND OF THE INVENTION

The present invention relates to fused bicyclic derivatives which exhibit activity as bone antiresorptive agents by inhibition of the osteoclast vitronectin receptor ($\alpha_v\beta_3$). The integrin $\alpha_v\beta_3$ has been shown to mediate
20 the invasion of cancerous melanoma cells into healthy tissue (Seftor et al., Proc. Natl. Acad. Sci, USA, **1992**, 89, 1557-1561) and to protect these cells against natural cell death cycle (apoptosis) (Montgomery et al., Proc. Natl. Acad. Sci. USA, **1994**, 91, 8856-8860). Vitronectin
25 receptor ($\alpha_v\beta_3$) antagonists have been shown to inhibit the growth of various solid tumors of human origin (Brooks et al., Cell, **1994**, 79, 1157-1164). More recently, $\alpha_v\beta_3$ has been shown to be involved in liver metastasis (Yun et al., Cancer Res., **1996**, 56, 3103-3111). Although angiogenesis
30 is an important and natural process in growth and wound healing, it is now appreciated that a variety of clinically relevant conditions are pathologically related to these processes, and that the integrin $\alpha_v\beta_3$ is involved. For example, $\alpha_v\beta_3$ was shown to be expressed on human wound tissue
35 but not on normal skin (Brooks, et al., Science, **1994**, 264, 569-571) and is preferentially expressed on angiogenic blood vessels, such as those feeding a growing/invading tumor. It has also been shown that antagonists of $\alpha_v\beta_3$ promote tumor regression by inducing apoptosis of the tumor
40 cells (Brooks et al., Cell, **1994**, 79, 1157-1164). The process of neovascularization (new blood vessel growth,

5 angiogenesis), which is critical for tumor growth and
metastasis, is also an important event in ocular tissue,
leading to diabetic retinopathy, glaucoma and blindness
(Adamis et al., Am. J. Ophthalm., 118, 445-450(1994); Hammes
et al., Nature Med., **1996**, 2,529-533; Friedlander, et al.,
10 Natl. Acad. Sci. U.S.A., 1996, 93, 9764-9769) and in
joints, promoting rheumatoid arthritis (Peacock et al., J.
Exp. Med., **1992**, 175, 1135-1138).

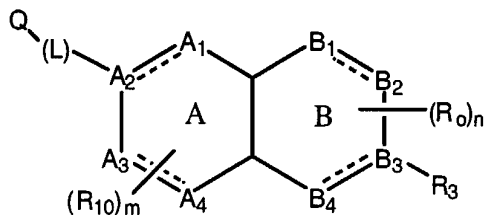
$\alpha_v\beta_3$ has been shown to play a pivotal role in the
proliferation and migration of smooth muscle and vascular
15 endothelial cells, a pathological process leading to
restenosis after balloon angioplasty (Choi et al., J. Vasc.
Surgery, **1994**, 19, 125-134; Matsuno et al., Circulation,
1994, 90, 2203-2206). At least one type of virus
(adenovirus) has been shown to utilize $\alpha_v\beta_3$ for entering host
20 cells (White et al., Current Biology, **1993**, 596-599).

Various bone diseases involve bone resorption, the
dissolution of bone matter, which is mediated by only one
known class of cells, the osteoclasts. When activated for
resorption, these motile cells initially bind to bone, a
25 process well known to be mediated by $\alpha_v\beta_3$ (Davies et al., J.
Cell. Biol., **1989** 109, 1817-1826; Helfrich et al., J Bone
Mineral Res., **1992**, 7, 335-343). It is also well known
that blockade of $\alpha_v\beta_3$ with antibodies or peptides containing
the sequence arginine-glycine-aspartic acid (RGD) blocks
30 osteoclast cell adhesion and bone resorption in vitro
(Horton et al., Exp. Cell Res. **1991**, 195, 368-375) and
that echistatin, an RGD containing protein, inhibits bone
resorption in vivo (Fisher et al., Endocrinology, **1993**,
132, 1411-1413). More recently, an RGD peptidomimetic has
35 likewise been shown to inhibit osteoclasts in vitro and, by
iv administration prevents osteoporosis in vivo (Engleman
et al., J. Clin. Invest., **1997**, 99, 2284-2292).

A series of bicyclic compounds having a nucleus
formed of two fused six-membered rings which include
40 isoquinoline, isoquinolone, tetrahydronaphthalene,

5 dihydronaphthalene or tetralone substituted with both basic and acidic functionality and which are useful in inhibition of platelet aggregation are disclosed in EP 0635492, WO96/22288, US5618843 and US5731324 and are described by Formula I

10



I

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and the result of glucocorticoid treatment.

All these conditions are characterized by bone loss, resulting from an imbalance between bone resorption (breakdown) and bone formation, which continues throughout life at the rate of about 14% per year on the average. However, the rate of bone turnover differs from site to site, for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition which leads to increased fracture risk.

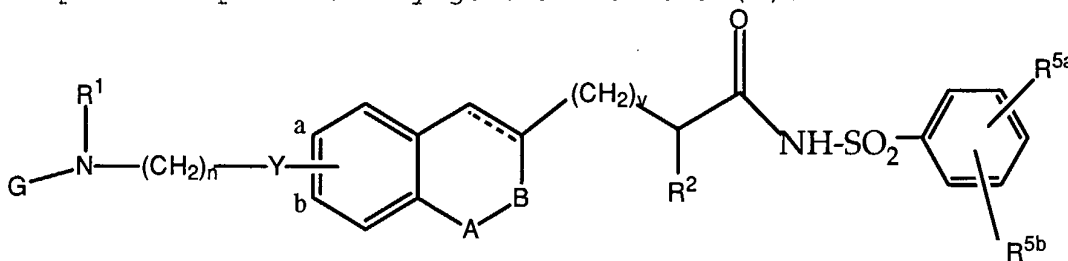
There are currently 20 million people with detectable fractures of the vertebrae due to osteoporosis in the United States. In addition, there are 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate

5 within the first two years, while 30% of the patients
require nursing home care after the fracture.

The minimal inhibition of platelet aggregation
mediated by $\alpha_{IIb}\beta_3$ integrin while selectively antagonizing
the $\alpha_v\beta_3$ integrin and thus being available as bone
10 antiresorptive agents is an important benefit of compounds
of the invention and is important in mammals, especially
man.

BRIEF SUMMARY OF THE INVENTION

Accordingly, the present invention discloses bicyclic
15 compounds represented by general Formula (I):



Formula (I)

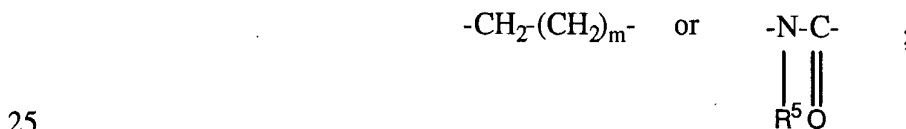
wherein:

----- represents the presence of an optional double
20 bond;

n is an integer of 2 to 5;

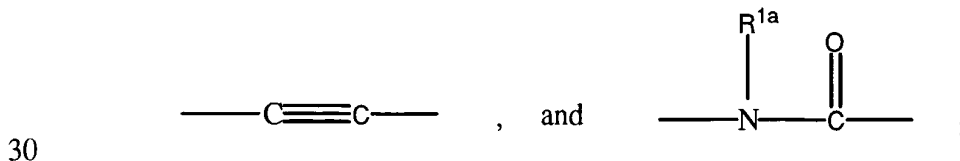
v is an integer of 0 or 1;

A-B is a diradical of the formulae:



m is an integer of 1 or 2;

Y is selected from the group consisting of -O-,
-CH₂-CH₂-, -CH=CH-,

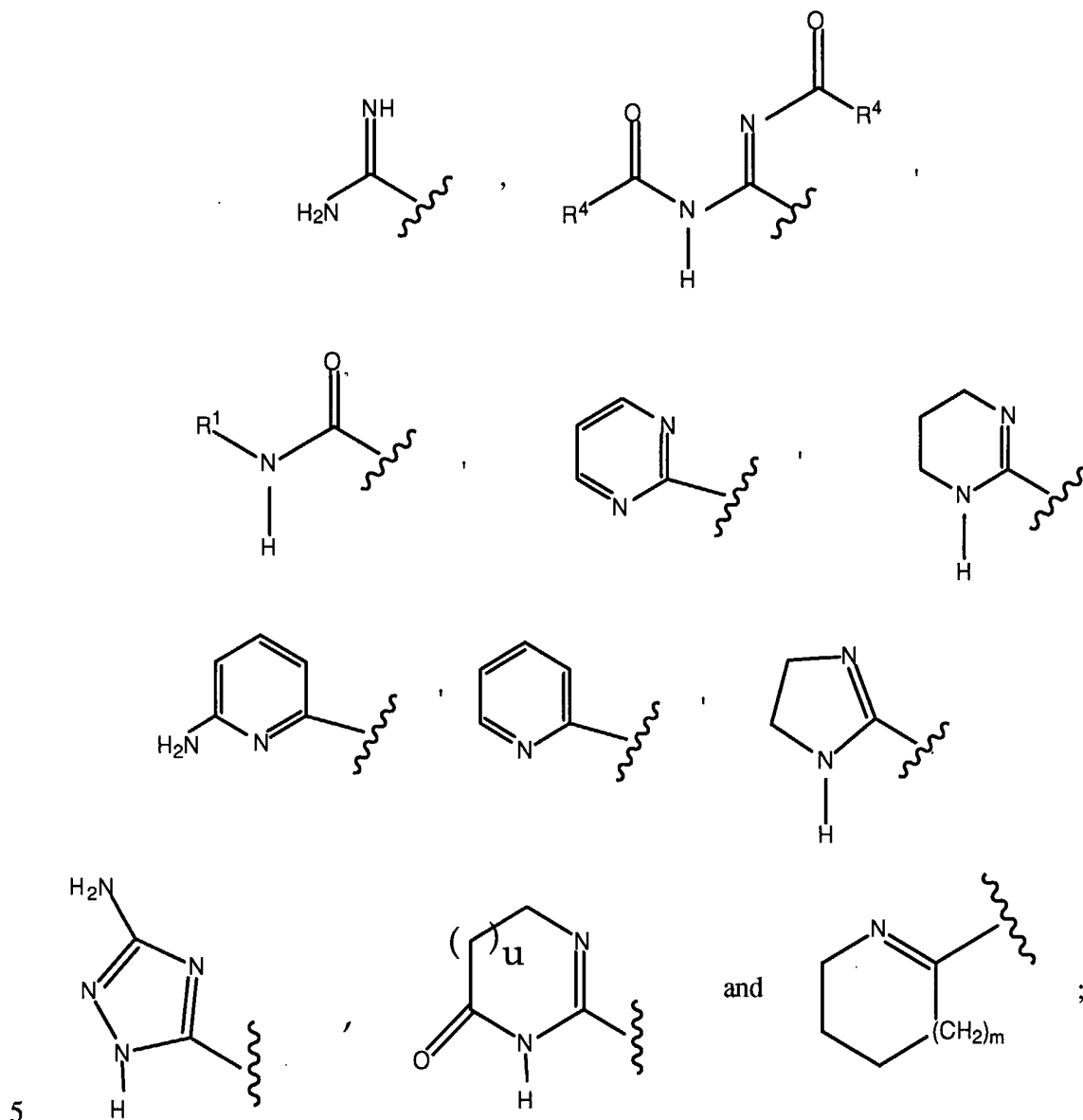


5 R¹ is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
10 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
heterocyclalkyl, wherein the alkyl moiety is a straight
15 chain alkyl of 1 to 6 carbon atoms and the heterocycl
moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
20 which may be the same or different, and are selected from
hydroxy, amino, halogen, straight chain alkyl of 1 to 6
carbon atoms, cyano and nitro;

 R^{1a} is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
25 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
30 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

 R² is hydrogen, -NHR¹, or -OR¹; aryl of 6 to 12 carbon
atoms optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
35 alkoxy of 1 to 6 carbon atoms, -S-alkyl of 1 to 6 carbon
atoms, cyano, nitro, halogen and phenyl; the heterocycl
moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and sulfur
40 optionally substituted with one or more substituents which

- 5 may be the same or different, and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with
- 10 one or more substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;
- 15 heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl moiety is selected from a 5- or 6-membered heterocyclic ring which contains 1 to 3 heteroatoms which may be the same or different, selected from nitrogen, oxygen and sulfur
- 20 optionally substituted with one or more substituents which may be the same or different, and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro;
- 25 G is a moiety selected from the group consisting of:



u is an integer of 0 or 1;

R⁴ is straight chain alkyl of 1 to 6 carbon atoms,
 10 branched chain alkyl of 3 to 7 carbon atoms, alkoxy, or
 phenylalkyloxy wherein the alkyl moiety is a straight chain
 alkyl of 1 to 6 carbon atoms and the phenyl moiety is
 optionally substituted with one or more substituents which
 may be the same or different and are selected from hydroxy,
 15 amino, halogen, straight chain alkyl of 1 to 6 carbon
 atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano,

5 nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino
of 1 to 6 carbon atoms;

R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
10 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
15 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
20 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
25 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
30 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
35 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

provided that the optional double bond ----- is a single
bond when A-B is the diradical-CH₂-(CH₂)_m-;
40 or a pharmaceutically acceptable salt thereof.

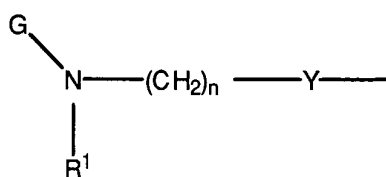
5 Among the preferred groups of compounds of Formula (I) of this invention including pharmaceutically acceptable salts thereof are those in the subgroups wherein:

10

a)

n is an integer of 2 to 4;

the moiety



15

is located at the a or b position of the bicyclic nucleus;

18 R^1 is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or two substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro;

22 heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted with one or two, substituents which may be the same or different, and are

26 selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro;

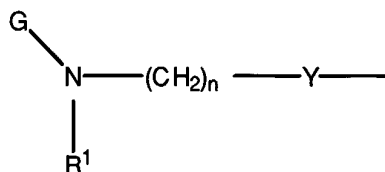
30 R^2 is hydrogen; aryl of 6 to 12 carbon atoms optionally substituted with one or more substituents selected from straight chain alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, nitro, and halogen; the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl; phenylalkyl wherein the

5 alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the
 10 alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl;

the optional double bond ----- is a single bond;
 15 where m, u, v, G, Y, A-B, R^{1a}, R⁴, R^{5a}, and R^{5b} are hereinbefore defined;

b)

20 n is an integer of 2 to 4;
 the moiety



is located at the a or b position of the bicyclic nucleus;
 25 A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is
 30 optionally substituted with one or two substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl
 35 moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted with one or two, substituents which may be the same or different, and are

5 selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro;

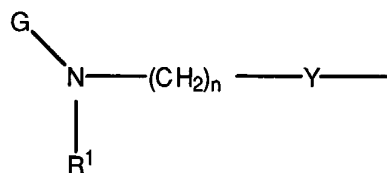
R^2 is hydrogen; aryl of 6 to 12 carbon atoms optionally substituted with one or more substituents
 10 selected from straight chain alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, $-NO_2$, and halogen; the heterocyclyl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 15 atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclylalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 20 atoms and the heterocyclyl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl;

the optional double bond ----- is a single bond;
 where m, u, v, G, Y, R^{1a} , R^4 , R^{5a} , and R^{5b} are hereinbefore
 25 defined;

c)

n is an integer of 2 to 4;

the moiety



30

is located at the a or b position of the bicyclic nucleus;
 R^1 is H;
 R^2 is H;
 35 R^5 is H;
 the optional double bond ----- is a single bond;
 where m, u, v, G, Y, A-B, R^{1a} , R^4 , R^{5a} , and R^{5b} are hereinbefore defined;

5

Among the more preferred groups of compounds of
Formula (I) of this invention including pharmaceutically
10 acceptable salts thereof are those in the subgroups
wherein:

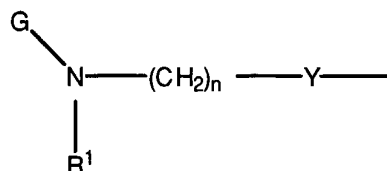
a)

n is an integer of 2 to 4;

15 m is an integer of 1;

v is an integer of 0;

the moiety



is located at the a or b position of the bicyclic nucleus;

20 Y is -O-;

R¹ is H;R² is H;R⁵ is H;

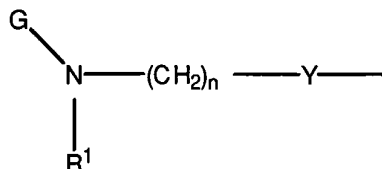
the optional double bond ----- is a single bond;

25 where u, G, A-B, R^{1a}, R⁴, R^{5a}, and R^{5b} are hereinbefore
defined;

b)

30 n is an integer of 2 to 4;

the moiety

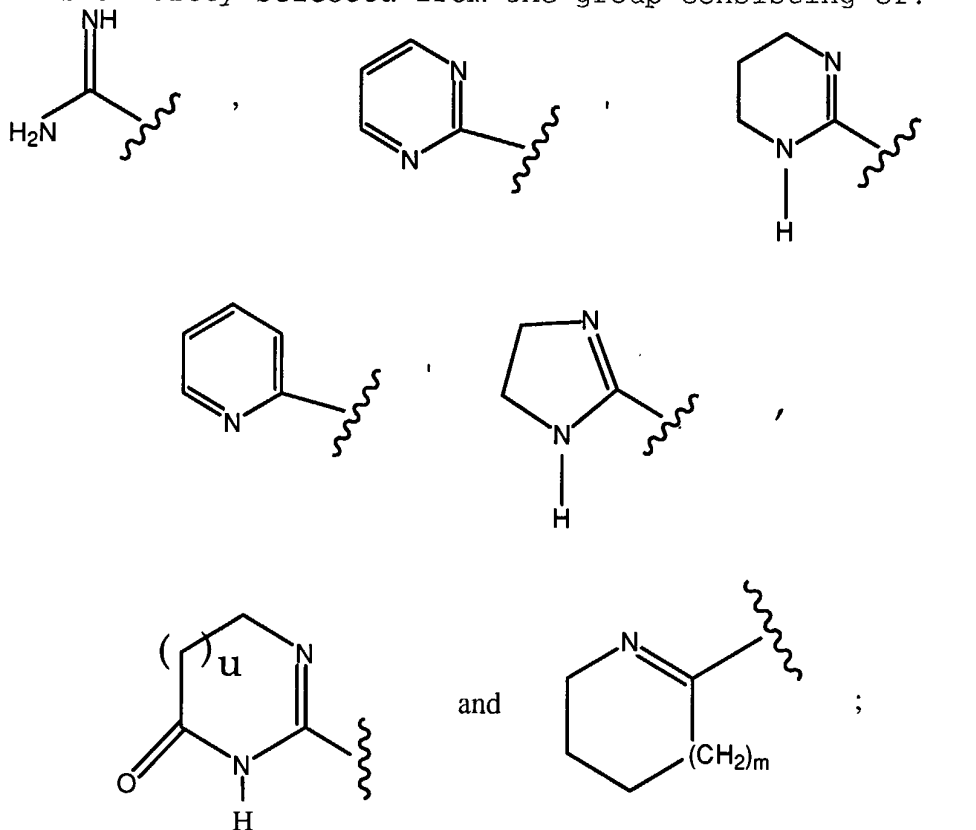


is located at the a or b position of the bicyclic nucleus;

R¹ is H;35 R² is H;

5 R⁵ is H;

G is a moiety selected from the group consisting of:

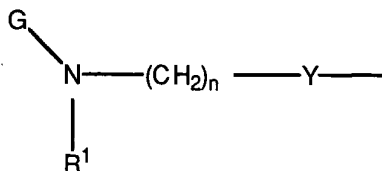


10 where -----, u, v, m, D, Y, R^{1a}, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

c)

n is an integer of 2 to 4;

15 the moiety



is located at the a or b-position of the bicyclic nucleus;

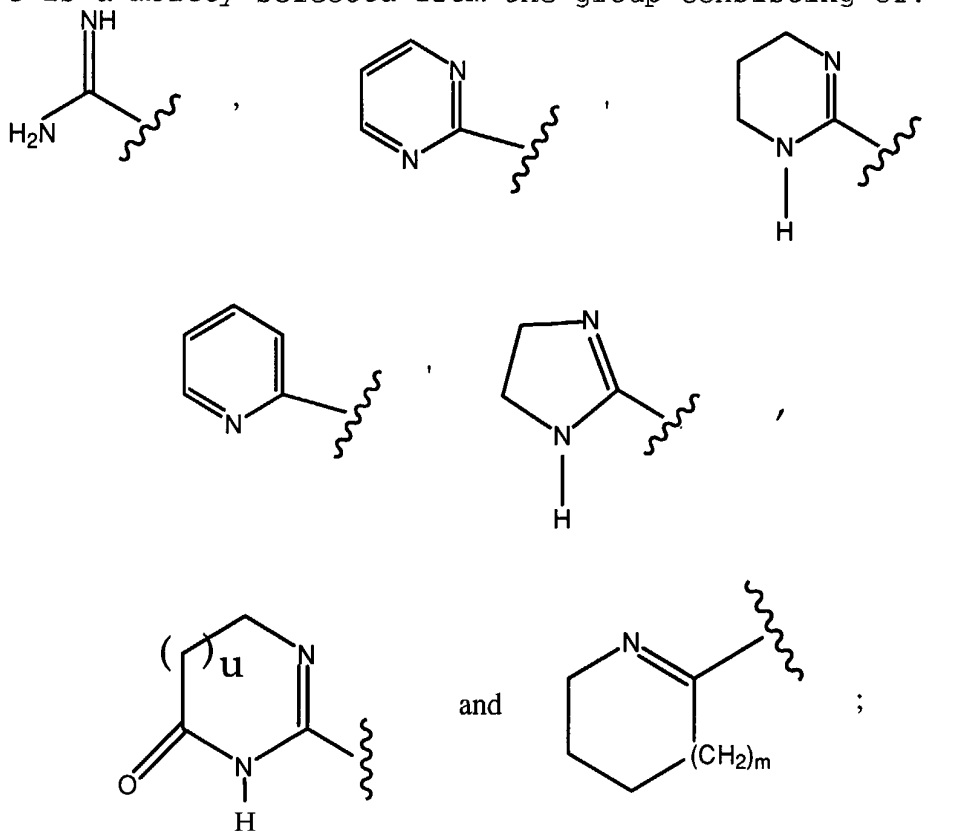
R¹ is H;

R² is H;

20 R⁵ is H;

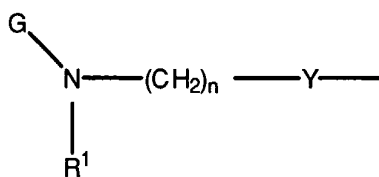
Y is -O-;

5 G is a moiety selected from the group consisting of:

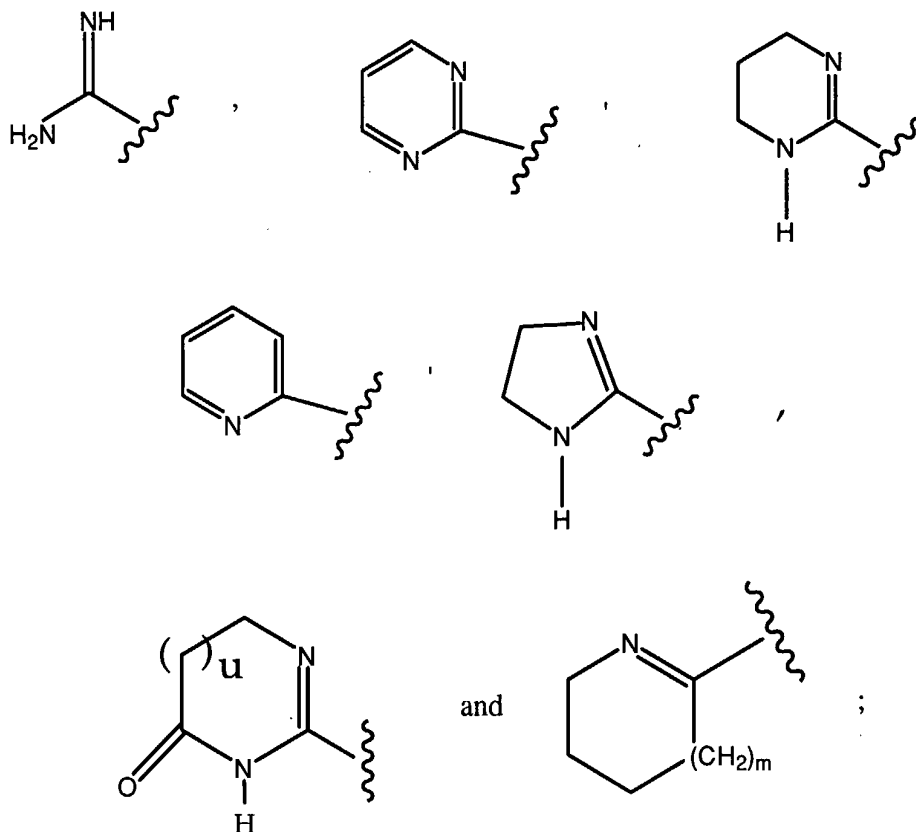


where -----, u, v, m, D, R^{1a}, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

10 d)
 n is an integer of 2 to 4;
 the moiety



is located at the b-position of the bicyclic nucleus;
 15 R¹ is H;
 R² is H;
 R⁵ is H;
 G is a moiety selected from the group consisting of:



5

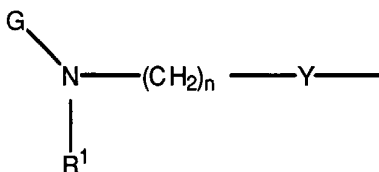
where -----, u, v, m, D, Y, R^{1a}, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

10

e)

n is an integer of 2 to 4;

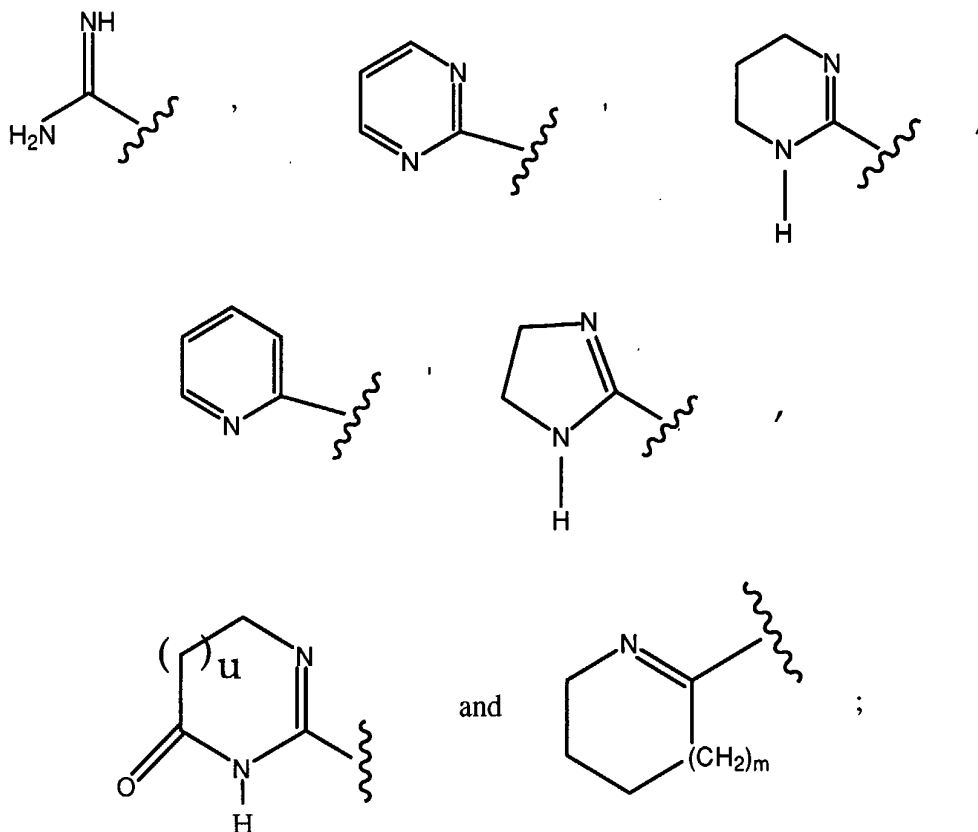
the moiety



is located at the b-position of the bicyclic nucleus;

15

G is a moiety selected from the group consisting of:



5

where ----, u, v, m, Y, R¹, R^{1a}, R², R⁴, R⁵, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

10

f)

n is an integer of 2 to 4;

R¹ is H;

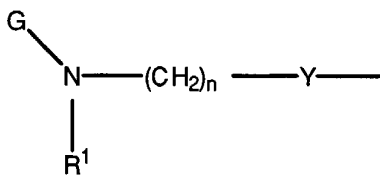
R² is H;

15

R⁵ is H;

A-B is the diradical -CH₂-(CH₂)_m-;

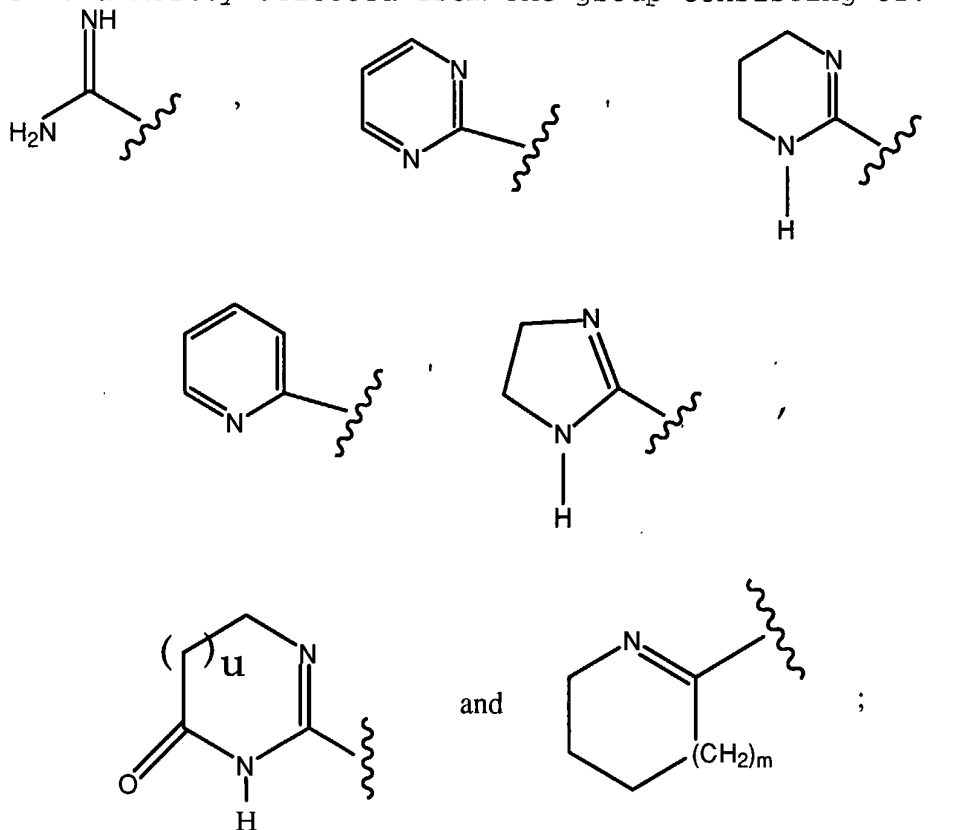
the moiety



20

is located at the a or b-position of the bicyclic nucleus;

5 G is a moiety selected from the group consisting of:



the optional double bond ----- is a single bond;
 where u, v, m, Y, R^{1a}, R⁴, R^{5a}, and R^{5b} are hereinbefore
 defined;

10

Among the specifically preferred compounds of Formula
 (I) of this invention including pharmaceutically acceptable
 15 salts thereof are those set forth below:

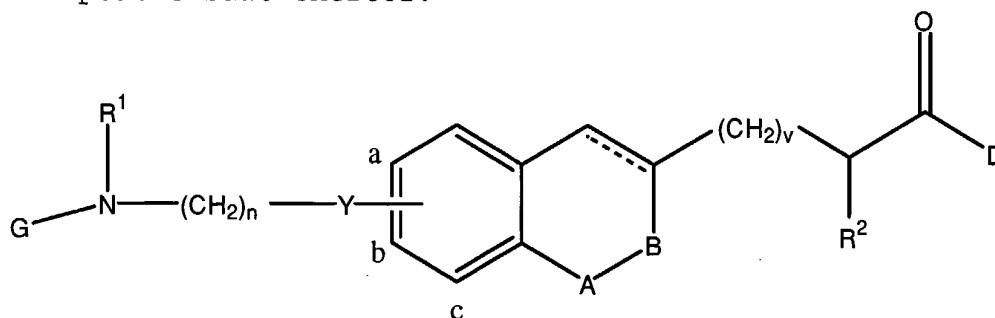
4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-
 propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-
 20 benzenesulfonamide, trifluoroacetic acid salt, and

4-Methyl-N-{{7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-
 tetrahydro-quinolin-3-yl}-acetyl}-benzenesulfonamide.

5

In particular, the present invention also provides a method of treatment of diseases characterized by bone resorption of mineralized tissue and by bone loss,
 10 resulting from an imbalance between bone resorption and bone formation such as osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-
 15 induced osteopenia and the result of glucocorticoid treatment in warm-blooded animals in need thereof, which comprises administering to said warm-blooded animals, preferably mammals, most preferably humans, an effective amount of a compound of Formulae (I) or (II) or a
 20 pharmaceutically acceptable salt thereof.

In addition the present invention also provides a method of blocking or inhibiting bone resorption by antagonizing the $\alpha_v\beta_3$ integrin receptor mediated binding of an osteoclast to a bone matrix which comprises
 25 administering to warm-blooded animals, preferably mammals, most preferably humans, an effective amount of a compound of general Formulae (I) or (II) or a pharmaceutically acceptable salt thereof.



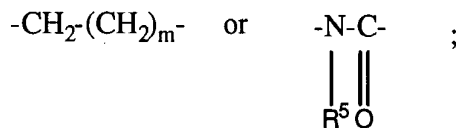
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Formula (II)

wherein:

----- represents the presence of an optional double bond;

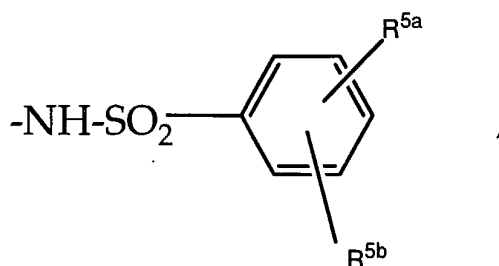
- 5 n is an integer of 2 to 5;
 v is an integer of 0 or 1;
 A-B is a diradical of the formulae:



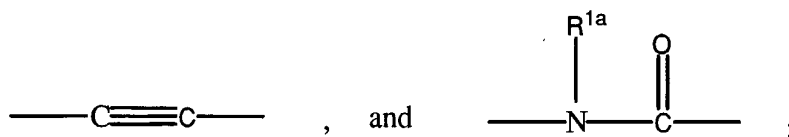
- 10 m is an integer of 1 or 2;
 D is a moiety selected from the group consisting of:



and



Y is selected from the group consisting of -O-,
 -CH₂-CH₂-, -CH=CH-,



- 15 R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more
- 20 substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;
- 25 heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl moiety is selected from a 5- or 6-membered heterocyclic

5 ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
which may be the same or different, and are selected from
hydroxy, amino, halogen, straight chain alkyl of 1 to 6
10 carbon atoms, cyano and nitro;

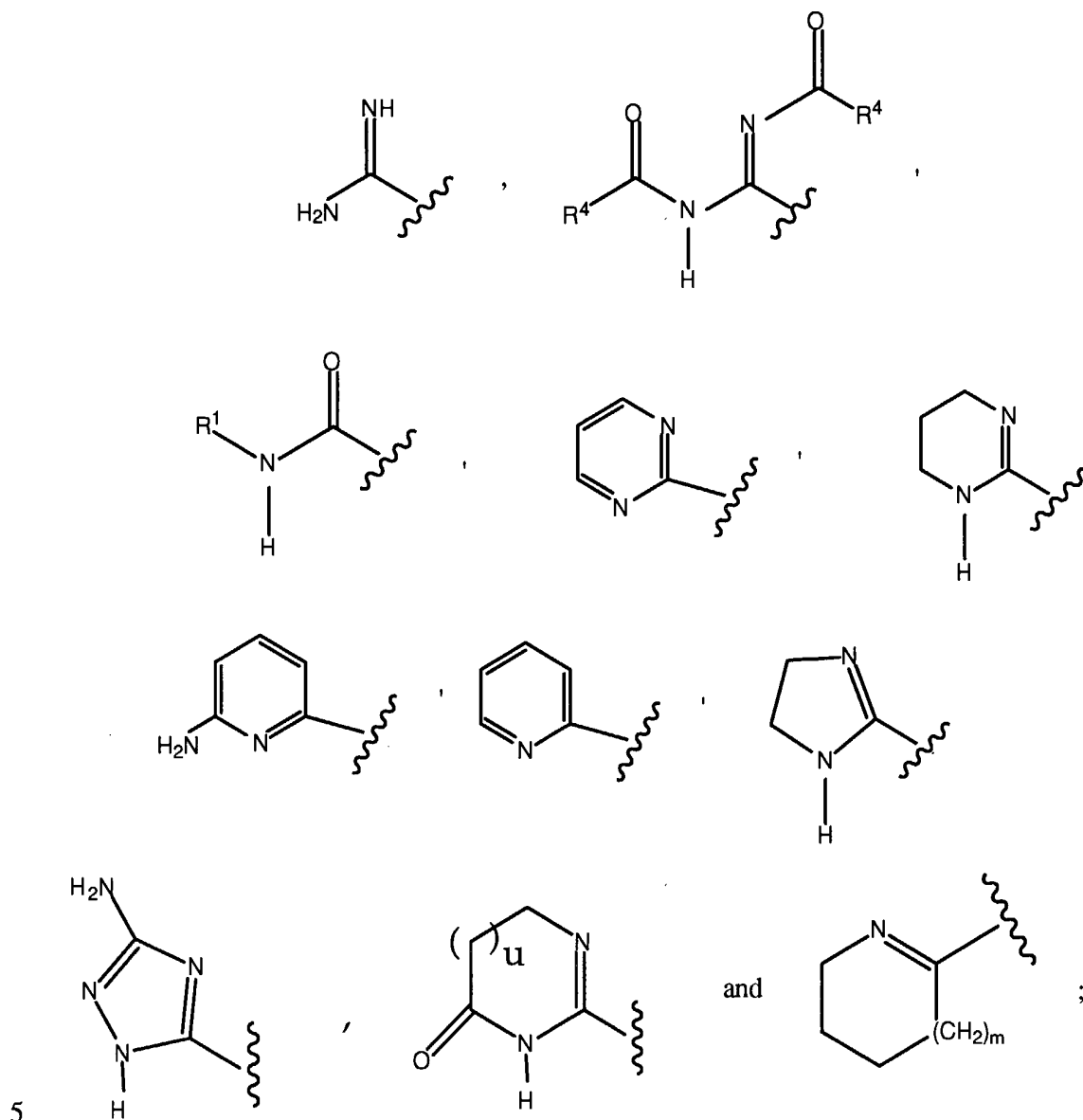
R^{1a} is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
15 substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

20 R^2 is hydrogen, $-NHR^1$, or $-OR^1$; aryl of 6 to 12 carbon
atoms optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
alkoxy of 1 to 6 carbon atoms, $-S$ -alkyl of 1 to 6 carbon
atoms, cyano, nitro, halogen and phenyl; the heterocyclyl
25 moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and sulfur
optionally substituted with one or more substituents which
may be the same or different, and are selected from
30 hydroxy, amino, halogen, straight chain alkyl of 1 to 6
carbon atoms, cyano and nitro; phenylalkyl wherein the
alkyl moiety is a straight chain alkyl of 1 to 6 carbon
atoms and the phenyl moiety is optionally substituted with
one or more substituents which may be the same or different
35 and are selected from hydroxy, amino, halogen, straight
chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of
3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6
carbon atoms, and dialkylamino of 1 to 6 carbon atoms;
heterocyclylalkyl, wherein the alkyl moiety is a straight
40 chain alkyl of 1 to 6 carbon atoms and the heterocyclyl
moiety is selected from a 5- or 6-membered heterocyclic

5 ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and sulfur
optionally substituted with one or more substituents which
may be the same or different, and are selected from
hydroxy, amino, halogen, straight chain alkyl of 1 to 6
10 carbon atoms, cyano and nitro;

R³ is H, straight chain alkyl of 1 to 6 carbon atoms
optionally substituted with a group selected from amino,
15 hydroxyl and carboxyl or branched chain alkyl of 3 to 7
carbon atoms optionally substituted with a group selected
from amino, hydroxyl and carboxyl;

G is a moiety selected from the group consisting of:



u is an integer of 0 or 1;

R^4 is straight chain alkyl of 1 to 6 carbon atoms,
 10 branched chain alkyl of 3 to 7 carbon atoms, alkoxy, or
 phenylalkyloxy wherein the alkyl moiety is a straight chain
 alkyl of 1 to 6 carbon atoms and the phenyl moiety is
 optionally substituted with one or more substituents which
 may be the same or different and are selected from hydroxy,
 15 amino, halogen, straight chain alkyl of 1 to 6 carbon
 atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano,

5 nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino
of 1 to 6 carbon atoms;

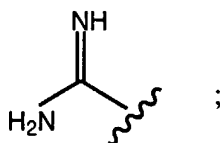
R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
10 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
15 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
20 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
25 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

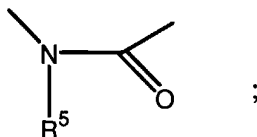
R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
30 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
35 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

with the proviso that Y is not O; n is not 3 or 4; R¹, R²,
R³ and R⁵ are not H; D is not -OR³; G is not

5



A-B is not

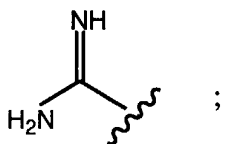


---- is not a single bond;

a) when v is 0 and substitution is at position a;

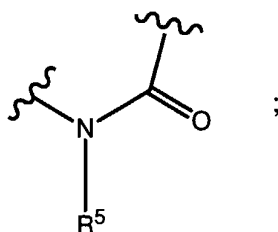
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with the additional proviso that n is not 2,3 or 4; G is not



15

---- is not a single bond; v is not 1; A-B is not

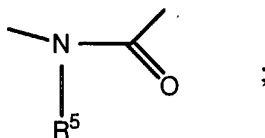


D is not -OR³;

a) when Y is -O-; R¹, R², R³ and R⁵ are H; and substitution is at position a;

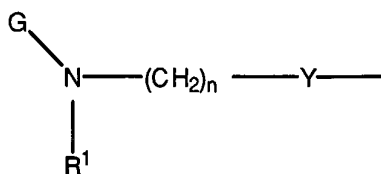
20

with the still further proviso that when A-B is the moiety



25

the moiety



5

is located at the a,b or c positions of the bicyclic nucleus;

and with the additional proviso that the optional double
 10 bond ----- is a single bond when A-B is the diradical-CH₂-
 (CH₂)_m-;
 or a pharmaceutically acceptable salt thereof.

For the compounds defined for Formulae (I) or (II) above
 15 and referred to herein, unless otherwise noted, the
 following terms are defined:

The term halogen may be selected from fluorine, chlorine,
 bromine and iodine, unless otherwise specified.

20

Phenyl as used herein refers to a 6-membered aromatic ring.

The term alkoxy means an alkyl group having a straight
 chain alkyl group attached through an oxygen bridge and
 25 including for example methoxy, ethoxy, n-propoxy, n-butoxy,
 and the like.

The term aryl when used alone means a homocyclic aromatic
 radical, whether or not fused, having 6 to 10 carbon atoms.
 30 Preferred aryl groups include phenyl, alpha-naphthyl and
 beta-naphthyl and the like optionally substituted.

The term heterocyclyl means an optionally substituted
 monocyclic heteroaromatic ring. Preferred are 2- or 3-
 furyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl.

35

- 5 The range of carbon atoms defines the total number of carbon atoms in the substituent group.

The compounds of Formulae (I) or (II) of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following: salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. The compounds can also be used in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety in vivo.

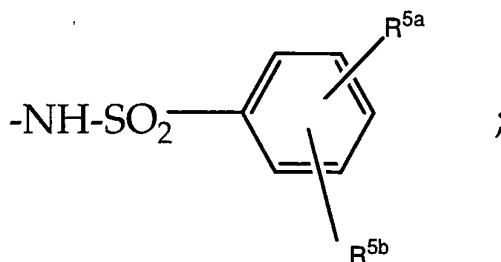
Among the preferred groups of compounds of Formula (II) of this invention including pharmaceutically acceptable salts thereof are those in the subgroups wherein:

a)

D is the moiety



and



30

R^3 is H;

5 where ----, n, m, u, v, G, Y, R¹, R^{1a}, R², R⁴, R^{5a}, and R^{5b}
are hereinbefore defined;

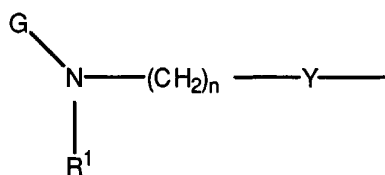
b)

10

n is an integer of 2 to 4;

v is an integer of 0;

the moiety



15

is located at the a or b position of the bicyclic nucleus;

R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon
atoms; phenylalkyl wherein the alkyl moiety is a straight
20 chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is
optionally substituted with one or two substituents which
may be the same or different and are selected from halogen,
straight chain alkyl of 1 to 6 carbon atoms, and nitro;
heterocyclalkyl, wherein the alkyl moiety is a straight
25 chain alkyl of 1 to 6 carbon atoms and the heterocycl
moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and
2-, 3- or 4-pyridyl optionally substituted with one or two,
substituents which may be the same or different, and are
selected from halogen, straight chain alkyl of 1 to 6
30 carbon atoms, and nitro;

R² is hydrogen; aryl of 6 to 12 carbon atoms
optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
35 alkoxy of 1 to 6 carbon atoms, nitro, and halogen; the
heterocycl moiety is selected from 2- or 3-furyl, 2- or
3-thienyl, and 2-, 3- or 4-pyridyl; phenylalkyl wherein the
alkyl moiety is a straight chain alkyl of 1 to 6 carbon

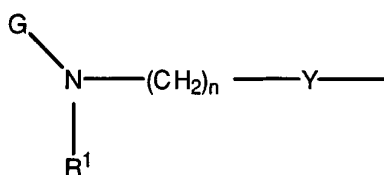
5 atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the
 10 atoms and the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl;

the optional double bond ----- is a single bond;
 where m, u, G, Y, D, A-B, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are
 15 hereinbefore defined;

c)

20 n is an integer of 2 to 4;
 v is an integer of 0;

the moiety



is located at the a or b position of the bicyclic nucleus;
 25 A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is
 30 optionally substituted with one or two substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl
 35 moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted with one or two, substituents which may be the same or different, and are

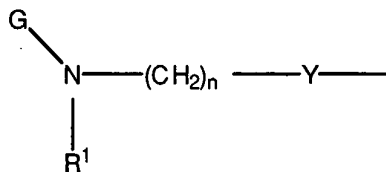
5 selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro;

R^2 is hydrogen; aryl of 6 to 12 carbon atoms optionally substituted with one or more substituents
 10 selected from straight chain alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, $-NO_2$, and halogen; the heterocyclyl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 15 atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclylalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 20 atoms and the heterocyclyl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl;

the optional double bond ----- is a single bond;
 where m, u, G, Y, D, R^{1a} , R^3 , R^4 , R^{5a} , and R^{5b} are
 25 hereinbefore defined;

d)
 n is an integer of 2 to 4;
 v is an integer of 0;

30 the moiety



is located at the a or b position of the bicyclic nucleus;
 R^1 is H;
 35 R^2 is H;
 R^5 is H;
 the optional double bond ----- is a single bond;

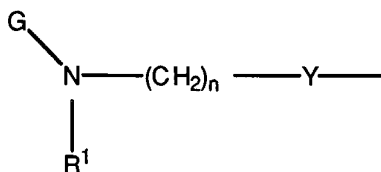
5 where m, u, G, Y, A-B, D, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are hereinbefore defined;

e)

n is an integer of 2 to 4;

10 v is an integer of 0;

the moiety



is located at the a or b position of the bicyclic nucleus;

R¹ is H;

15 R² is H;

A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

Y is $-\text{O}-$;

the optional double bond $-----$ is a single bond;

where m, u, D, G, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are

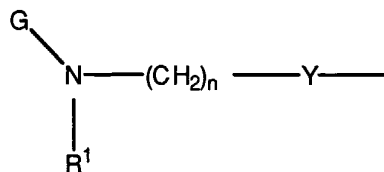
20 hereinbefore defined;

f)

n is an integer of 2 to 4;

v is an integer of 0;

25 the moiety



is located at the a or b position of the bicyclic nucleus;

R¹ is H;

R² is H;

30 R⁵ is H;

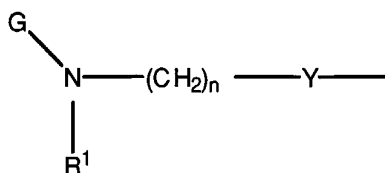
Y is $-\text{O}-$;

where $-----$, u, G, D, A-B, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are hereinbefore defined;

5 Among the more preferred groups of compounds of Formula (II) of this invention including pharmaceutically acceptable salts thereof are those in the subgroups wherein:

- 10 a)
 n is an integer of 2 to 4;
 m is an integer of 1;
 v is an integer of 0;

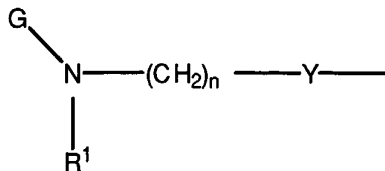
the moiety



- 15 is located at the a or b position of the bicyclic nucleus;
 Y is -O-;
 R¹ is H;
 R² is H;
 20 R⁵ is H;
 the optional double bond ----- is a single bond;
 where u, G, D, A-B, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are hereinbefore defined;

- 25 b)
 n is an integer of 2 to 4;
 m is an integer of 2;
 v is an integer of 0;

the moiety



- 30 is located at the a or b position of the bicyclic nucleus;
 Y is -O-;
 R¹ is H;
 R² is H;
 35 R⁵ is H;

5 the optional double bond ----- is a single bond;
 where u, G, D, A-B, R^{1a}, R³, R⁴, R^{5a}, and R^{5b} are
 hereinbefore defined;

10 Among the particularly preferred groups of compounds
 of Formula (II) of this invention including
 pharmaceutically acceptable salts thereof are those in the
 subgroups
 wherein:

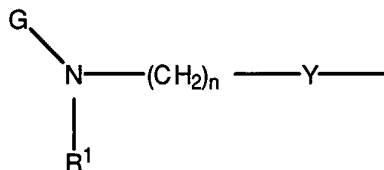
15

a)

n is an integer of 2 to 4;

v is an integer of 0;

20 the moiety



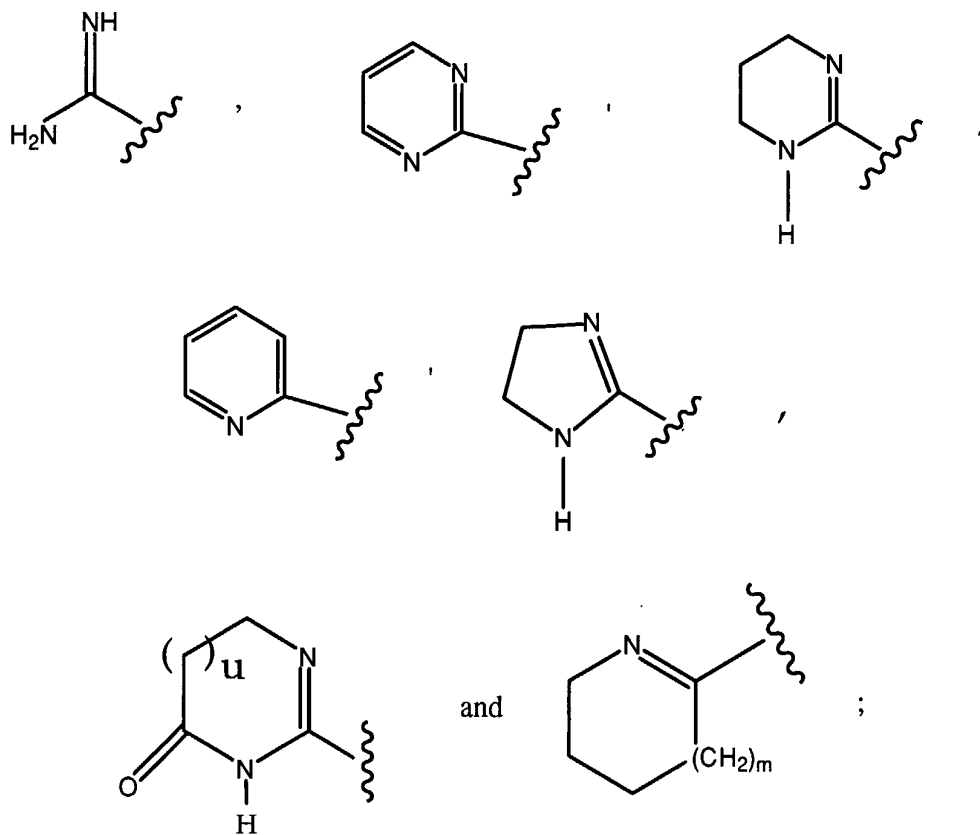
is located at the a or b position of the bicyclic nucleus;

R¹ is H;

R² is H;

25 R⁵ is H;

G is a moiety selected from the group consisting of:



5

where -----, u, m, D, Y, R^{1a}, R³, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

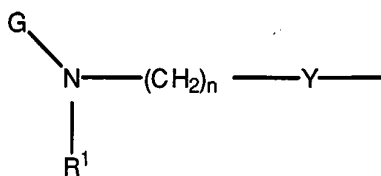
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b)

n is an integer of 2 to 4;

v is an integer of 0;

the moiety



15

is located at the a or b-position of the bicyclic nucleus;

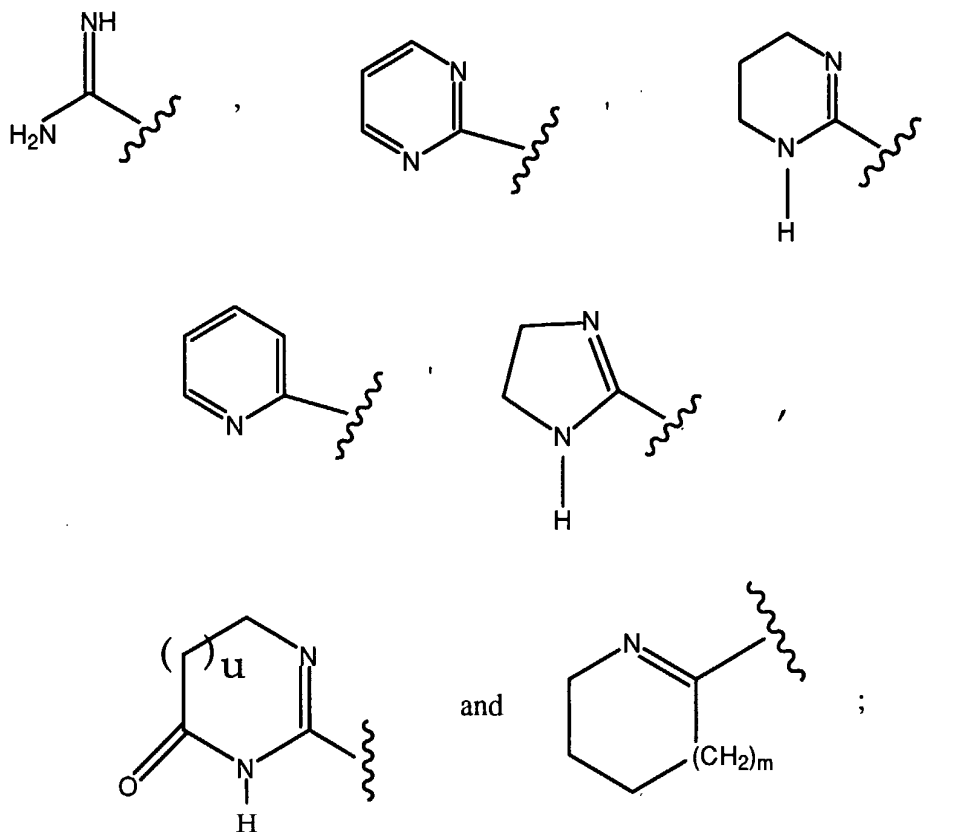
R¹ is H;

R² is H;

R⁵ is H;

20 Y is -O-;

G is a moiety selected from the group consisting of:



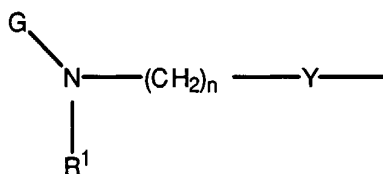
where -----, u, m, D, R^{1a}, R³, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

c)

10 n is an integer of 2 to 4;

v is an integer of 0;

the moiety



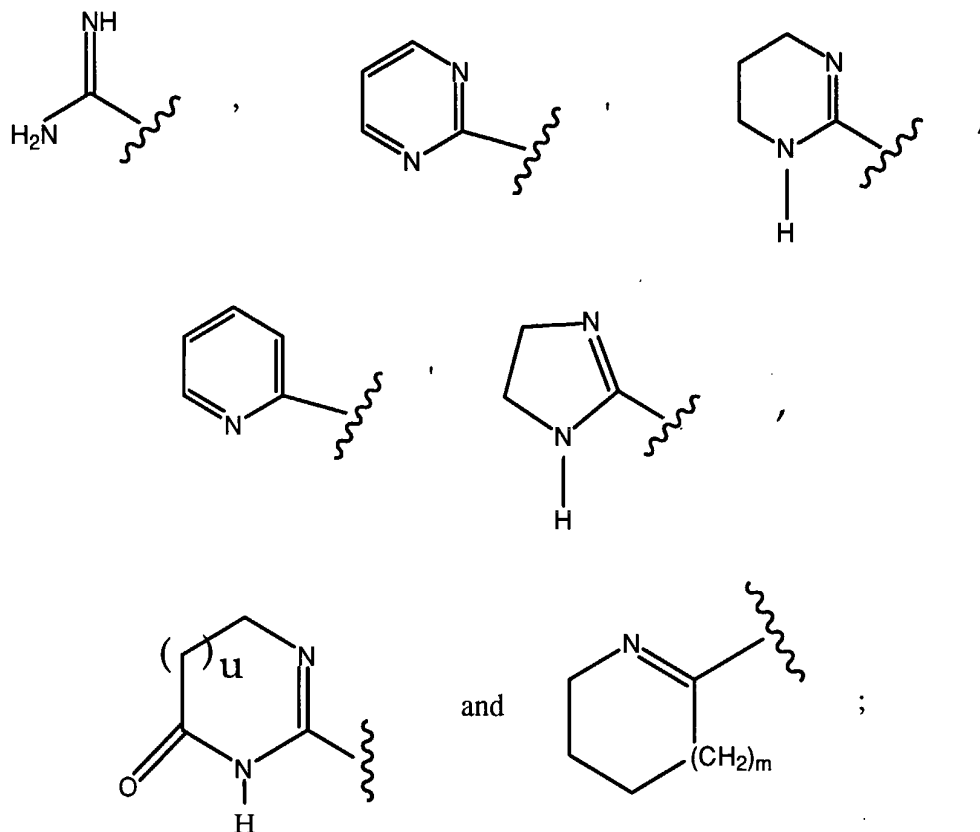
is located at the b-position of the bicyclic nucleus;

15 R¹ is H;

R² is H;

R⁵ is H;

G is a moiety selected from the group consisting of:



5

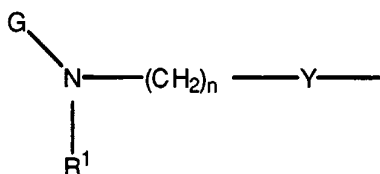
where -----, u, m, D, Y, R^{1a}, R³, R⁴, A-B, R^{5a}, and R^{5b} are hereinbefore defined;

10

d)

n is an integer of 2 to 4;

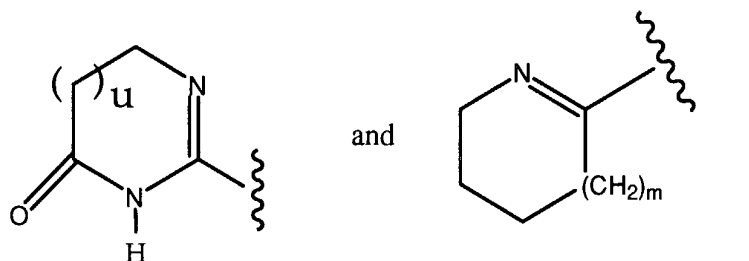
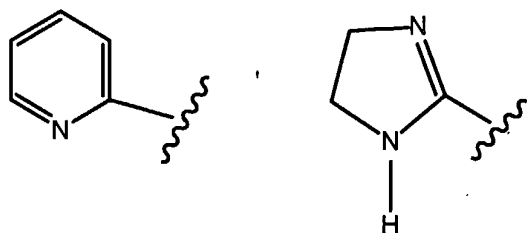
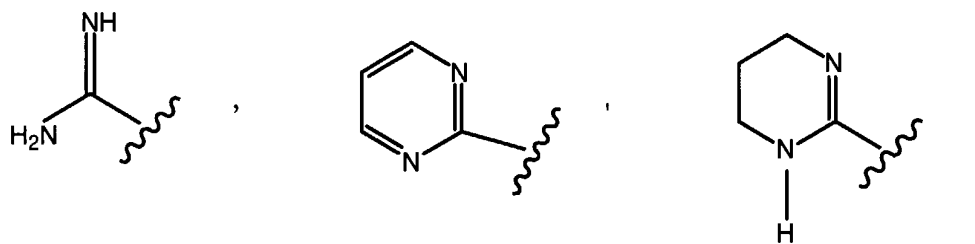
the moiety



is located at the a or b-position of the bicyclic nucleus;

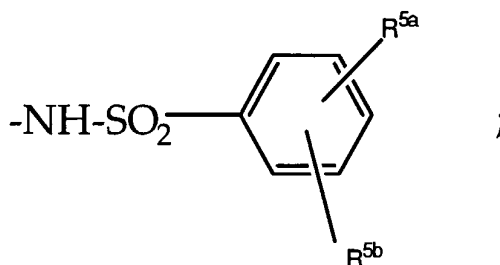
15

G is a moiety selected from the group consisting of:



5

D is a moiety



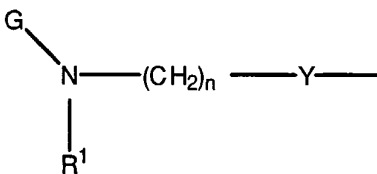
where -----, u, v, m, Y, R^1 , R^{1a} , R^2 , R^4 , R^5 , A-B, R^{5a} , and R^{5b} are hereinbefore defined;

10

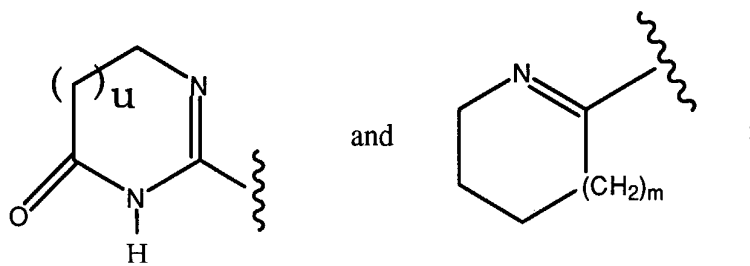
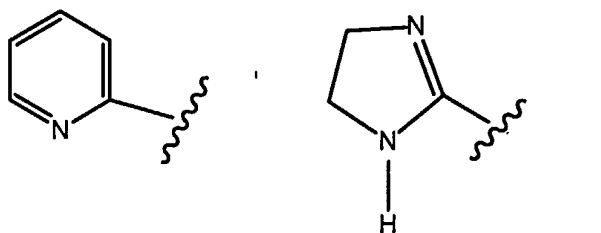
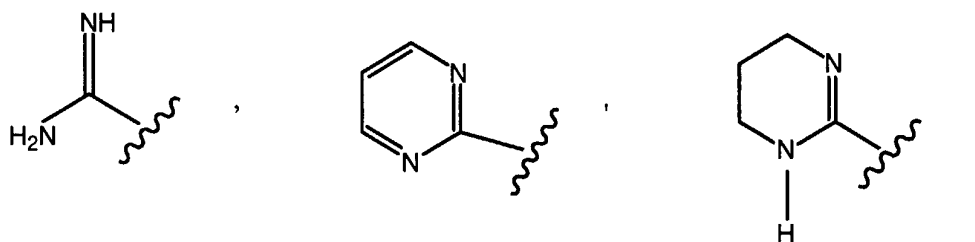
e)

n is an integer of 2 to 4;

the moiety

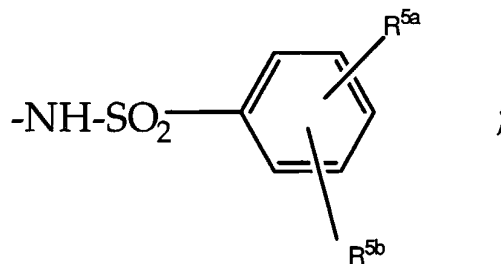


15 is located at the b-position of the bicyclic nucleus;
G is a moiety selected from the group consisting of:



5

D is a moiety



10 where -----, u , v , m , Y , R^1 , R^{1a} , R^2 , R^4 , R^5 , A-B, R^{5a} , and R^{5b} are hereinbefore defined;

f)

n is an integer of 2 to 4;

15

R^1 is H;

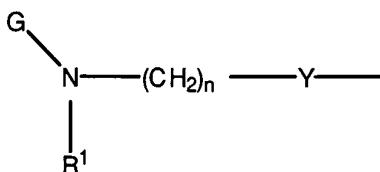
R^2 is H;

R^5 is H;

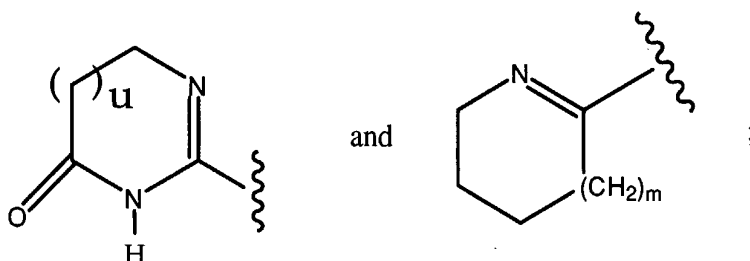
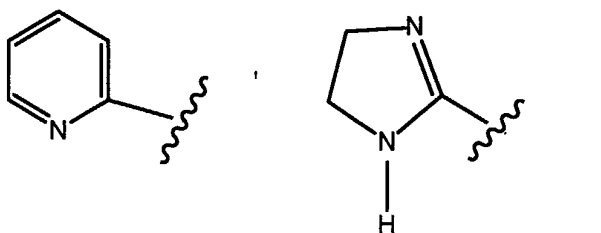
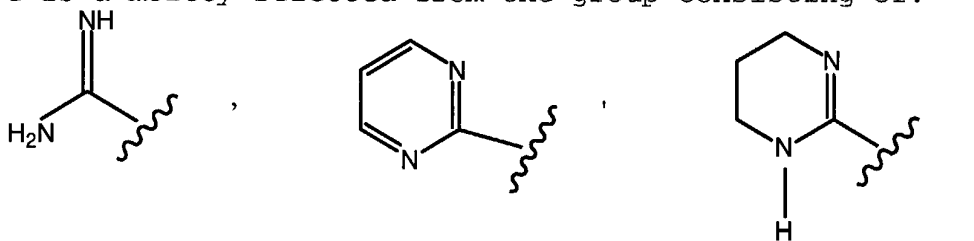
A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

5

the moiety

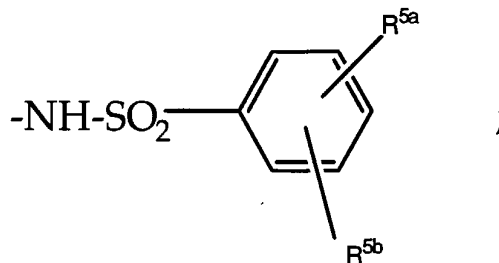


is located at the a or b-position of the bicyclic nucleus;
G is a moiety selected from the group consisting of:



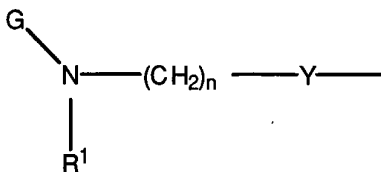
10

D is a moiety

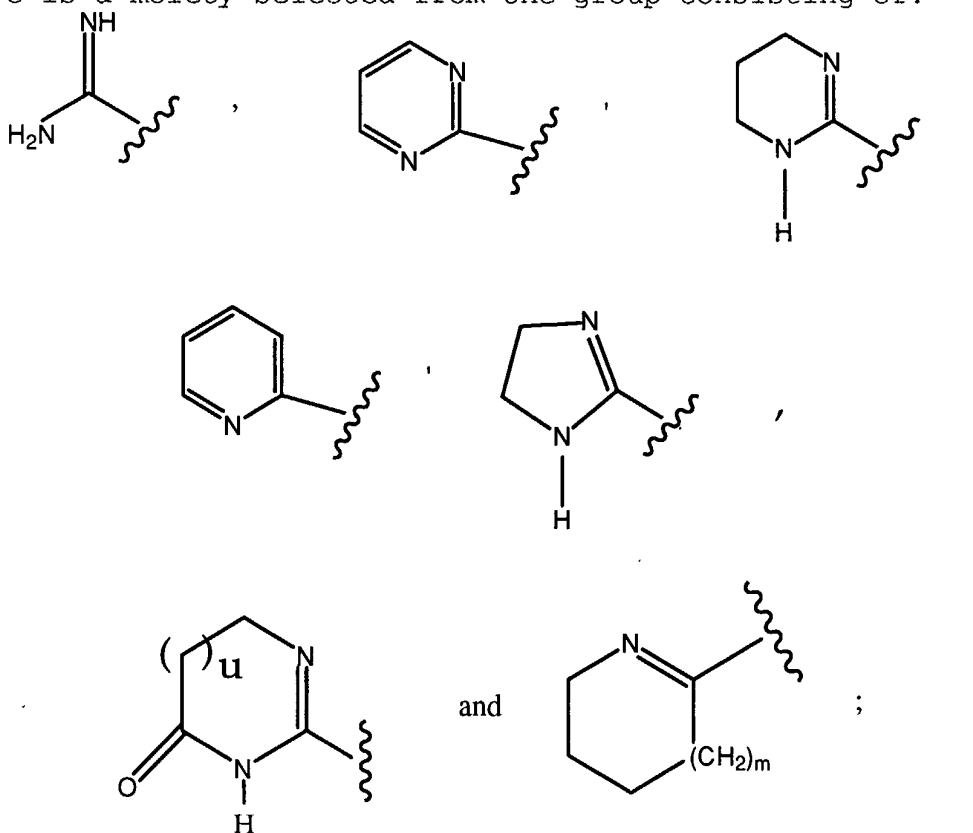


the optional double bond ----- is a single bond;
where u, v, m, Y, R^{1a}, R⁴, R^{5a}, and R^{5b} are hereinbefore
15 defined;

- 5 g)
 n is an integer of 2 to 4;
 the moiety



- is located at the a or b-position of the bicyclic nucleus;
 10 G is a moiety selected from the group consisting of:



D is a moiety $-\text{OR}^3$;
 R^3 is H;

- 15 where -----, u, v, m, Y, R^1 , R^{1a} , R^2 , R^4 , R^5 , A-B, R^{5a} , and R^{5b} are hereinbefore defined;

- Among the specifically preferred compounds of Formula
 20 (II) of this invention including pharmaceutically acceptable salts thereof are those set forth below:

5

[6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester,

10

[6-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid trifluoroacetate,

[7-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid trifluoroacetate,

15

[2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid hydrochloride,

20

[2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,

[2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,

25

[7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid trifluoroacetate,

[6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid trifluoroacetate,

30

[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,

35

[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,

[7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,

40

[7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

5

[7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

10

[7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

[7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

15

[7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

20

[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate

[1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid

25

[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

[1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,

30

[7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Hydrochloride,

35

[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid,

[7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

40

[7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,

- 5 [7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-
10 naphthalen-2-yl}-acetic acid methyl ester,
- {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-
naphthalen-2-yl}-acetic acid,
- 15 {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
20 1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester bis(hydrochloride),
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
25 1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid ethyl ester, acetic acid salt,
- 4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-benzenesulfonamide, trifluoroacetic acid salt,
30
- [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,
- 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
35 quinolin-3-yl]-propionic acid,
- 3-[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid,
- 40 [8-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,

5

[8-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,

10

[1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate,

3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid nitric acid salt,

15

4-Methyl-N-{{7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetyl}-benzenesulfonamide and

[8-(5-Guanidino-pentoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid.

20

Some of the compounds of the hereinafter described schemes have centers of asymmetry. The compounds may, therefore, exist in at least two and often more stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with other stereoisomers in any proportion and thus includes, for instance, racemic mixture of enantiomers as well as the diastereomeric mixture of isomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

35

The present invention accordingly provides a pharmaceutical composition which comprises a compound of Formulae (I) or (II) of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

40

5 DETAILED DESCRIPTION OF THE INVENTION

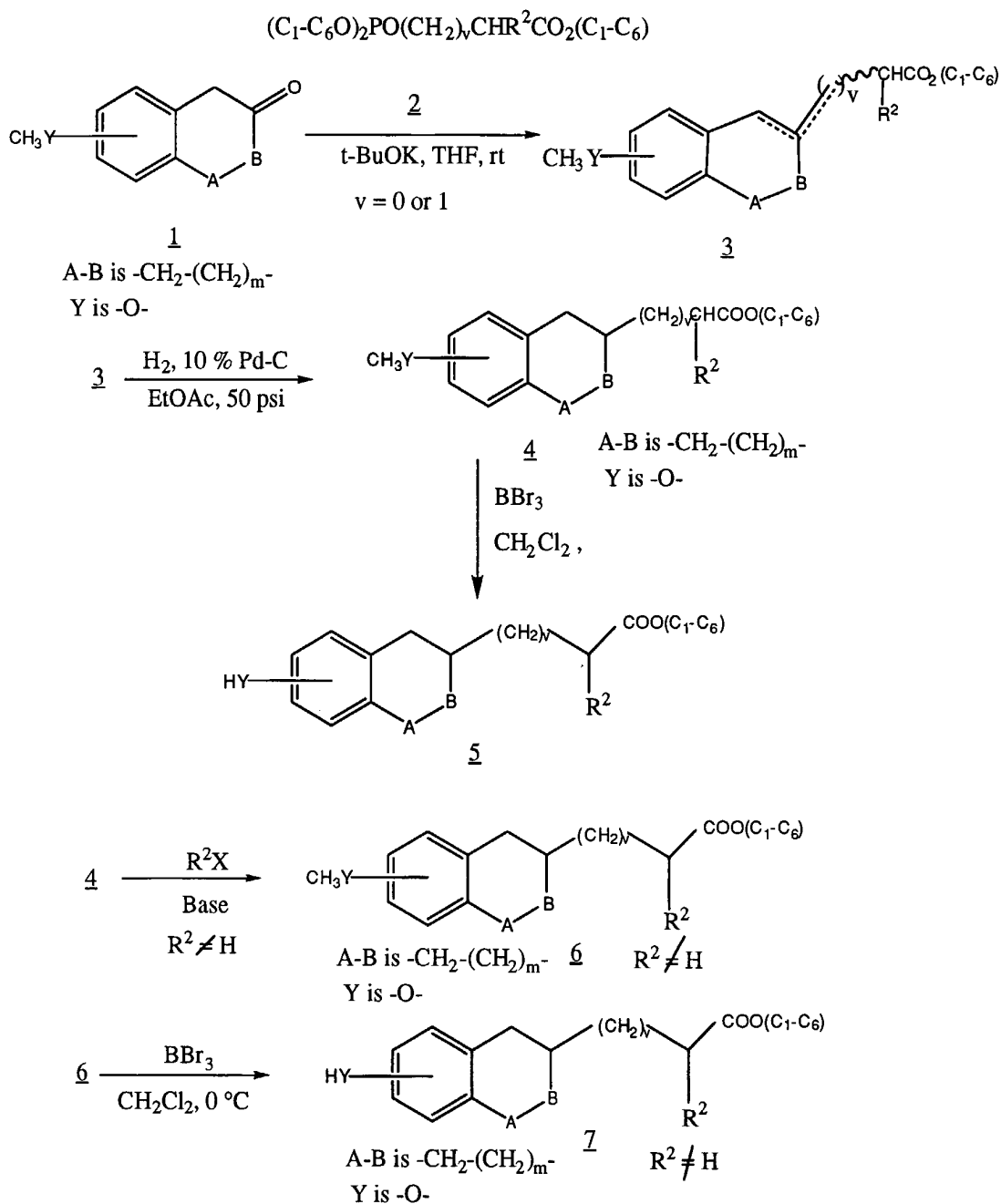
The compounds of the present invention may be prepared according to the following reaction schemes.

In Scheme I, bicyclic ketone 1 where Y is -O-, A-B is the diradical -CH₂-(CH₂)_m-, and m is 1 or 2 is
10 reacted with tri(C₁-C₆)alkyl phosphonoacetate 2 where v and R² are hereinbefore defined in the presence of potassium tert-butoxide to give olefin 3. Tri(C₁-C₆)alkyl phosphonoacetate 2 may be prepared using the conditions as described in U.S. Patent Nos. 5,312,828 and 5,473,092.

15 Bicyclic ketone 1 where m is 1 can be prepared from dimethoxynaphthalene as described by S. Coppinga et al., J. Med. Chem., 36, 2891-2898 (1993) or as described by A. Cordi et al, J.Med.Chem., 38, 4056-4069(1995) and where m is 1 or 2 as described in G. Pandey et al., Tetrahedron
20 Lett. 1993, 34, 6631-6634. Catalytic hydrogenation of olefin 3 in the presence of palladium-on-carbon affords ester 4. Treating ester 4 with boron tribromide in methylene chloride at 0°C gives phenol 5 where Y is -O-, A-B is the diradical -CH₂-(CH₂)_m, and v, m and R² are
25 hereinbefore defined. Alkylation of ester 4 where v is 0 or 1 with R²X where R² is hereinbefore defined provided R² is not H, in the presence of a base such as sodium methoxide and where X is a leaving group which includes but is not limited to -Cl, -Br, -I and methanesulfonyl gives ester 6.

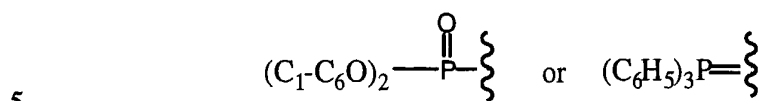
30 Treating ester 6 with boron tribromide in methylene chloride at 0°C gives phenol 7 where Y is -O-, R² is hereinbefore defined excluding hydrogen, A-B is the diradical -CH₂-(CH₂)_m-, and v and m are hereinbefore defined.

SCHEME I

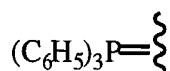


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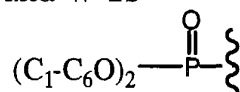
As described in Scheme II; nitrobenzaldehyde 8 where R is straight chain alkyl of 1 to 6 carbon atoms is reacted with diester 9, in acetic acid where v and R² are hereinbefore defined and W is a moiety



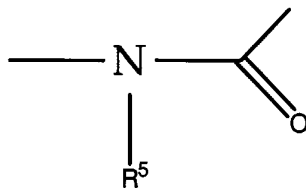
to give the corresponding diester 10 where R, R² and v are hereinbefore defined. Diester 9 where v is an integer of 0, R² is H and W is



10 can be prepared in situ from a distraight chain lower alkyl of 1 to 6 carbon atoms maleate and triphenyl phosphine in acetic acid, according to the modified method of Kadin, S.B. and Lamphere, C.H., J. Org. Chem., 49, 4999 (1984), and in the case where v is an integer of 1 from ethyl α -
15 bromo-glutanate (E. Schwenk and D. Papa, J. Am. Chem. Soc., 70 3626-3627 (1948)). Diester 9 where v and R² are hereinbefore defined and W is

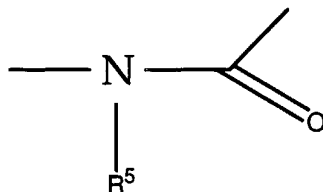


may be prepared using the conditions as described in P.G. Baraldi et al, J.Chem.Soc., Perkin Trans. I, 2501-
20 2505(1984) and GB1423495. Reduction of the nitro and olefinic groups of diester 10 by catalytic hydrogenation (10% Pd/C) followed by spontaneous cyclization gives tetrahydroquinolinone 11 where R, R² and v are hereinbefore
25 defined and the moiety A-B is the diradical



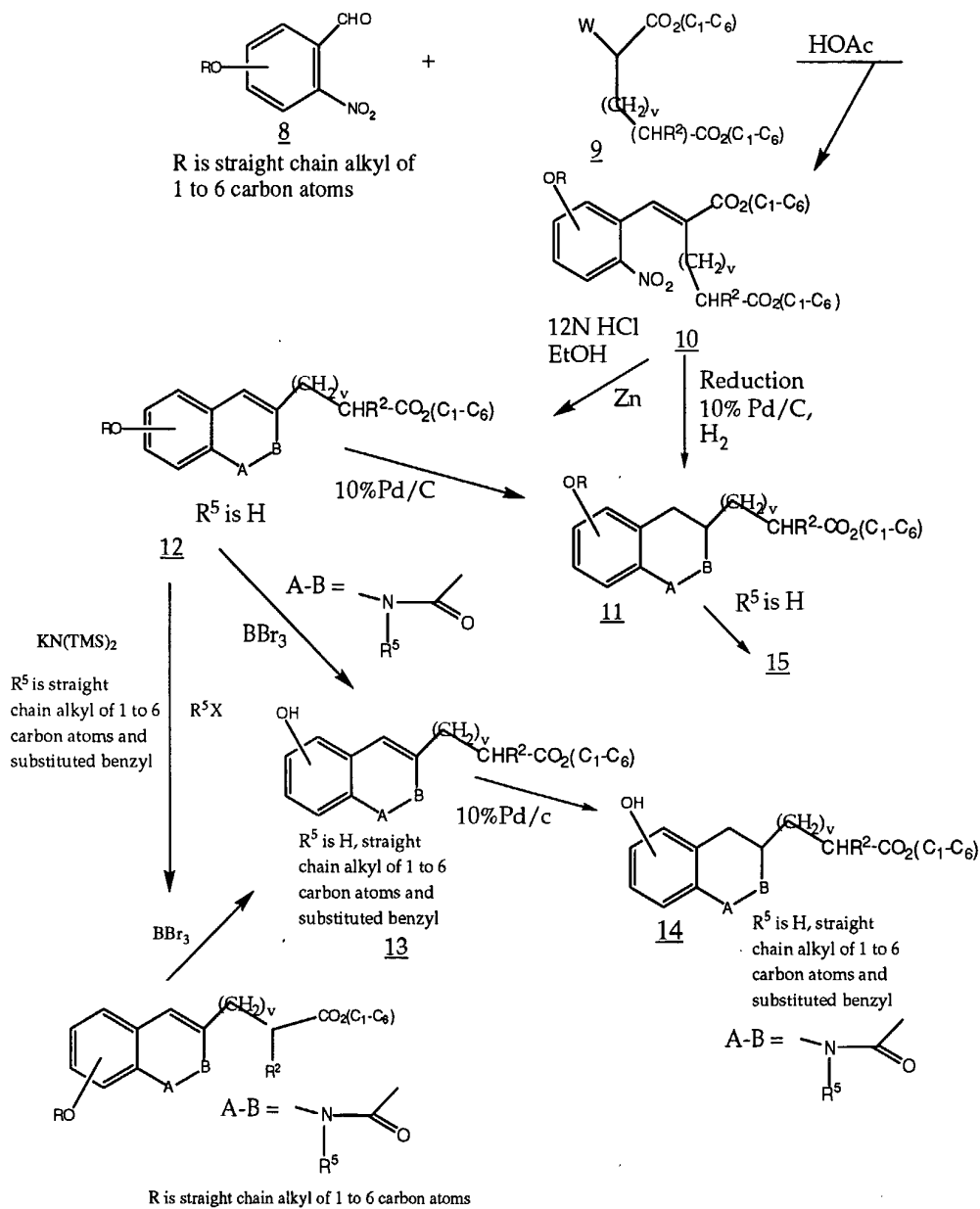
where R⁵ is H. Reduction of the nitro group of diester 10 using zinc in 12N HCl-ethyl alcohol followed by spontaneous cyclization gives substituted (1,2-dihydro-3-yl)alkanoate
30 ester 12 where R, R² and v are hereinbefore defined and R⁵ is H. Alternatively, as also shown in Scheme II, substituted (1,2-dihydro-3-yl)alkanoate ester 12 where R is hereinbefore defined may be converted to phenol 13 by reaction with borontribromide followed by catalytic

- 5 reduction in the presence of palladium-on-carbon to give phenol 14 where R^2 and v are hereinbefore defined and the moiety A-B is the diradical

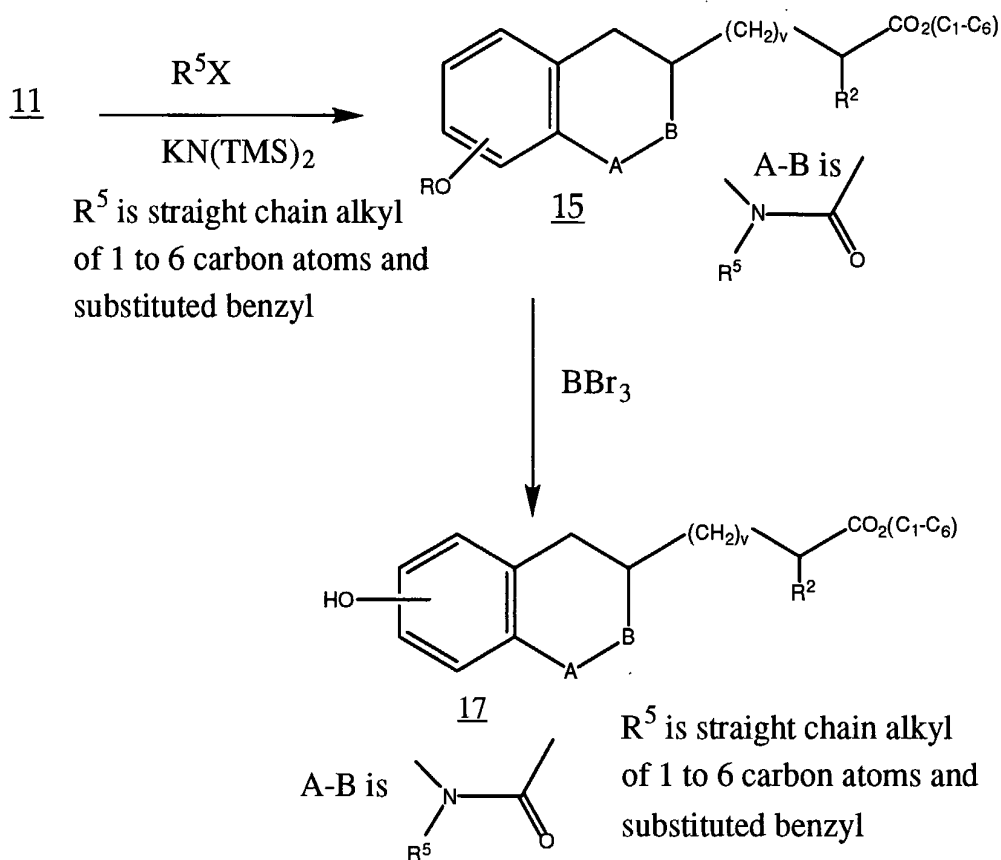


- where R^5 is H. Catalytic reduction of substituted (1,2-dihydro-3-yl) alkanate ester 12 where R , R^2 and v are hereinbefore defined and R^5 is H in the presence of palladium-on-carbon affords substituted tetrahydroquinolinone 11 where R , R^2 and v are hereinbefore defined and R^5 is H.
- 15 Again, referring to Scheme II, (1,2-dihydro-3-yl)alkanoate ester 12 where R^5 is H is alkylated with $R^5 X$ where R^5 is hereinbefore defined excluding hydrogen and X is a leaving group which includes but is not limited to -Cl, -Br, -I and methanesulfonyl in the presence of
- 20 potassium bis(trimethylsilyl)amide ($KN(TMS)_2$) to give ester 16. Treating ester 16 with boron tribromide can afford phenol 13.

SCHEME II



SCHEME II (CONT'D)



Again referring to Scheme II, tetrahydroquinolinone 11

where R and R² are hereinbefore defined and R⁵ is H is

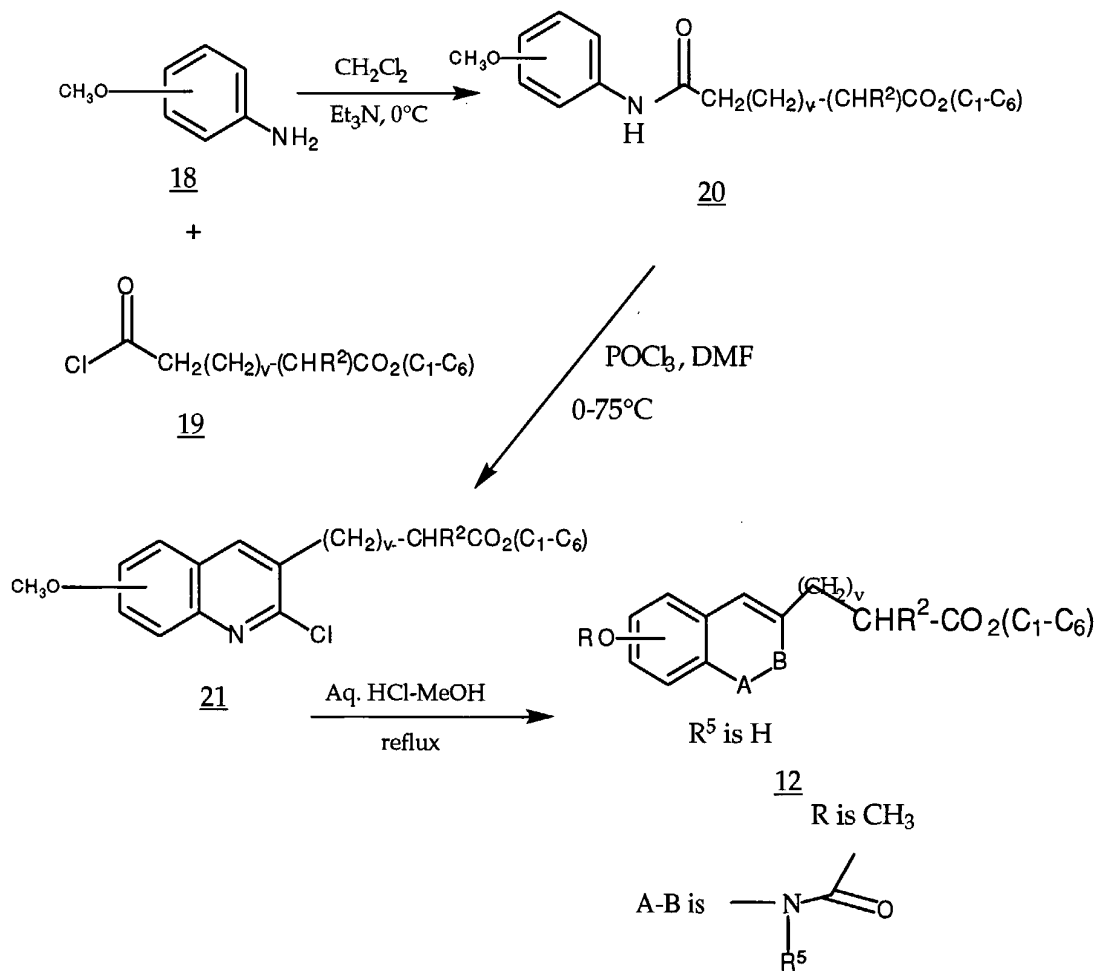
10 alkylated with R⁵X where R⁵ is hereinbefore defined but is not limited to -Cl, -Br, -I and methanesulfonyl in the presence of potassium bis(trimethylsilyl)amide (KN(TMS)₂) to give ester 15. Treating ester 15 with boron tribromide can afford phenol 17.

15 Additionally, a method of preparing substituted (1,2-dihydro-3-yl)alkanoate ester 12 is shown in Scheme III using the method as described by O. Meth-Cohn et al, J. Chem. Soc. Perkin I, 1537-1543 (1981). Methoxy substituted aniline 18 is reacted with acid chloride 19 where v and R² are hereinbefore defined to give amide 20. Acid chloride 19 is prepared from the corresponding half acid-ester by

20

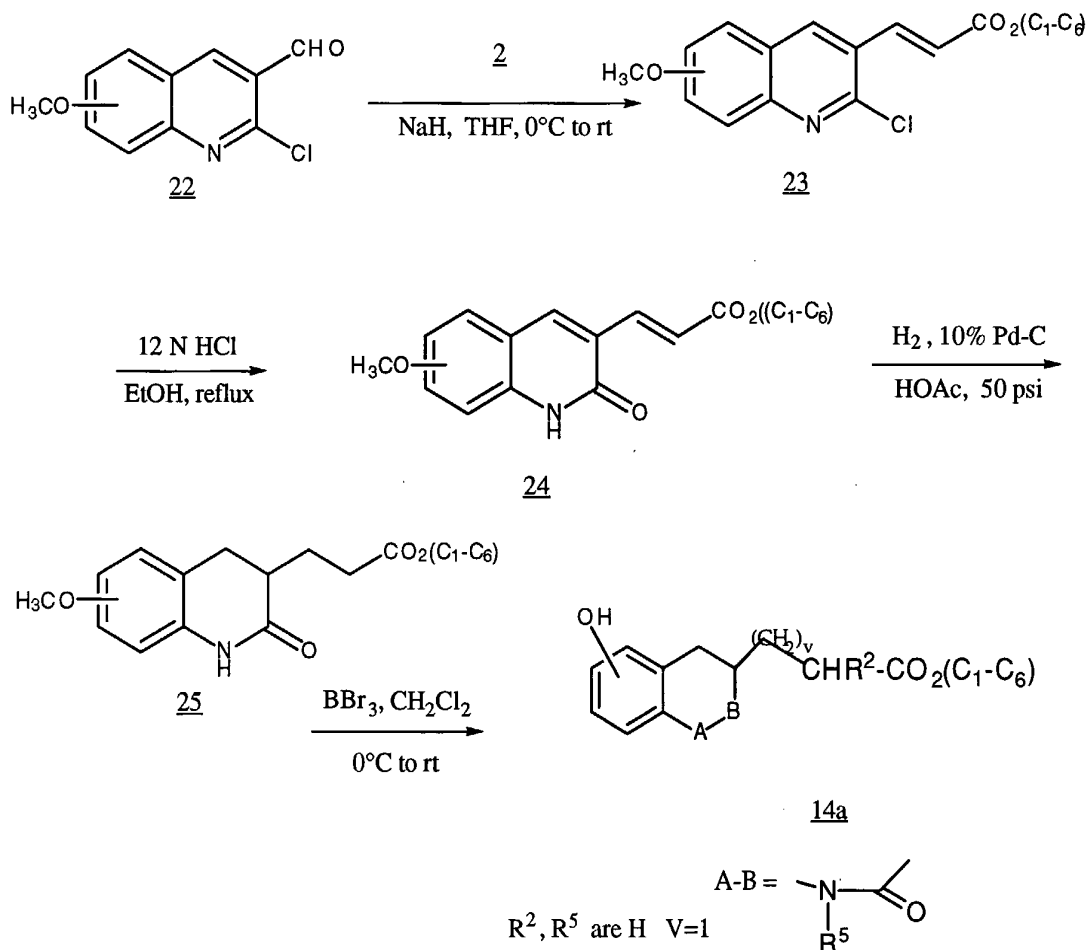
5 reaction with thionyl chloride or oxalyl chloride. Further
 reaction of amide 20 where v and R² are hereinbefore
 defined with phosphorous oxychloride in N,N-
 dimethylformamide affords 2-chloro-substituted quinoline
21. Hydrolysis of 2-chloro-substituted quinoline 21 with
 10 aqueous HCl in methanol affords substituted (1,2-dihydro-3-
 yl)alkanoate ester 12 (R is CH₃), where v and R² are
 hereinbefore defined.

SCHEME III



- 5 As described in Scheme IV, aldehyde 22 is reacted with tri(C₁-C₆)alkyl phosphonoacetate 2 where v is 0 and R² is H in the presence of sodium hydride in tetrahydrofuran to give ester 23 which is hydrolyzed with 12N HCl to afford (1,2-dihydro-3-yl)alkanoate ester 24. Reduction of (1,2-
- 10 dihydro-3-yl)alkanoate ester 24 with hydrogen in the presence of 10% Pd/C in acetic acid affords tetrahydroquinolinone 25 which is further reacted with BBr₃ in methylene chloride to give phenol 14a where V is 1, R² is H and R⁵ is H.

SCHEME IV

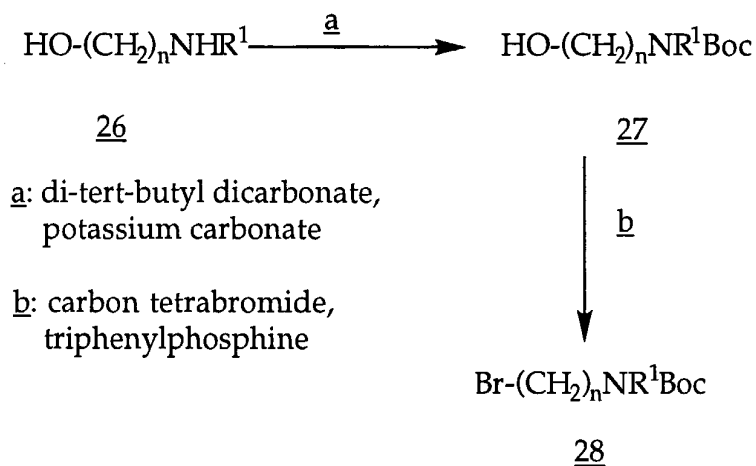


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As shown in Scheme V, substituted amino alcohol 26 where R¹ and n are hereinbefore defined is converted to tert-butyl carbamate 27 by reaction with di-tert-butyl dicarbonate in the presence of potassium carbonate and

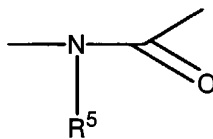
- 5 which is further reacted with carbon tetrabromide in the presence of triphenylphosphine to give (bromoalkyl)carbamic acid tert-butyl ester 28 where R¹ and n are hereinbefore defined.

SCHEME V



10

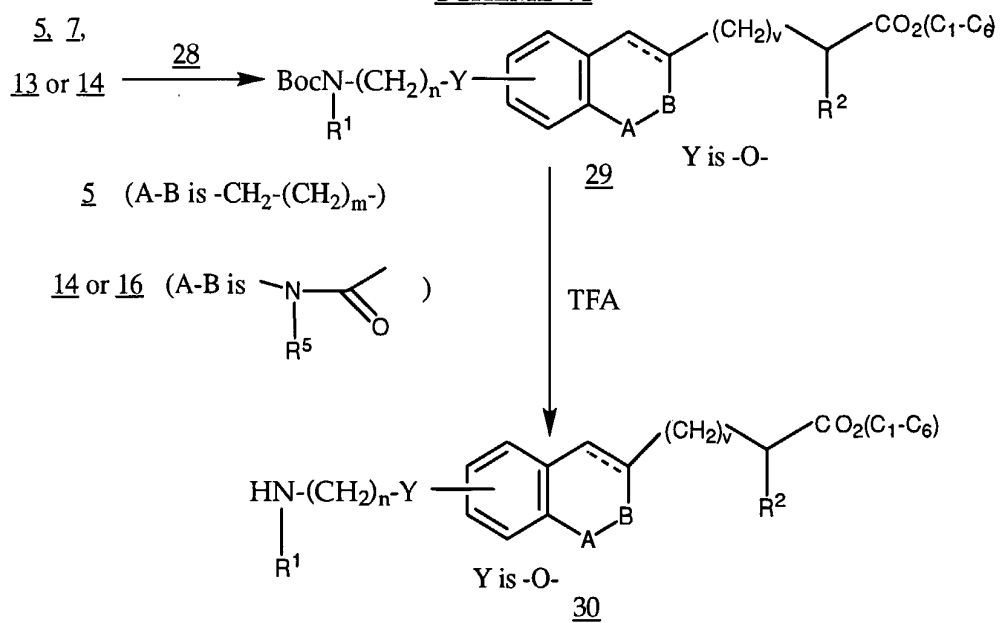
As shown in Scheme VI, independent alkylation of phenol 5, 7, 13, or 14, where Y is -O-, A-B, m, v, are hereinbefore defined and R² and R⁵ are as defined for each phenol and ---- is an optional double bond when A-B is



with (bromoalkyl) carbamic acid tert-butyl ester 28 where R¹ and n are hereinbefore defined using sodium ethoxide in N,N-dimethylformamide gives ether 29 where R¹, R², R⁵, n, v, A-B and m are hereinbefore defined and Y is -O-. Removal of the tert-butyl ester of ether 29 with trifluoroacetic acid (TFA) gives amine 30.

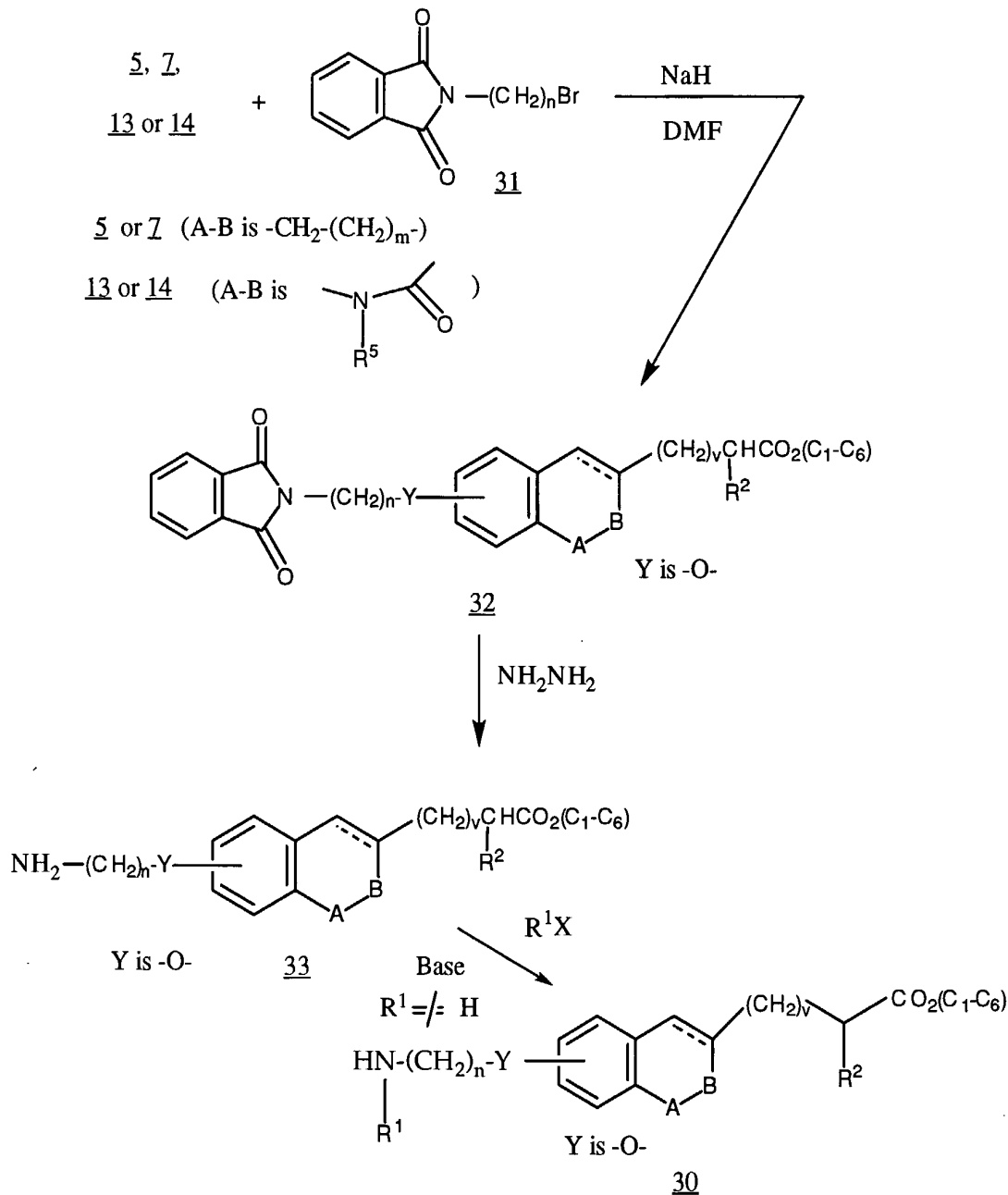
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SCHEME VI



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Scheme VII

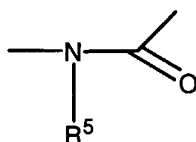


An alternative to using bromoalkylcarbamic acid t-butylester **28** is shown in Scheme VII where independent alkylation of phenol **5**, **7**, **13**, or **14** with N-(bromoalkyl)-phthalimide **31** where n is hereinbefore defined, in the presence of sodium hydride in N,N-dimethylformamide affords

10

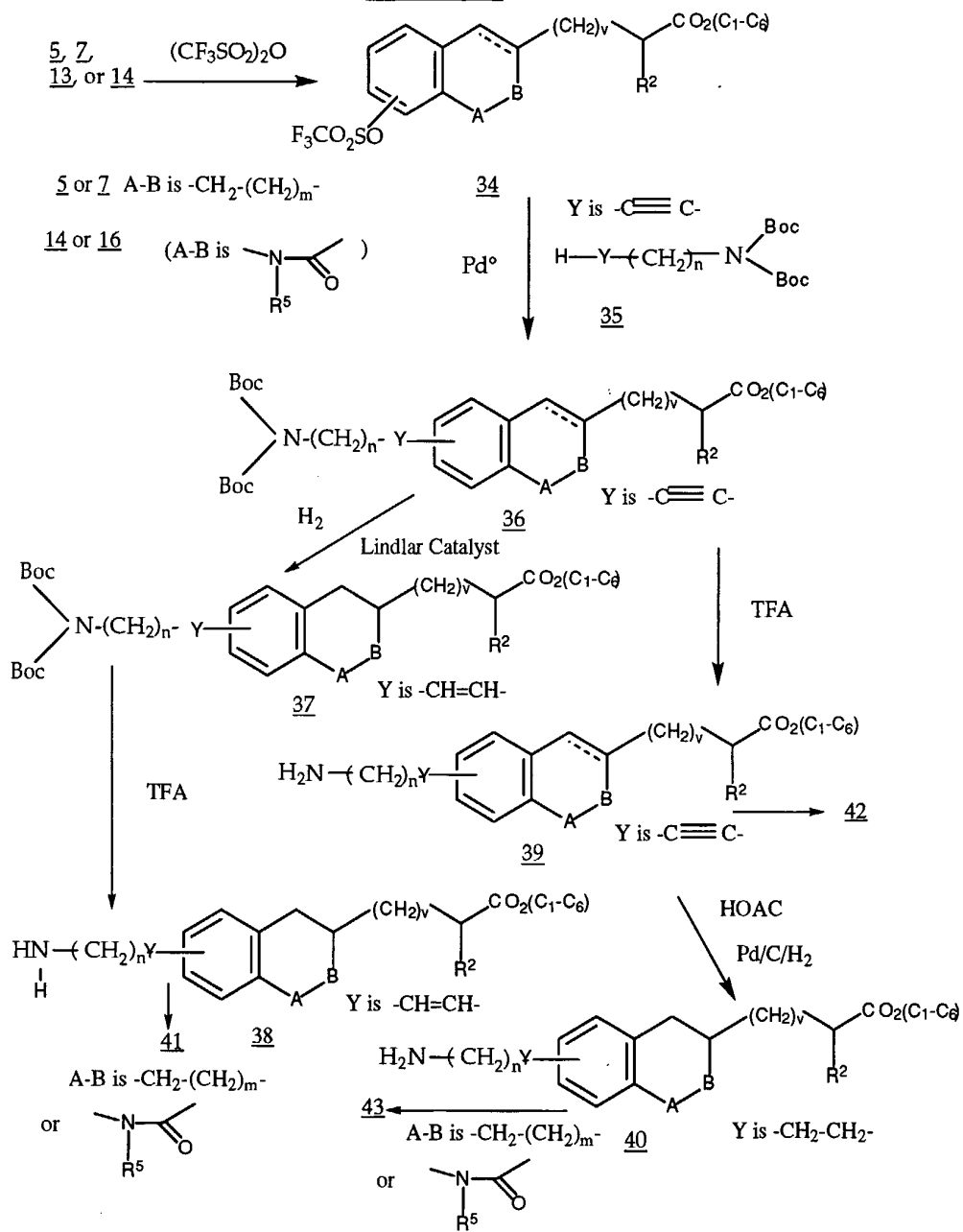
5 ester 32 where Y is -O- and v, n, m, A-B, R², and R⁵ are hereinbefore defined and

----- is an optional double bond when A-B is

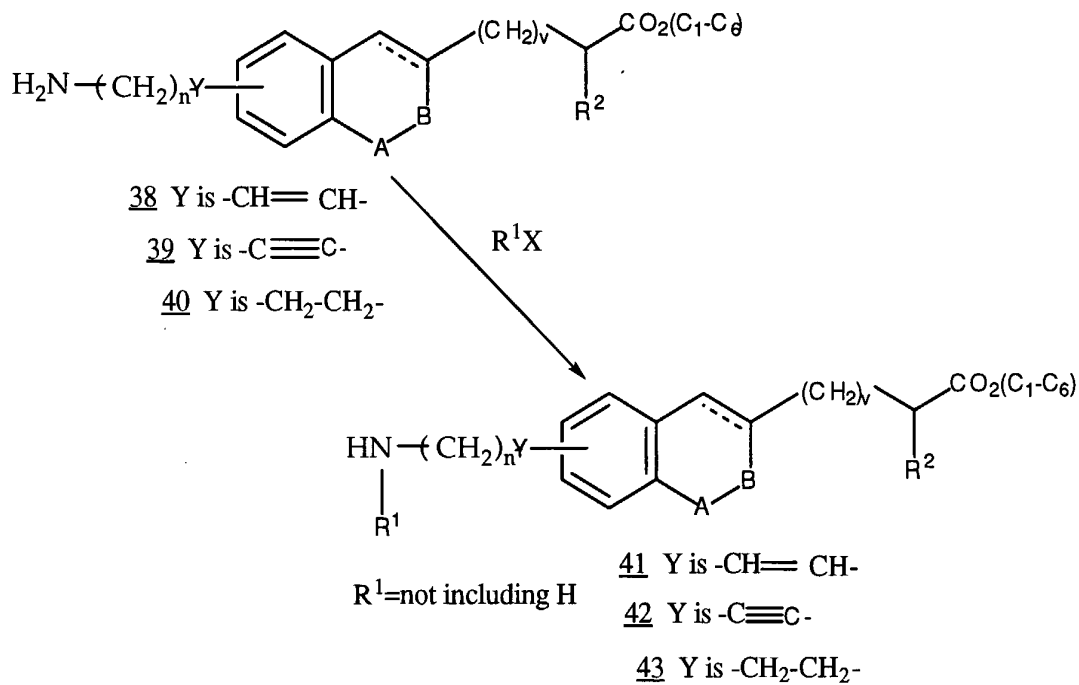


10 The phthalimide blocking group of ester 32 is removed by reaction with hydrazine in isopropyl alcohol to give amine 33 where Y is -O-, and R⁵, R², v, n, m and A-B are hereinbefore defined. Ester 33 may be alkylated with R¹X where R¹ is not H in the presence of base to give amine 30.

SCHEME VIII



SCHEME VIII (CONT'D)



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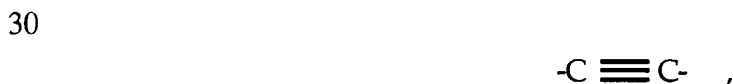
As outlined in Scheme VIII, phenol 5, 7, 13, or
 10 14, where Y is -O- and A-B, m, and v are hereinbefore
 defined and R² and R⁵ are as defined for each phenol which
 can be independently reacted with trifluoro-methane
 sulfonic anhydride (Tf₂O) to give triflate 34. Palladium
 mediated coupling of triflate 34 with tert-butyloxycarbonyl
 15 (Boc) protected acetylene 35 where n is hereinbefore
 defined and Y is:



gives acetylene 36 where Y is:



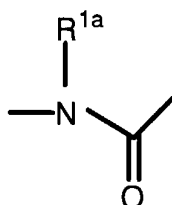
and A-B, R², R⁵, n, m and v are hereinbefore defined.
 Reduction of acetylene 36 with hydrogen in the presence of
 Lindlar catalyst gives olefin 37 where Y is -CH=CH- and A-
 B, R⁵, R², v, n, m are hereinbefore defined and ----- is a
 25 single bond. Olefin 37 can be reacted with trifluoroacetic
 acid to give amine 38 where Y is -CH=CH- and A-B, R², R⁵, n,
 m and v are hereinbefore defined and ----- is a single
 bond. Acetylene 36 can be reacted with trifluoroacetic
 acid to give amine 39 where Y is



and A-B, R², R⁵, n, m and v are hereinbefore defined.
 Reduction of amine 39 in the presence of palladium-on-
 carbon and hydrogen in acetic acid gives amine 40 where Y
 35 is -CH₂-CH₂- and A-B, R², R⁵, n, m and v are hereinbefore
 defined. Independent alkylation of amines 38, 39, and 40
 with R¹X where R¹ is hereinbefore defined, provided that R¹
 is not H, in the presence of base such as sodium methoxide

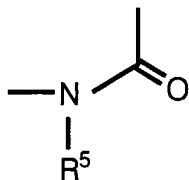
5 and X is a leaving group gives amines 41, 42, and 43 respectively.

Compounds of Formulae (I) or (II) wherein Y is



10

where R^{1a} is hereinbefore defined;
A-B is the diradical



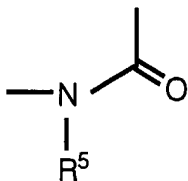
15

R⁵ is H straight chain alkyl of 1 to 6 carbon atoms and substituted benzyl, n is an integer from 2 to 4 and v is an integer of 0 or 1 may be prepared as shown in Scheme IX, where tert-butyl-3-nitro-4-bromomethyl-benzoate 44 (Y. Kashman and J.A. Edwards, J. Org. Chem. 43, 1538-1540 (1978)) is first reacted with pyridine in ethanol followed by further reaction with p-nitrosodimethylamine in the presence of aqueous 2.0 N sodium hydroxide followed by further treatment with aqueous 6 N sulfuric acid affords aldehyde 45 using the conditions described in Organic Synthesis, Collective Volume V, page 825. Reaction of aldehyde 45 with diester 9 where v and R² are hereinbefore defined gives tert-butyl ester 46. Catalytic hydrogenation of tert-butyl ester 46 in the presence of 10% Pd/C and spontaneous cyclization gives lactam 47 where A-B is the diradical

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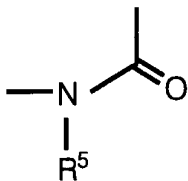


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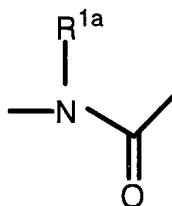
where R^2 and v are hereinbefore defined and R^5 is H.

Alkylation of lactam 47 with R^5X where R^5 is hereinbefore defined excluding H and X is a leaving group hereinbefore defined in the presence of base can form ester 48.

Hydrolysis of lactam 47 and ester 48 with aqueous 4 N hydrochloric acid in dioxane gives carboxylic acid 49 where R^2 , v and R^5 are hereinbefore defined. Reaction of carboxylic acid 49 with 1-hydroxybenzotriazole hydrate (HOBT) and carbodiimide 50 where n is hereinbefore defined gives ester 51 where A-B is the diradical



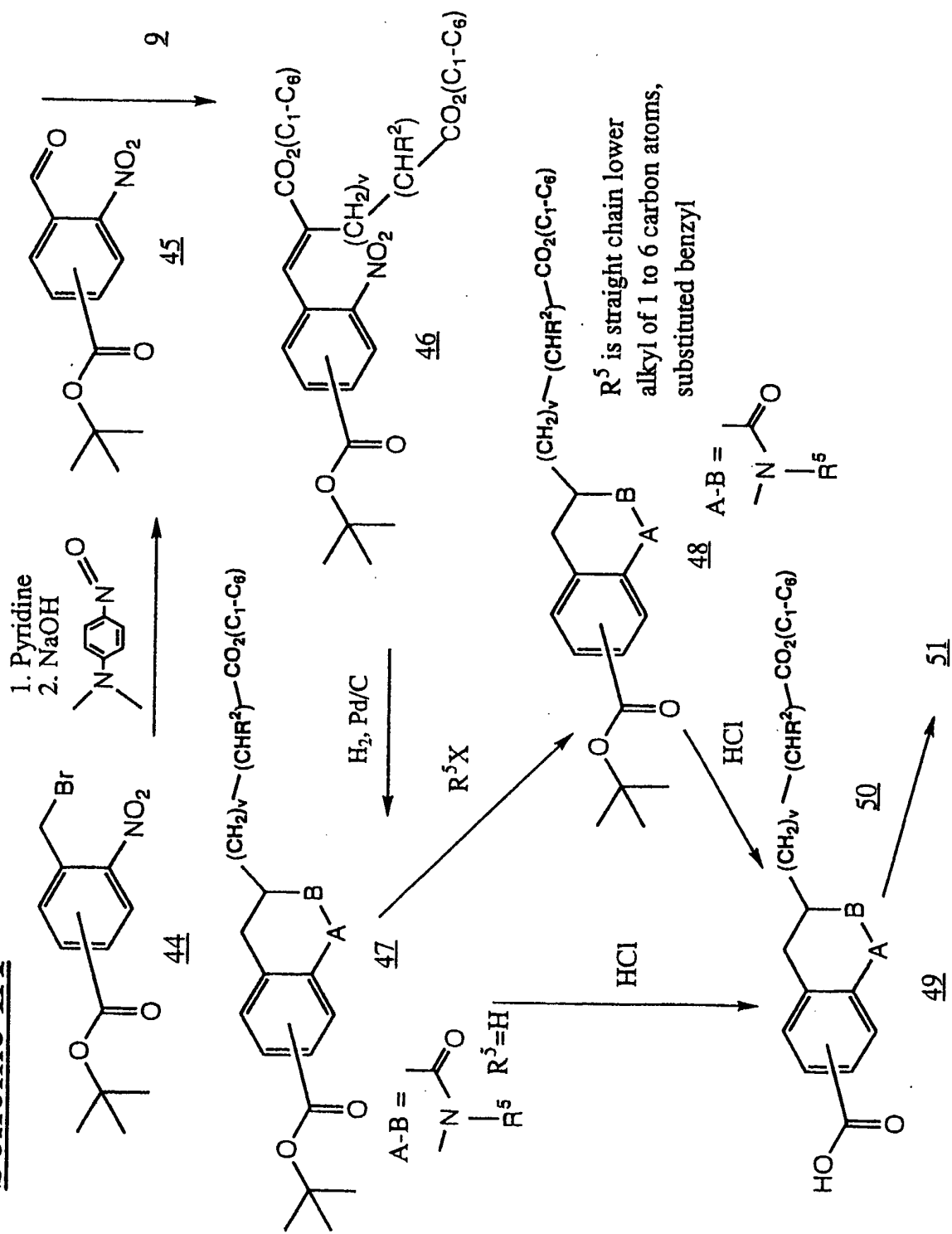
20 Y is



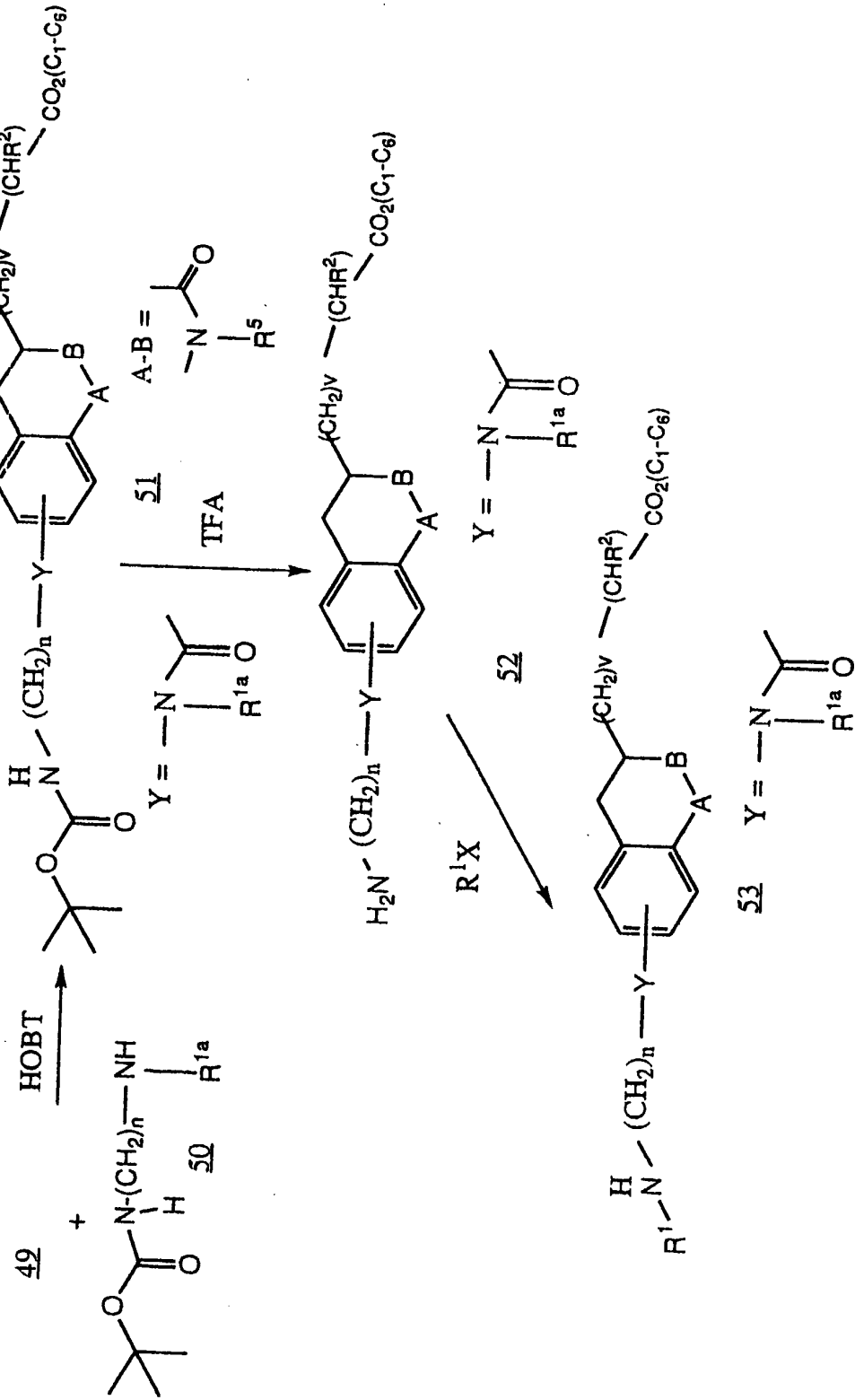
and R^{1a} , R^2 , R^5 , n and v are hereinbefore defined. The N-tertbutoxycarbonyl blocking group on ester 51 is removed by stirring with trifluoroacetic acid in methylene chloride to give amine 52. Alkylation of amine 52 with R^1X where R^1 is hereinbefore defined excluding H can afford amine 53.

30

Scheme IX

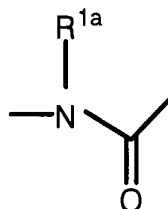


SCHEME IX (CONT'D)

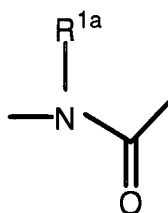


5

Compounds of Formulae (I) or (II) wherein Y is



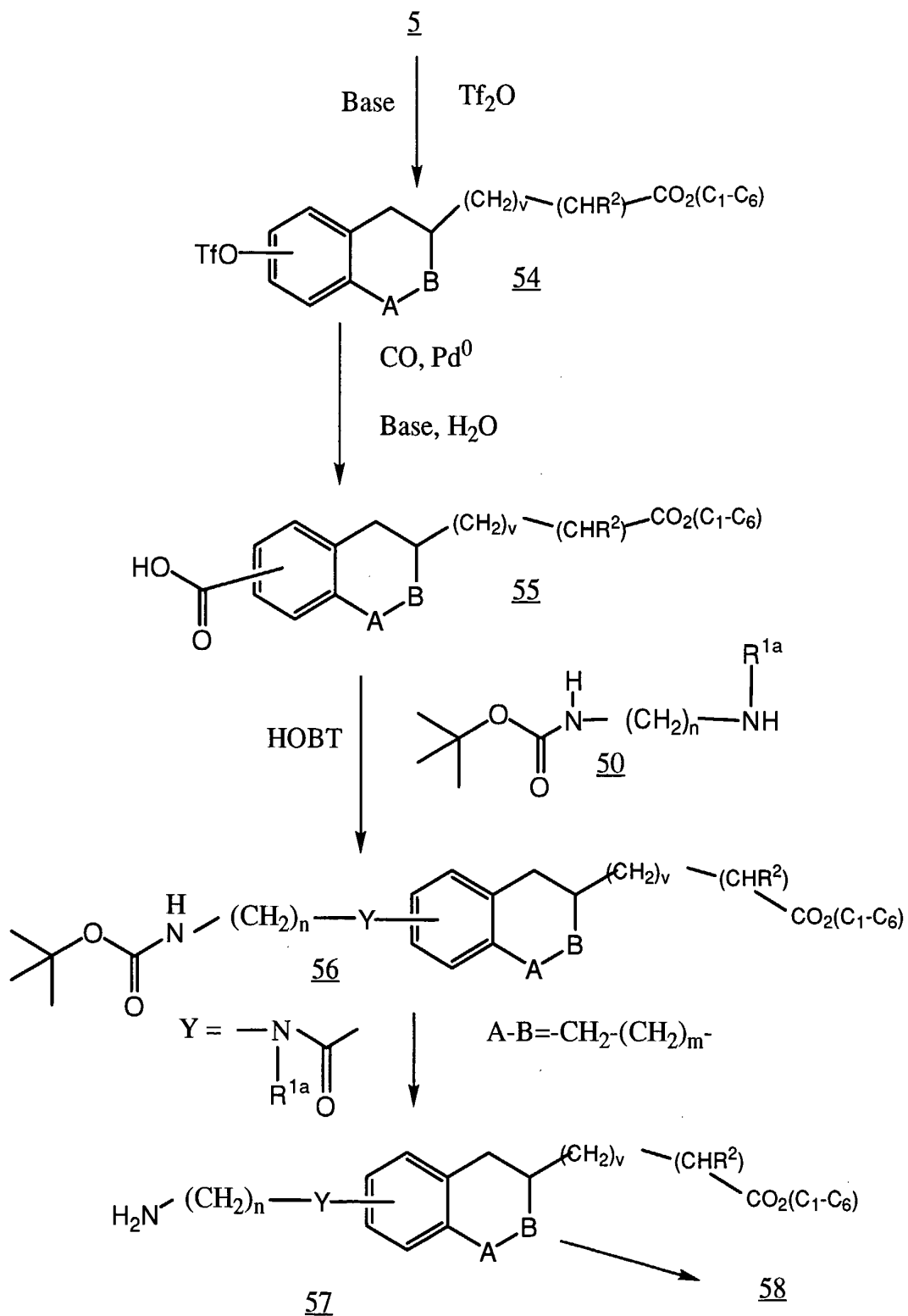
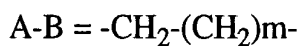
A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$, R^{1a} and m are hereinbefore
 10 defined may be prepared as shown in Scheme X, where phenol
5 can be reacted with trifluoromethane sulfonic anhydride
 ($\text{ Tf}_2\text{O}$) to give triflate 54 which can be further reacted
 with CO in the presence of Pd^0 followed by treatment with
 aqueous base to give carboxylic acid 55 where A-B is the
 15 diradical
 $-\text{CH}_2-(\text{CH}_2)_m-$, and m , v and R^2 are hereinbefore defined.
 Reaction of carboxylic acid 55 with 1-hydroxybenzo-triazole
 hydrate (HOBT) and carbodiimide 50 where n and R^{1a} are
 hereinbefore defined can give ester 56. The N-tertbutoxy-
 20 carbonyl blocking group on ester 56 may be removed by
 stirring with trifluoroacetic acid in methylene chloride to
 form amine 57 where n , v , R^{1a} and R^2 are hereinbefore
 defined, Y is

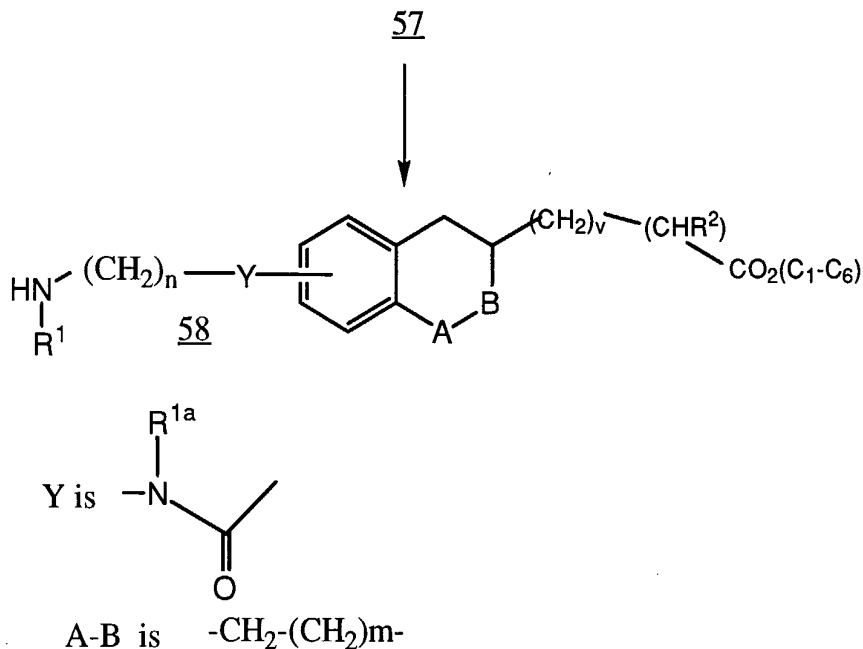


25

and A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$. Alkylation of amine 57
 with R^1X where R^1 is hereinbefore defined excluding H can
 afford amine 58.

SCHEME X



SCHEME X(CONTD)

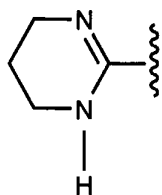
5

As shown in Scheme XI, amines 30, 38, 39, 40, 41, 42, 43, 52, 53, 57, and 58 are independently reacted with a G-reagent 59 where G is hereinbefore defined using the

10 conditions and methods as described in WO 97/36862, WO 97/33887, WO 97/37655 and CA2199923 with the exception where G is pyrimidine, the preferred method is to in situ activate amines 30, 38, 39, 40, 41, 42, 43, 52, 53, 57, and

15 58 with trimethylsilyl chloride in the presence of 2-bromopyrimidine in refluxing anhydrous 1,4-dioxane to give ester 60. G-reagent 59 includes but is not limited to those in Table A. In particular, alkylation of amines 30, 38, 39, 40, 41, 42, 43, 52, 53, 57, and 58 with 2-methylthio-

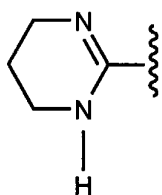
20 3,4,5,6-tetrahydro-pyrimidine hydroiodide, a G-reagent 59, using the conditions as described (WO 96/37492 Example 83) can give ester 60 where G is



5

Alternatively, condensation of amines 30, 38, 39, 40, 41, 42, 43, 52, 53, 57, and 58 with N,N'-bis(tert-butoxycarbonyl)-2-(1H)-tetrahydropyrimidine-thione followed by deprotection with hydrochloric acid can give ester 60

10 where G is



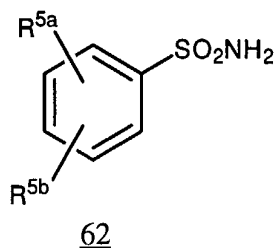
Independent base hydrolysis of ester 60 with aqueous base gives carboxylic acid 61. Suitable bases include sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate and potassium carbonate.

15

5

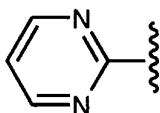
Again referring to Scheme XI, carboxylic acid 61 was reacted with substitutedbenzenesulfonamide 62

10



where R^{5a} and R^{5b} are hereinbefore defined in the presence of 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride, dimethylaminopyridine and N,N-dimethylformamide (DMF) to give substitutedbenzenesulfonamide 63 and v, n, m, G, A-B, R^1 , R^{1a} , R^2 , R^5 , R^{5a} and R^{5b} are hereinbefore defined.

Reduction of carboxylic acid 61 where G is the selected moiety

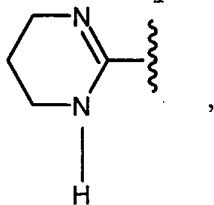


and where Y is $-\text{CH}=\text{CH}-$, or



25

in the presence of hydrochloric acid, acetic acid and an alcohol ($\text{C}_1\text{-C}_6$)OH followed by reaction with an alcohol ($\text{C}_1\text{-C}_6$)OH in the presence of hydrochloric acid gives an ester where G is reduced to the tetrahydropyrimidine moiety



30

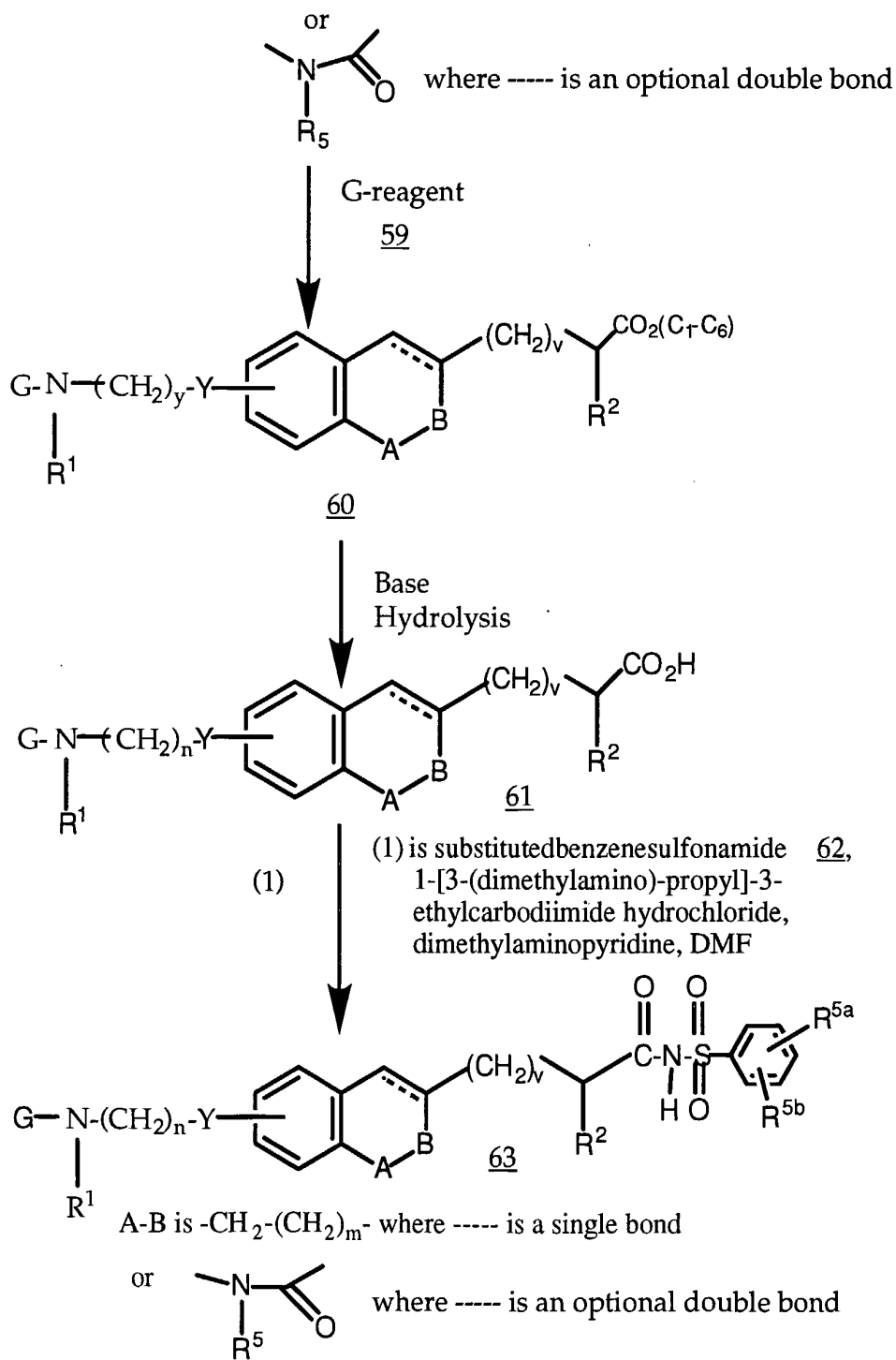
5 Y is reduced to $-\text{CH}_2-\text{CH}_2-$ and the optional double bond ---- is also reduced to a single bond and v, n, m, A-B, R^1 , R^{1a} , R^2 , and R^5 are hereinbefore defined.

10

SCHEME XI

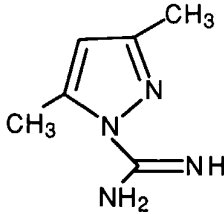
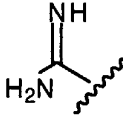
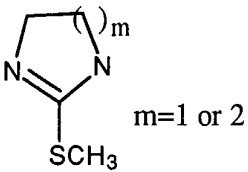
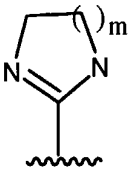
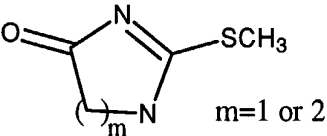
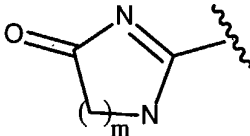
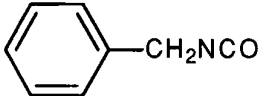
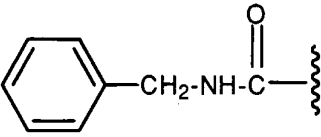
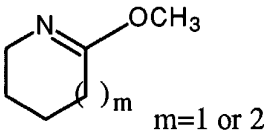
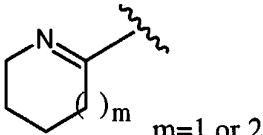
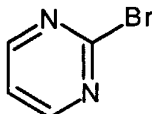
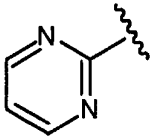
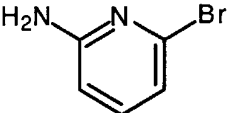
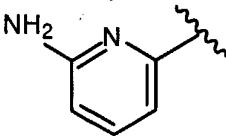
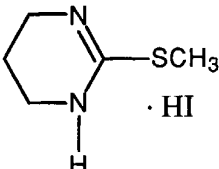
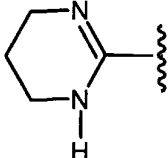
30, 38, 39, 40, 41, 42, 43, 52, 53, 57 and 58

A-B is $-\text{CH}_2-(\text{CH}_2)_m-$ where ----- is a single bond



5

TABLE A

<u>G-Reagent 59</u>	<u>Ester Product</u> <u>60</u> <u>G-Moiety</u>
	
 <p>m=1 or 2</p>	
 <p>m=1 or 2</p>	
 <p>(C₁-C₆)NCO</p>	
 <p>m=1 or 2</p>	 <p>m=1 or 2</p>
	
	
 <p>· HI</p>	

5

The compounds of the present invention can be prepared readily according to hereinbefore described reaction schemes and hereinafter described examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The most particularly preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention.

5

10 Representative compounds of the present invention were
evaluated in the following pharmacological test procedures
which measured Vitronectin Receptor ($\alpha_V\beta_3$) Binding,
Osteopontin ($\alpha_V\beta_3$) Cell Attachment, Osteoclast Bone Pitting,
PTH-induced hypercalcemia and ADP-Induced Platelet
15 Aggregation and which further show that the compounds of
the present invention selectively antagonize the ($\alpha_V\beta_3$)
integrin while not displaying ADP-induced platelet
aggregation mediated by a fibrinogen ($\alpha_{IIb}\beta_3$) integrin.

20 **Vitronectin Receptor ($\alpha_V\beta_3$) Binding Test Procedure**

Measuring the effect of compounds on the $\alpha_V\beta_3$ -
ligand interaction.

Reagents

25 Plasma Membrane Isolation: 15 confluent T₁₅₀ flasks
of 512P5 cells ($\alpha_V\beta_3$ - overexpressing cell line) were washed 2X
with Dulbecco's phosphate buffered saline (D-PBS) without
calcium or magnesium, pH 7.1. Cells were harvested with 10
mL of trypsin/EDTA and collected by centrifugation. The cell
pellet was washed 2X with 0.5 mg/mL of soybean trypsin
30 inhibitor, and resuspended at 10% weight/volume in
homogenization buffer (25 mM Tris-HCl, pH=7.4; 250 mM
sucrose). The cell suspension was homogenized with 2x30
seconds bursts of a Polytron homogenizer. The homogenate
was centrifuged at 3000g for 10 minutes at 4°C. The
35 supernatant was collected, measured, and made 100 mM in
NaCl and 0.2 mM in MgSO₄. The supernatant was centrifuged
at 22,000g for 20 minutes at 4°C, the pellet was resuspended in
7 mL of membrane buffer (25 mM Tris-HCl, pH=7.4; 100 mM
NaCl; 2 mM MgCl₂) by 5 strokes of a Dounce homogenizer
40 (tight pestle) and recentrifuged at 22,000g for 20 minutes at
4°C. The pellet was resuspended in 0.5 mL/flask of

5 membrane buffer (stock membranes) and frozen at -80°C .
Prior to use, stock membranes were Dounce homogenized
and diluted 2 μL to 1000 μL in membrane buffer.

Compound Dilution: The stock compounds
were dissolved in an appropriate vehicle (typically DMSO)
10 and subsequently diluted in assay buffer composed as follows:
25 mM Tris-HCl (pH=7.4), 100 mM NaCl, 2 mM MgCl_2 , 0.1%
BSA.

Plate Preparation

15 Wells of Multiscreen-FB assay plates (Millipore
MAFB NOB 50) were blocked with 150 μL of 0.1%
polyethylenimine for 2 hours at 4°C . Following incubation
the wells were aspirated and washed with isotonic saline
solution.

Binding Assay

20 125 μL of assay buffer was added to each well.
Next, 25 μL of labeled ligand was added to each well. 25 μL of
unlabeled ligand was added to non-specific binding wells
(NSB). 25 μL of assay buffer was added to all other wells. 2 μL
25 of compound was added to appropriate sample wells, and 2
 μL of DMSO was added to NSB and total binding (TB) wells.
Finally, 25 μL of membrane was added to each well.

The plates were covered and incubated at 37°C
for 2 hours in a humidified incubator. Wells were aspirated
30 on a Millipore vacuum manifold, and the wells were washed
with 150 μL isotonic saline solution. Wells were again
aspirated. The plates were then dried for 1 hour in an 80°C
vacuum drying oven. Plates were placed on a Millipore filter
punch apparatus, and filters are placed in 12 x 75 mm
35 polypropylene culture tubes. The samples were counted on a
Packard gamma counter.

Example

Using ^{125}I - Echistatin (specific activity = 2000
Ci/mmol) supplied by Amersham at a final concentration of
40 50pM, the following parameters were routinely observed;

Input 80000 cpm

5 Total Counts 8000 cpm
 Non-specific binding 200 cpm

Analysis of Results:

10 The individual well activity was expressed as a
 percentage of the specific binding; % Max, and reported as the
 mean \pm standard deviation. Dose-inhibition relationships
 were generated for dose (X-axis) vs. % Max (Y-axis) for active
 compounds using a non-linear regression computer program
 (PS-NONLIN), and IC₅₀ values with corresponding 95%
 confidence intervals were estimated from 50% of maximal
 15 attachment.

Reference Compounds:

20 Various Arginine-Glycine-Aspartic Acid (RGD)-
 containing peptides were assessed for the ability to inhibit
 $\alpha_v\beta_3$ binding and the corresponding IC₅₀ values with 95%
 confidence intervals were generated; peptide structures are
 given by the standard single letter designation for amino
 acids. Values obtained compared favorably with adhesion
 assay results.

25	Peptide	IC ₅₀ (μ M)	95% Confidence
Interval	G <u>PenGRGDSP</u> CA	0.064	0.038 to 0.102
	GRGDSP	1.493	1.058 to 2.025
	GRGDTP	0.490	0.432 to 0.556
30	GRGDS	0.751	0.690 to 0.817
	RGDS	1.840	1.465 to 2.262
	GRGDNP	0.237	0.144 to 0.353
	GdRGDSP	0.692	0.507 to 0.942
	GRGESP	inactive at 100 μ M	

35 References

1. Nesbitt, S. A. And M. A. Horton, (1992), A nonradioactive biochemical characterization of membrane proteins using enhanced chemiluminescence, Anal. Biochem., 206 (2), 267-72.

5

Osteopontin- α v β 3 Cell Attachment Test Procedure

10

Measuring the effect of compounds on the RGD-dependent attachment of cells to osteopontin mediated by the α v β 3 integrin.

Reagents

15

Cell Suspension Media: The cells were suspended for assay in the tissue culture media used for normal culture maintenance buffered with 25 mM HEPES (pH 7.4) without serum supplementation.

20

Compound Dilution Media: The stock compounds were dissolved in an appropriate vehicle (typically DMSO) and subsequently diluted in the tissue culture media used for normal culture maintenance buffered with 25 mM HEPES (pH 7.4) supplemented with 0.2% BSA (no serum); final vehicle concentration is $\leq 0.5\%$.

Plate Preparation

25

Human recombinant osteopontin (prepared as described in Stubbs, J. III, Connective Tissue Research, (1996) 35, (1-4), 393-399) was diluted to an appropriate concentration in Dulbecco's phosphate buffered saline (D-PBS) without calcium or magnesium, pH 7.1. 100 μ L of this solution was incubated in the wells of PRO-BIND assay plates (Falcon 3915) for 2 hours at 37 $^{\circ}$ C. Following incubation the wells were aspirated and washed once with D-PBS; plates can either be used immediately or stored for up to 1 week at 4 $^{\circ}$ C. Prior to assay, the wells were blocked with 1% bovine serum albumin (BSA) in cell suspension media for 1 hour at 37 $^{\circ}$ C. Following the blocking period, wells were aspirated and washed once with D-PBS.

30

Cell Suspension

5 $\alpha_v\beta_3$ -expressing cell lines are maintained by standard
tissue culture techniques. For assay, the cell monolayer was washed
three times with D-PBS, and the cells were harvested with 0.05%
trypsin/0.53 mM EDTA (GIBCO). The cells were pelleted by low-
10 speed centrifugation and washed three times with 0.5 mg/mL
trypsin inhibitor in D-PBS (Sigma). The final cell pellet was
resuspended in cell suspension media at a concentration of 10^6
cells/mL.

Attachment Assay

15 Incubation: 100 μ L of diluted test compound was added
to osteopontin-coated wells (in triplicate) followed by 100 μ L of cell
suspension; background cell attachment was determined in
uncoated wells. The plate was incubated at 25 $^\circ$ C in a humidified air
atmosphere for 1.5 hours. Following the incubation period, the
wells were gently aspirated and washed once with D-PBS.

20 Cell Number Detection: The number of cells attached
was determined by an MTT dye conversion assay (Promega)
according to the manufacturer's instructions. Briefly, MTT dye was
diluted in cell suspension media (15:85) and 100 μ L was added to
each well. The assay plates were incubated for 4 hours at 37 $^\circ$ C in a
25 humidified 5% CO₂/95% air atmosphere, followed by the addition
of 100 μ L stopping/solubilization solution. The assay plates were
covered and incubated at 37 $^\circ$ C in a humidified air atmosphere
overnight. After the solubilization period, the optical density of the
wells was measured at a test wavelength of 570 nM with a reference
30 measurement taken simultaneously at 630 nM.

Analysis of Results:

The individual well optical density was expressed as a
percentage of the maximal attachment (% Max) wells minus
background attachment, and reported as the mean \pm standard

5 deviation. Dose-inhibition relationships were generated for dose (X-axis) vs. % Max (Y-axis) for active compounds using a non-linear regression computer program (PS-NONLIN), and IC₅₀ values with corresponding 95% confidence intervals were estimated from 50% of maximal attachment.

10 Reference Compounds:

Various Arginine-Glycine-Aspartic Acid (RGD)-containing peptides, and monoclonal antibodies were assessed for the ability to inhibit osteopontin- $\alpha_v\beta_3$ attachment and the corresponding IC₅₀ values with 95% confidence intervals were generated in the SK-MEL-24 human malignant melanoma cell line; peptide structures are given by the standard single letter designation for amino acids:

5	Peptide	IC ₅₀ (95% Confidence
	Interval)	
	<u>GPenGRGDSPCA</u>	0.58 μ M (0.51 TO 0.67)
	n-Me-GRGDSP	4.0 μ M (3.4 TO 4.7)
10	GRGDSP	4.1 μ M (3.4 TO 4.9)
	GRGDTP	5.2 μ M (3.4 TO 4.9)

	Antibody	Dilution	% Maximal Attachment (mean \pm SD)
	α v β 5(P1F6)	1:1000	111 \pm 3.3
15		1:100	112 \pm 2.6
		1:10	111 \pm 3.3
	α v β 3 (LM609)	1:1000	0
20		1:100	5.1 \pm 1.7

Literature References:

Ruoslahti, R. Fibronectin and its receptors. Ann. Rev. Biochem. 57:375-413, 1988.

25 Hynes, R.O. Integrins: Versatility, modulation, and signaling in cell adhesion. Cell. 69: 11-25, 1992.

- 5 The results of this test procedure on representative compounds of this invention are shown in Table I.

10 Table I
Vitronectin Receptor ($\alpha_v\beta_3$) Binding And Measurement Of The
Effect Of Compounds On Integrin ($\alpha_v\beta_3$)-Mediated Attachment Of
Cells To Osteopontin

EXAMPLE NO.	($\alpha_v\beta_3$) _{RECEPTOR BINDING} (IC ₅₀)	($\alpha_v\beta_3$) _{CELL ATTACHMENT} (IC ₅₀)
31	88% @ 30 μ M	100% @ 100 μ M
37	2.9 μ M	8.9 μ M
40	130% @ 30 μ M	47 μ M
61	1.7 μ M	62.2 μ M
62	1.4 μ M	14 μ M
63	3.9 μ M	32.8 μ M
84	11.4 μ M	24.5 μ M
85	15.7 μ M	111.4 μ M
86	7.3 μ M	21.1 μ M
100	30.9 % @ 100 μ M	79 μ M
101	8.9 μ M	11.5 μ M
112	7.0 μ M	19.7 μ M
113	4.0 μ M	17.8 μ M
121	2.6 μ M	15.1 μ M
122	3.6 μ M	8.3 μ M
149		71.5% @ 100 μ M 96.3% @ 20 μ M
172	2.7 μ M	27.3 μ M
184	67.5% @ 30 μ M	85% @ 100 μ M 108% @ 20 μ M
185		96.8% @ 100 μ M 102% @ 20 μ M
186		68.9% @ 100 μ M 113% @ 20 μ M
200	31.4% @ 100 μ M	145 μ M
201	5.8 μ M	25.4 μ M
202	50% @ 30 μ M	86 μ M

<p style="text-align: center;"><u>Table I (Cont'd)</u> <u>Vitronectin Receptor ($\alpha_v\beta_3$) Binding And Measurement Of</u> <u>The Effect Of Compounds On Integrin ($\alpha_v\beta_3$)-Mediated</u> <u>Attachment Of Cells To Osteopontin</u></p>		
EXAMPLE NO.	($\alpha_v\beta_3$) _{RECEPTOR BINDING} (IC50)	($\alpha_v\beta_3$) _{CELL ATTACHMENT} (IC50)
212	98.7% ₃ μ M 98.3% ₁₀ μ M 101.6% ₃₀ μ M 99.3% ₁₀₀ μ M	
213	54 % @ 100 μ M	
214	0.42 μ M	0.479 μ M
215	2 ^a μ M	37.4 μ M
216	60 μ M	
217	14.651 ^b μ M	
222		100% ₁₀₀ μ M
223	100% ₃₀ μ M	104% ₂₀ μ M 108% ₁₀₀ μ M
224	100% ₃₀ μ M	100% ₂₀ μ M
228	57% ₃₀ μ M	88% ₁₀₀ μ M
229	100% ₃₀ μ M	82% ₁₀₀ μ M
230		100% @ 100 μ M
231	55.9% ₃₀ μ M	93% ₁₀₀ μ M
232	75.3% ₃₀ μ M	97% ₁₀₀ μ M
234	100% ₃₀ μ M	85% ₁₀₀ μ M
235	100% ₃₀ μ M	91% ₁₀₀ μ M
237	100% ₃₀ μ M	114% ₁₀₀ μ M 86.2% ₂₀ μ M
238	100% ₃₀ μ M	97.9% ₁₀₀ μ M 102% ₂₀ μ M
<u>239</u>	<u>70%₃₀ μM</u>	<u>67.5%₁₀₀ μM</u> <u>99.7%₂₀ μM</u>
<u>246</u>		<u>84.2%₁₀₀ μM</u> <u>102%₂₀ μM</u>

<u>Table I (Cont'd)</u> <u>Vitronectin Receptor ($\alpha_v\beta_3$) Binding And</u> <u>Measurement Of The Effect Of Compounds On Integrin</u> <u>($\alpha_v\beta_3$)-Mediated Attachment Of Cells To Osteopontin</u>		
EXAMPLE NO.	($\alpha_v\beta_3$)_(IC50) RECEPTOR BINDING	($\alpha_v\beta_3$)_(IC50) CELL ATTACHMENT
248	1.53 mM	
250	<u>102% @ 30 μM</u>	<u>89% @ 100 μM</u> 90% @ 10 μ M

5

a Average of two determinations.
b Trifluoroacetic acid salt.

OSTEOCLAST BONE PITTING

10

The test procedure was conducted as described by R.J. Murrills and D.W. Dempster, Bone, 11, 333-344(1990). Briefly, 4 x 4 x 0.2mm slices of devitalized bovine cortical bone were numbered, placed in the wells of 96-well culture plates and wetted with 100ul of Medium 199 containing Hanks salts, 10mM HEPES, pH 7.0 (Medium 199/Hanks). Bone cell suspensions containing osteoclasts were prepared by mincing the long bones of neonatal rats (Sprague-Dawley , 4-6 days old) in Medium 199/Hanks.

15 100uL of the suspension were then plated onto each slice and incubated 30 minutes to allow osteoclasts to adhere. The slices were rinsed to remove non-adherent cells and incubated 24h in Medium 199 containing Earle's salts, 10mM HEPES and 0.7g/L NaHCO₃, which equilibrates at pH

20 6.9 in a 5% CO₂ atmosphere. At this pH the adherent osteoclasts excavate an adequate number of resorption pits for assay purposes. Slices were fixed in 2.5% glutaraldehyde and osteoclasts counted following tartrate-resistant acid phosphatase staining. In

5 experiments in which osteoclast numbers were
significantly reduced in a particular treatment, a check
is made for non-specific cytotoxicity by counting the
number of contaminant fibroblast-like cells following
toluidine staining. All cells were stripped from the
10 slice by sonication on 0.25M NH₄OH and the resorption
pits formed by the osteoclasts during the experiment
stained with toluidine blue. Resorption pits were
quantified by manually counting.

5

Statistics

The experiments were conducted according to a block design with osteoclasts from each animal exposed to each treatment. Three replicate slices were used per treatment per animal, such that a total of 96 slices were examined for an experiment involving four animals and eight treatments (including control). Several parameters were recorded on a "per slice" basis: number of pits, number of osteoclasts, number of pits per osteoclast, number of fibroblast-like bone cells. SAS or JMP statistical software were used for statistical analysis. If analysis of variance reveals significant effects in the experiment, those treatments differing significantly from control were identified using Dunnett's test. IC50s were calculated using dose-response curves.

20

Reference Compound: Rat calcitonin.25 Clinical Relevance:

Osteoclasts are responsible for the bone loss that occurs at the onset of osteoporosis and anti-resorptive drugs directed against the osteoclast are a requirement for patients losing bone. Calcitonin and bisphosphonates, both used as anti-resorptives in the clinic, show significant osteoclast inhibitory activity in this test procedure. Hence it is a reasonable test procedure in which to identify novel anti-resorptives.

35

The results of this test procedure on representative compounds of this invention is shown in Table II.

5

Table II
OSTEOCLAST BONE PITTING TEST PROCEDURE

<u>EXAMPLE NO.</u>	<u>BONE PITTING INHIBITION</u>
37	30% @ 238 μ M
40	39% @ 238 μ M
61	32% @ 271 μ M
84	57% @ 223 μ M
85	33% @ 273 μ M
86	70% @ 280 μ M
100	38% @ 264 μ M
101	51% @ 221 μ M
121	30% @ 228 μ M
122	IC ₅₀ = 159 μ M
158	13% @ 216 μ M
172	15% @ 190 μ M
184	37% @ 271 μ M
185	58% @ 239 μ M
186	2% @ 228 μ M 6% @ 228 μ M 23% @ 228 μ M
200	20% @ 254 μ M
201	45% @ 256 μ M
202	37% @ 240 μ M
214	19% @ 19 μ M
215	90% @ 200 μ M
216	95% @ 200 μ M
217	51% @ 1 μ M
222	-58% @ 22 μ M
223	-72% @ 226 μ M
224	-62% @ 216 μ M
228	7% @ 230 μ M
229	2% @ 214 μ M
230	15% @ 230 μ M

<u>Table II (Cont'd)</u>	
<u>OSTEOCLAST BONE PITTING TEST PROCEDURE</u>	
EXAMPLE NO.	BONE PITTING INHIBITION
231	-34% and -51% @ 230 μ M
232	-70% @ 216 μ M
234	8% @ 230 μ M
235	-50% @ 221 μ M
237	-21% @ 222 μ M -71% @ 222 μ M
238	-20% @ 215 μ M
239	33% @ 19.1 μ M
246	52% @ 26.2 μ M
250	-5% @ 215 μ M

5

Effects of test compounds on PTH-induced hypercalcemia of thyro-parathyroidectomized male rats.

10

Male thyro-parathyroidectomized (TPTX) rats (Charles River) were randomly assigned to groups of 7 rats/group. Following a baseline serum calcium determination an Alzet 1003D minipump (Alza Corporation, Palo Alto, CA) loaded with 0.3 mg/ml PTH (Bachem, Philadelphia, PA) was implanted subcutaneously in each rat. For evaluation of prophylactic effects of a test drug, another minipump with appropriate concentration of the test drug solution was implanted subcutaneously at a site away from PTH minipump or implanted as a pellet of the test compound away from the PTH minipump. Alternatively, test drugs were administered by oral gavage as a solution or uniform suspension in an appropriate medium depending on the physical properties of the test compound. A group of 7 unimplanted TPTX rats was set aside as a normal control group. Twenty hours after minipump implantation blood was collected from each rat to confirm the presence of hypercalcemia (judged by elevation of serum calcium levels, 2 SD > normal non-implanted level). At various intervals between 0.5 and 24 hours after dosing (usually one to three time points), blood was collected from each rat and the serum evaluated for total calcium. Serum calcium levels were measured using

25

5 the Nova 7 + 7 calcium auto analyzer spectrophotometrically using the Sigma test kit (#587A). Test results were determined by the difference in serum calcium between vehicle and treatment group following PTH administration, using a oneway analysis of variance with Dunnett's test or other multiple comparison methods and are displayed in Tables III-V.

10

References:

1. Takeuchi M, Sakamoto S, Kawamuki K, Kudo M, Abe T, Fujita S, Murase K, and Isomura Y, (1990). Synthesis and structure activity relationship of new bisphosphonate derivative. Abstract #53, 199th American Chemical Society Meeting, Boston, MA.
2. Fisher J, Caulfield M, Sato M, Quartuccio H, Gould R, Garsky V, Rodan G, Rosenblatt M, (1993). Inhibition of osteoclastic bone resorption in vivo by echistatin, an "arginyl-glycyl-aspartyl" (RGD)-containing protein. Endocrinology, Vol. 132 (3) 1411-1413.

20

Table III. Representative In Vivo Biological Data (TPTX rat)

25

Ex. No.	Dose	Change in Serum Calcium (mg / dL)
Vehicle		2.20 ± 0.26 *
Cyclo(-Arg-Gly-Asp-D-Phe-Val) ^a	100mg/kg.sc	-0.90+ 0.28
216	100mg/kg.po	0.64 _ 0.27 *

0.64 a)p< 0.01 when compared to vehicle control

30

a)M. Gurrath et al., Eur. J. Biochem. 210, 911-921(1992)

5 Table IV - Effects of Echistatin on Serum Calcium in TPTX Male Rats

Treatment ^a	N	Change in Serum Calcium ^b
Normal Controls	6	0.58 + 0.11
TPTX		
TPTX Controls	7	-0.19 +0.17
with rat PTH(1-34) 0.15(g/kg/hr, s.c.)		
Example 37 100 mg/kg, s.c. pellet	6	1.57* +0.06
Cyclo(-Arg-Gly-Asp-D- Phe-Val) ^c 100 mg/kg s.c. pellet	8	1.63* +0.33
Salmon Calcitonin 5IU/rat, s.c.	7	0.37** +0.20
Placebo	8	2.58 +0.26

10 aTPTX surgery was performed on male rats who were placed on deionized water and a low calcium diet. Baseline blood samples were collected and Alzet 2001 osmotic micropumps delivering PTH(1-34) at a rate of 0.15(g/kg/hr were implanted. Sustained release pellets delivering compounds at 100 mg/kg/day were simultaneously implanted into the respective treatment group. Salmon calcitonin was dosed and the salmon calcitonin group bled exactly 1.5 hours after dosing.

bMean (9mg/dl)+SEM

*p<0.05 vs TPTX + PTH + placebo

15 **p<0.01 vs TPTX + PTH + placebo

c) M. Gurrath et al., Eur.J. Biochem. 210, 911-921(1992)

5

Table V - Effects of Compounds on Serum Calcium in TPTX Male Rats Treated with rPTH(1-34)				
Treatment ^c	N	Change in Serum Calcium after 3 hours ^d	N	Change in Serum Calcium after 6 hours ^d
Example 37 100 mg/kg, s.c.	6	1.72 ±0.38	6	2.22 ±0.31
Cyclo(-Arg-Gly-Asp-D-Phe-Val) ^e	7	0.69 ±0.28	7	1.20* ±0.26
Vehicle corn oil, s.c.	7	1.26 ±0.18	7	2.13 ±0.21

Effects of Compounds on Serum Calcium in TPTX Male Rats Treated with rPTH(1-34)				
Treatment ^c	N	Change in Serum Calcium after 3 hours ^d	N	Change in Serum Calcium after 6 hours ^d
Example 37 100 mg/kg, s.c.	9	0.97 ±0.20	8	2.21 ±0.18
Cyclo(-Arg-Gly-Asp-D-Phe-Val) ^e	10	0.58** ±0.28	10	1.44* ±0.35
Vehicle corn oil, s.c.	9	1.70 ±0.25	10	2.33 ±0.39

5

Table V (cont'd) - Effects of Compounds on Serum Calcium in TPTX Male Rats Treated with rPTH(1-34)				
Treatment ^c	N	Change in Serum Calcium after 3 hours ^d	N	Change in Serum Calcium after 6 hours ^d
Example 37 100 mg/kg, s.c.	8	0.95 ±0.20	8	1.80 ±0.44
Cyclo(-Arg- Gly-Asp-D- Phe-Val) ^e	8	0.01** ±0.28	8	0.63 ±0.33
Vehicle corn oil, s.c.	6	1.17 ±0.19	7	1.47 ±0.23

Effects of Compounds on Serum Calcium in TPTX Male Rats Treated with rPTH(1-34)				
Treatment ^c	N	Change in Serum Calcium after 3 hours ^d	N	Change in Serum Calcium after 6 hours ^d
Example 37 100 mg/kg, s.c.	7	1.31 ±0.10	7	1.63 ±0.13
Cyclo(-Arg- Gly-Asp-D- Phe-Val) ^e	7	0.51** ±0.16	7	1.07 ±0.28
Vehicle corn oil, s.c.	6	1.37 ±0.11	6	1.67 ±0.17

^cAll animals were treated with rPTH(1-34), 0.45µg/kg/hr, by Alzet 1003D osmotic micropumps

^dMean (mg/dl) ±SEM

10 ^{*}p<0.05 vs corresponding Vehicle value

^{**}p<0.01 vs corresponding Vehicle value

^e M. Gurrath et al., Eur.J. Biochem. 210, 911-921(1992)

5 Measurement of the Effect of Compounds on ADP-
 Induced Platelet Aggregation

Measuring the effect of compounds on ADP-induced platelet
aggregation mediated by a fibrinogen- $\alpha_{IIb}\beta_3$ integrin
10 interaction.

Test Procedure:

Human Platelets: Platelet-enriched plasma was obtained
commercially from a donor pool. The plasma was tested
prior to shipment and found to be negative for HIV, HCV and
15 Hepatitis B. Platelet-rich plasma (PRP) was obtained by
diluting plasma to an approximate final concentration of 3×10^6
platelets per mL in platelet poor plasma (PPP).
PPP was the supernatant of a lowspeed centrifugation of
plasma.

20 Adenosine diphosphate (ADP): ADP was obtained commercially
and diluted to 1mM (stock solution) in distilled, deionized
water (ddH₂O).

Platelet Aggregation

Incubation: PRP and PPP were prewarmed in a water bath at
25 37°C. The sample compounds were dissolved

in an appropriate vehicle (typically DMSO) and diluted
in vehicle to 100X of the testing concentration. PRP plus
sample compound in a final volume of 500 uL was added
to a pre-warmed cuvette in a ChronoLog aggregometer.

30 A control containing PRP and 5 uL of vehicle was treated
similarly to the test cuvette; final vehicle concentration
was 1%. The two cuvettes were incubated with stirring
(1000 rpm) at 37°C. for 5 minutes. Five hundred
microliters of PPP was used as a reference (100%
35 aggregation).

5 Aggregation: To begin the test, ADP was added yielding
a final concentration of 20 uM to both samples (plus and
minus sample compound). Light transmittance was monitored
continuously and compared to the reference cuvette. After
five minutes, the test was terminated and the slope and
10 maximal amplitude of the resulting aggregation plot was
calculated by the aggregometer.

Analysis of Results

The percent of maximal aggregation is the ratio of the
15 maximal aggregations of the sample cuvette to the control
multiplied by 100 (% Max) and reported as the mean +/-
standard deviation. Dose-inhibition relationships were
generated for dose (X-axis) vs. % Max (Y-axis) for active
compounds using a non-linear regression computer program
20 (PS-NONLIN) and IC_{50} values with corresponding 95%
confidence intervals were estimated from 50% of maximal
aggregation.

Reference compounds

25 Known Arginine-Glycine-Aspartic Acid (RGD)-
containing peptides, and snake venoms were tested for their
ability to inhibit ADP induced platelet aggregation;
peptide structures are given by the standard single letter
designation for amino acids. Results are shown in Table VI.

5

TABLE VI

<u>Peptide</u>	IC ₅₀ (95% Confidence Interval)
Echistatin (Snake venom distegrin)	15.6 nM
SC-47,643	33 μ M (18 to 51)
GPenGRGDSPCA	46.3 μ M (3.7 to 98.5)
GRGDF	53.2 μ M (31 to 78)
RGDF	97.6 μ M (88 to 106)
cyclic RGDFV	115 μ M (114 to 116)
n-Me-GRGDSP	208 μ M
GRGDSP	Inactive at 200 μ M
GRGDTP	Inactive at 200 μ M
GRGDNP	Inactive at 200 μ M
GRGESP	Inactive at 200 μ M

5

References:

- Foster M., Hornby E., Brown S., Kitchin J., Hann M. and P. Ward. Improved Potency and Specificity of ARG-GLYASP (RGD) Containing Peptides as Fibrinogen Receptor Blocking
10 Drugs. Thromb Res 1993; 72:231-245.
- Ramjit D., Lynch J., Sitko G., Mellott J., Holahan M., Stabilito I., Stranierie M., Zhang G., Lynch R., Manno P., Chang C., Nutt R., Brady S., Veber D., Anderson P., Shebuski R., Friedman P. and R. Gould. Antithrombotic
15 Effects of MK-0852, a Platelet Fibrinogen Receptor Antagonist, in Canine Models of Thrombosis. J. Pharmacol Exp Ther 1993; 266(3):1501-1511.

- 5 Platelet Aggregation Test Results for sample compounds are displayed in Table VII.

TABLE VII
Platelet Aggregation Test Results $\alpha_{IIb}\beta_3$

Example Number	Percent of Maximal
31	IC ₅₀ = 160.15 μ M
37	IC ₅₀ = 82.4 μ M
40	IC ₅₀ = 148 μ M
61	85.33@200 μ M
62	IC ₅₀ = 169 μ M
63	51.5@200 μ M
84	62@200 μ M
85	93.3@200 μ M
86	80.9@200 μ M
100	IC ₅₀ = 216 μ M
101	IC ₅₀ = 107 μ M
112	80.4@200 μ M
113	77.1@200 μ M
121	62@200 μ M
122	IC ₅₀ = 57 μ M
149	90.2@200 μ M

155	83.7@200 μ M
172	71.5@200 μ M
184	85.5@200 μ M
185	94.8@200 μ M
200	94@200 μ M
201	85@200 μ M
202	IC ₅₀ = 87 μ M
214	58@200 μ M
215	IC ₅₀ = 151 μ M
217	98@200 μ M
222	90.3@200 μ M
223	IC ₅₀ = 54 μ M
224	IC ₅₀ = 53 μ M
228	83.7@200 μ M
229	IC ₅₀ = 146 μ M
230	95.2@200 μ M
231	78.3@200 μ M
232	IC ₅₀ = 155 μ M
234	74.3@200 μ M

235	81.1@200 μ M
237	96.5@200 μ M
238	94@200 μ M
239	83.7@200 μ M
247	100%@200 μ M
250	69@200 μ M

5

When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in a sustained release form. For most large mammals the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

40 These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous

5 routes. Solid carriers include starch, lactose, dicalcium
phosphate, microcrystalline cellulose, sucrose and kaolin,
while liquid carriers include sterile water, polyethylene
glycols, non-ionic surfactants and edible oils such as
10 corn, peanut and sesame oils, as are appropriate to the
nature of the active ingredient and the particular form of
administration desired. Adjuvants customarily employed in
the preparation of pharmaceutical compositions may be
advantageously included, such as flavoring agents, coloring
agents, preserving agents, and antioxidants, for example,
15 vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from
the standpoint of ease of preparation and administration
are solid compositions, particularly tablets and hard-
filled or liquid-filled capsules. Oral administration of
20 the compounds is preferred.

These active compounds may also be administered
parenterally or intraperitoneally. Solutions or
suspensions of these active compounds as a free base or
pharmacologically acceptable salt can be prepared in water
25 suitably mixed with a surfactant such as hydrox-
ypropylcellulose. Dispersions can also be prepared in
glycerol, liquid, polyethylene glycols and mixtures thereof
in oils. Under ordinary conditions of storage and use,
these preparations contain a preservative to prevent the
30 growth of microorganisms.

The pharmaceutical forms suitable for injectable
use include sterile aqueous solutions or dispersions and
sterile powders for the extemporaneous preparation of
sterile injectable solutions or dispersions. In all cases,
35 the form must be sterile and must be fluid to the extent
that easy syringability exists. It must be stable under
conditions of manufacture and storage and must be preserved
against the contaminating action of microorganisms such as
bacteria and fungi. The carrier can be a solvent or
40 dispersion medium containing, for example, water, ethanol

5 (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The compounds of Formulae (I) and (II) of this invention are useful in treating conditions in mammals characterized by bone resorption of mineralized tissue such as in osteoporosis, hypercalcemia of malignancy, osteopenia
10 due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia or glucocorticoid treatment.

15 In particular, compounds of Formulae (I) and (II) of this invention are therapeutically useful in the treatment and/or prevention of osteoporosis in mammals.

The compounds of this invention and their preparation can be understood further by the following
20 examples, but should not constitute a limitation thereof.

5

Example 1(6-Methoxy-3,4-dihydro-1H-naphthalen-2-ylidene)-acetic acid ethyl ester

A solution of triethyl phosphonoacetate (14.1 g, 63.0 mmol) in tetrahydrofuran (60 mL) was treated with potassium tert-butoxide (7.1 g, 63 mmol) at room temperature. After 10 min, a solution of 6-methoxy-2-tetralone (7.4 g, 42 mmol) in tetrahydrofuran (200 mL) was added via cannula. After 2.5 h, additional potassium tert-butoxide (0.9 g, 8 mmol) was added. After 4 h, the reaction mixture was poured into water (1L) and extracted with ethyl acetate (3 x 500 mL). The combined extracts were dried (MgSO₄) and concentrated to give a brown oil (8.6 g). Flash chromatography (330 g silica; 1%, then 2% EtOAc-hexane) gave the title compound (4.4 g, 43% yield) as a pale yellow oil.

¹H NMR (CDCl₃, 300 MHz): δ 1.27 (t, J=7 Hz, 3H, CH₂CH₃), 2.32 (t, J=8 Hz, 2H, CH₂CH₂C=), 2.82 (t, J=8 Hz, 2H, CH₂CH₂C=), 3.18 (s, 2H, ArCH₂C=), 3.78 (s, 3H, OCH₃), 4.16 (q, J=7 Hz, 2H, CO₂CH₂), 6.29 (s, 1H, CH=), 6.66 (overlapping s, d, J=9 Hz, 2H, ArH), 6.93 (d, J=9 Hz, 1H, ArH).

Example 2(7-Methoxy-3,4-dihydro-1H-naphthalen-2-ylidene)-acetic acid ethyl ester

The title compound is prepared according to the procedure of Example 1 except that 7-methoxy-2-tetralone is used in place of 6-methoxy-2-tetralone. The product is obtained as a clear colorless oil.

35

Example 3E- and Z-(2-Methoxy-5,7,8,9-tetrahydro-benzocyclohepten-6-ylidene)-acetic acid ethyl ester and (2-Methoxy-8,9-dihydro-7H-benzocyclohepten-6-yl)-acetic acid ethyl ester

The title compound was prepared according to the procedure of Example 1 except that 2-methoxy-5,7,8,9-

40

5 tetrahydrobenzocyclohepten-6-one (S. Uemura, K. Ohe and N. Sugita, J. Chem. Soc. Perkin Trans. I, 1697, (1990) was used in place of 6-methoxy-2-tetralone.
 ^1H NMR (CDCl_3 , 300 MHz): δ 1.20-1.25 (overlapping m, 3H, total, CH_2CH_3), 1.82 and 2.02 (m, 2H total, ArCH_2CH_2),
10 2.36, 2.44 and 3.07 (t, $J=6.5$ Hz, 3H total, $\text{CH}_2\text{CH}_2\text{C}=\text{}$), 2.75-2.85 (overlapping m, 2H total, ArCH_2CH_2), 3.14, 3.46 and 4.02 (s, 2H total, $\text{ArCH}_2\text{C}=\text{}$, $=\text{CCH}_2\text{CO}_2$), 3.76 and 3.78 (s, 3H total, OCH_3), 4.06-4.20 (overlapping m, 2H total, CO_2CH_2), 5.63, 5.71, and 6.33 (s, 1H total, $\text{CH}=\text{}$), 6.65-6.71
15 (overlapping m, 2H total, ArH), 7.00-7.08, and 7.34 (overlapping m, d, 1H total, ArH).

Example 4

E- and Z-(3-Methoxy-5,7,8,9-tetrahydro-benzocyclohepten-6-ylidene)-acetic acid ethyl ester and (3-Methoxy-8,9-
20 dihydro-7H-benzocyclohepten-6-yl)-acetic acid ethyl ester

The title compound is prepared according to the procedure of Example 1 except that 3-methoxy-5,7,8,9-tetrahydrobenzocyclohepten-6-one (G. Pandey, K.K. Girija and M. Karthikeyan, Tet. Letters 34 (41) 6631 (1993)) is
25 used in place of 6-methoxy-2-tetralone.

Example 5

(6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester

A solution of (6-methoxy-3,4-dihydro-1H-naphthalen-2-ylidene)-acetic acid ethyl ester (4.4 g, 18
30 mmol) in ethyl acetate (35 mL) was hydrogenated over 10% Pd-C (0.9 g) at 50 psi and left overnight. The reaction mixture was filtered through diatomaceous earth and washed with ethyl acetate (200 mL). The filtrate was concentrated
35 to give the title compound (4.0 g, 91% yield) as a clear, colorless oil.

^1H NMR (CDCl_3 , 300 MHz): δ 1.27 (t, $J=7$ Hz, 3H, CH_2CH_3), 1.46 (m, 1H, ArCHHCHH), 1.95 (m, 1H, ArCHHCHH), 2.25 (m, 1H, CH), 2.34-2.47 (overlapping m, d, $J=7$ Hz, 3H, ArCHHCH ,
40 CHHCO_2), 2.79-2.87 (overlapping m, 3H, ArCHHCHH , ArCHHCH), 3.77 (s, 3H, OCH_3), 4.16 (q, $J=7$ Hz, 2H, CO_2CH_2), 6.62 (d,

5 J=2.5 Hz, 1H, ArH), 6.68 (dd, J=2.5 Hz, 8.5 Hz, 1H, ArH),
6.96 (d, J=8.5 Hz, 1H, ArH).

Example 6

10 (7-Methoxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid
ethyl ester

The title compound is prepared according to the
procedure of Example 5 except that (7-methoxy-3,4-dihydro-
napthalen-2-ylidene)-acetic acid ethyl ester is used in
place of (6-methoxy-3,4-dihydro-napthalen-2-ylidene)-acetic
15 acid ethyl ester. The product is obtained as a clear
colorless oil.

Example 7

(2-Methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-
acetic acid ethyl ester

20 The title compound was prepared according to the
procedure of Example 5 except that E- and Z-(2-methoxy-
5,7,8,9-tetrahydro-benzocyclohepten-6-ylidene)-acetic acid
ethyl ester and (2-methoxy-8,9-dihydro-7H-benzocyclo-
hepten-6-yl)-acetic acid ethyl ester is used in place of
25 (6-methoxy-3,4-dihydro-1H-napthalen-2-ylidene)-acetic acid
ethyl ester. ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (t, J=7 Hz,
3H, CH₂CH₃), 1.45-1.63 (m, 2H, CHCH₂CH₂CH₂), 1.74-1.95
(overlapping m, 2H, CHCH₂CH₂CH₂), 2.00-2.27 (overlapping m,
3H, CHCH₂CO₂), 2.73 (m, 4H, ArCH₂), 3.77 (s, 3H, OCH₃),
30 4.14 (q, J=7 Hz, 2H, CO₂CH₂), 6.61 (dd, J=2.5 Hz, 8 Hz, 1H,
ArH), 6.66 (d, J=2.5 Hz, 1H, ArH), 6.97 (d, J=8 Hz, 1H,
ArH).

Example 8

35 (3-Methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-
acetic acid ethyl ester

The title compound is prepared according to the
procedure of Example 5 except that E- and Z-(3-methoxy-
5,7,8,9-tetrahydro-benzocyclohepten-6-ylidene)-acetic acid
ethyl ester and (3-methoxy-8,9-dihydro-7H-benzocyclo-
40 hepten-6-yl)-acetic acid ethyl ester is used in place of
(6-methoxy-3,4-dihydro-1H-napthalen-2-ylidene)-acetic acid

5 ethyl ester.

5

Example 9(6-Hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester

A solution of (6-methoxy-1,2,3,4-tetrahydro-
10 naphthalen-2-yl)-acetic acid ethyl ester (2.0 g, 8.1 mmol)
in methylene chloride (8 mL) was treated with 1.0 M BBr₃-
CH₂Cl₂ solution (40 mL, 40 mmol) at 0°C in an oven-dried
flask. After 1 h, the resulting mixture was concentrated
in vacuo and the residue treated with ice-cold ethanol and
15 concentrated. Ethanol treatment and concentration was
repeated twice more to give a syrup which was partitioned
between saturated sodium bicarbonate and methylene
chloride. The organic layer was separated and dried (MgSO₄)
and concentrated in vacuo to give 1.7g of a brown syrup.
20 Chromatography (60 g silica; 5-20% ethyl acetate-hexane
afforded the title compound (1.1 g) as a pale yellow oil
which slowly crystallized.

¹H NMR (CDCl₃, 300 MHz): δ 1.28 (t, J=7 Hz, 3H, CH₃), 1.44
25 (m, 1H, ArCHHCHH), 1.92 (m, 1H, ArCHHCHH), 2.23 (m, 1H,
CH), 2.35-2.44 (overlapping m, d, J=7 Hz, 3H, ArCHHCH,
CHHCO₂), 2.74-2.84 (overlapping m, 3H, ArCHHCHH, ArCHHCH),
4.17 (q, J=7 Hz, 2H, CO₂CH₂), 4.60-5.40 (broad, 1H, ArOH),
6.55-6.62 (overlapping m, 2H, ArH), 6.90 (d, J=8 Hz, 1H,
30 ArH).

5

Example 10(7-Hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester

The title compound was prepared according to the procedure of Example 9 except that (7-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester was used in place of (6-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester. The crude brown oil was purified by flash chromatography on silica gel by elution with 0.25% methyl alcohol-ammonia/chloroform affording the title compound (1.9 g) as an amber syrup.

Example 11(2-Hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester

The title compound was prepared according to the procedure of Example 9 except that (2-methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester is used in place of (6-methoxy-3,4-dihydro-1H-naphthalen-2-yl)-acetic acid ethyl ester.

^1H NMR (CDCl_3 , 300 MHz): δ 1.26 (t, J=7 Hz, 3H, CH_3), 1.47-1.62 (m, 2H, CHCHHCHH), 1.75-1.95 (overlapping m, 2H, CHCHHCHH), 2.00-2.30 (overlapping m, 3H, CH , CHHCO_2), 2.69 (m, 4H, ArCHH), 4.15 (q, J=7 Hz, 2H, CO_2CH_2), 4.88 (s, 1H, ArOH), 6.54 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.59 (d, J=2.5 Hz, 1H, ArH), 6.89 (d, J=8 Hz, 1H, ArH).

Example 12(3-Hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester

The title compound is prepared according to the procedure of Example 9 except that (3-methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester is used in place of (6-methoxy-3,4-dihydro-1H-naphthalene-2-yl)-acetic acid ethyl ester.

Example 13

(2-Hydroxy-ethyl)-carbamic acid tert-butyl ester

5 A solution of 2-amino-ethan-1-ol (11.8 mL, 195
mmol) in 2:1 tert-butanol-water (330 mL) was treated with
di-tert-butyl dicarbonate (40.8 g, 187 mmol) and potassium
carbonate (51.5 g, 373 mmol) at 0°C. After 5-10 min when
vigorous bubbling had subsided, the reaction slurry was
10 warmed to room temperature. After 1.5 h, the mixture was
concentrated to a wet paste and diluted with water (50 mL).
The aqueous phase was extracted with ethyl acetate (3 x 150
mL), dried (K₂CO₃) and concentrated to give the title
compound (29.4 g, 98% yield) as a pale yellow oil.
15 ¹H NMR (DMSO-d₆, 300 MHz): δ 1.35 (s, 9H, CH₃), 2.96 (m,
2H, NCH₂), 3.34 (m, 2H, OCH₂), 4.55 (m, 1H, OH), 6.66 (m,
1H, NH).

Example 14

20 (3-Hydroxy-propyl)-carbamic acid tert-butyl ester

The title compound is prepared according to the
procedure of Example 13 except that 3-amino-1-propanol is
used in place of 2-amino-ethan-1-ol.

Example 15

25 (4-Hydroxy-butyl)-carbamic acid tert-butyl ester

The title compound is prepared according to the
procedure of Example 13 except that 4-amino-1-butanol is
used in place of 2-amino-ethan-1-ol.

Example 16

30 (2-Bromo-ethyl)-carbamic acid tert-butyl ester

A solution of triphenylphosphine (38.1 g, 145
mmol) in 3:2 ether-methylene chloride (300 mL) was treated
portionwise with carbon tetrabromide (48.2 g, 145 mmol).
After 10 min, (2-hydroxy-ethyl)-carbamic acid tert-butyl
35 ester (15.6 g, 96.8 mmol) was added via pipet and the
mixture stirred under nitrogen. After 24 h, the reaction
mixture was vacuum filtered, washed with ether and the
filtrate concentrated to give an orange oil (39.6 g).
Flash chromatography (600 g silica; CH₂Cl₂, then 1%, 2% and
40 4% MeOH-CH₂Cl₂) gave the title compound (5.1 g, 40% yield

5 based on recovered (2-hydroxy-ethyl)-carbamic acid tert-butyl ester, 6.3 g) as a clear, colorless oil.

^1H NMR (DMSO- d_6 , 300 MHz): δ 1.37 (s, 9H, CH_3), 3.28 (m, 2H, NCH_2), 3.41 (t, $J=6.5$ Hz, 2H, CH_2Br), 7.09 (broad m, 1H, NH).

5

Example 17(3-Bromo-propyl)-carbamic acid tert-butyl ester

The title compound is prepared according to the procedure of Example 16 except that 3-amino-1-propanol is used in place of 2-amino-ethan-1-ol.

10

Example 18(4-Bromo-butyl)-carbamic acid tert-butyl ester

The title compound is prepared according to the procedure of Example 16 except that 4-amino-1-butanol is used in place of 2-amino-ethan-1-ol.

15

Example 19[7-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

A solution of (7-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester (2.5g, 10.7mmol) in N,N-dimethylformamide (16 mL) was treated with a solution of sodium ethoxide (21 wt%) in ethanol (4.0 mL, 10.7 mmol) at 25°C and after 10 min, (3-bromo-propyl)-carbamic acid tert-butyl ester (2.5 g, 10.5 mmol) was added. After 4 days, the solution was treated with 0.1N ammonium chloride (200 mL) and extracted with ether(3 x 200 ml). The combined extracts were washed with 5% sodium bicarbonate (200 ml) followed by water(5 x 200 ml). The organic layer was dried (MgSO₄) and evaporated in vacuo to give 4.0 g of a clear amber oil. Flash chromatography (200 g silica; CH₂Cl₂, then 0.5% MeOH (saturated with NH₃)-CH₂Cl₂) afforded the title compound (2.6 g, 63% yield) as a clear colorless oil.

20

25

30

5

Example 20

[7-(2-tertbutoxycarbonylamino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

10

The title compound is prepared according to the procedure of Example 19 except that (2-bromo-ethyl)-carbamic acid tert-butyl ester is used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester.

15

Example 21

[7-(4-tertbutoxycarbonylamino-butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

20

The title compound is prepared according to the procedure of Example 19 except that (4-bromo-butyl)-carbamic acid tert-butyl ester is used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester.

Example 22

[6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

25

The title compound is prepared according to the procedure of Example 19 except that (6-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester. The product is a clear oil.

30

Example 23

[6-(2-tertbutoxycarbonylamino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

35

The title compound is prepared according to the procedure of Example 19 except that (2-bromo-ethyl)-carbamic acid tert-butyl ester is used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester and (6-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester.

40

5

Example 24

[6-(4-tertbutoxycarbonylamino-butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester

The title compound is prepared according to the
10 procedure of Example 19 except that (4-bromo-butyl)-
carbamic acid tert-butyl ester is used in place of (3-
bromo-propyl)-carbamic acid tert-butyl ester and (6-
hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid
ethyl ester is used in place of (7-hydroxy-1,2,3,4-
15 tetrahydro-napthalen-2-yl)-acetic acid ethyl ester.

Example 25

[6-(3-Amino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate

[6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-
20 tetrahydro-napthalen-2-yl]-acetic acid ethyl ester (1.3 g,
3.3 mmol) and trifluoroacetic acid (2.6 mL) were combined
in methylene chloride (25 mL) at 25°C. After 18 h, the
solution was concentrated in vacuo to give a sticky solid
which is triturated with ether (100 mL) for 45 minutes to
25 give the trifluoroacetate salt of the title compound (1.2g)
as a white powder.

Example 26

[6-(3-Amino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate

30 The title compound is prepared according to the
procedure of Example 25 except that [6-(2-tert-
butoxycarbonylamino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-
yl]-acetic acid ethyl ester is used in place of [6-(3-
tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-
35 napthalen-2-yl]-acetic acid ethyl ester.

Example 27

[6-(4-Amino-butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate

40 The title compound is prepared according to the
procedure of Example 25 except that [6-(4-tertbutoxy-

5 carbonylamino-butoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid ethyl ester is used in place of [6-(3-
tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-
naphthalen-2-yl]-acetic acid ethyl ester.

Example 28

10 [7-(3-Amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-
yl]-acetic acid ethyl ester trifluoroacetate

The title compound is prepared according to the
procedure of Example 25 except that [7-(3-tert-
butoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
15 2-yl]-acetic acid ethyl ester is used in place of [6-(3-
tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-
naphthalen-2-yl]-acetic acid ethyl ester.

Example 29

20 [7-(2-Amino-ethoxy)-1,2,3,4-tetrahydro-naphthalen-2-
yl]-acetic acid ethyl ester trifluoroacetate

The title compound is prepared according to the
procedure of Example 25 except that [7-(2-tertbutoxy-
carbonylamino-ethoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid ethyl ester is used in place of [6-(3-
25 tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-
naphthalen-2-yl]-acetic acid ethyl ester.

Example 30

[7-(4-Amino-butoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid ethyl ester trifluoroacetate

30 The title compound is prepared according to the
procedure of Example 25 except that [7-(4-tertbutoxy-
carbonylamino-butoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid ethyl ester is used in place of [6-(3-
tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-
35 naphthalen-2-yl]-acetic acid ethyl ester.

Example 31

[6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-naphthalen-
2-yl]-acetic acid ethyl ester

40 A suspension of [6-(3-amino-propoxy)-1,2,3,4-
tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester
trifluoroacetate salt(1.21 g, 2.98 mmol), 3,5-di-

5 methylpyrazole carboxamide nitrate (0.66 g, 3.28 mmol)
and diisopropylethylamine (1.1 mL, 6.31 mmol) in 3:1
dioxane-water (8.5 mL) was heated at reflux for 24 h. The
cooled solution was concentrated in vacuo to yield 2.21 g
of a viscous oil. Purification by reverse phase HPLC by
10 elution with 5-50%-acetonitrile:0.1% trifluoroacetic acid
in water afforded the title compound (0.91 g, 68%) as a
clear, colorless oil.

Example 32

[6-(2-Guanidino-ethoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
15 acetic acid ethyl ester

The title compound is prepared according to the
procedure of Example 31 except that [6-(2-amino-ethoxy)-
1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester
trifluoroacetate salt is used in place of [6-(3-amino-
20 propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid
ethyl ester trifluoroacetate salt.

Example 33

[6-(4-Guanidino-butoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
25 acetic acid ethyl ester

The title compound is prepared according to the
procedure of Example 31 except that [6-(4-amino-butoxy)-
1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester
trifluoroacetate salt is used in place of [6-(3-amino-
30 propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid
ethyl ester trifluoroacetate salt.

Example 34

[7-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-naphthalen-
35 2-yl]-acetic acid ethyl ester

The title compound is prepared according to the
procedure of Example 31 except that [7-(3-amino-propoxy)-
1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester
trifluoroacetate salt is used in place of [6-(3-amino-
40 propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid
ethyl ester trifluoroacetate salt.

Example 35

5 [7-(2-Guanidino-ethoxy)-1,2,3,4-tetrahydro-naphthalen-
 2-yl]-acetic acid ethyl ester

The title compound is prepared according to the procedure of Example 31 except that [7-(2-amino-ethoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate salt is used in place of [6-(3-amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate salt.

Example 36

15 [7-(4-Guanidino-butoxy)-1,2,3,4-tetrahydro-naphthalen-
 2-yl]-acetic acid ethyl ester

The title compound is prepared according to the procedure of Example 31 except that [7-(4-amino-butoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate salt is used in place of [6-(3-amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate salt.

Example 37

25 [6-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
 2-yl]-acetic acid trifluoroacetate

A solution of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester (0.88 g, 1.97 mmol) in 8 ml of ethyl alcohol was treated with 8.0 ml (4.0 mmol) of 0.5 N sodium hydroxide and refluxed for 30 minutes. The cooled solution was treated with 1.5 ml of trifluoroacetic acid and evaporated in vacuo. The resulting oil was dissolved in 100 ml of ethyl alcohol and concentrated in vacuo to give 1.49 g of a colorless glass which was dissolved in 5 ml of 1:1 N,N-dimethylformamide:water and chromatographed on a C₁₈ reverse phase column to give 0.68 g of the title compound as the trifluoroacetate salt as a white powder.

Mp. 134-36 °C.

IR (KBr): 3440 (s), 3230 (m), 1708 (s), 1665 (s), 1640 (s), 1440 (m), 1190 (s), 1143 (s), 848 (m), 800 (m), 730 (m) cm⁻¹.

5 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.36 (m, 1H, ArCHHCHH), 1.84-
1.92 (overlapping m, 3H, ArCHHCHH, NCH₂CH₂), 2.04 (m, 1H,
CH), 2.25 (d, J=7 Hz, 2H, CHHCO₂), 2.32 (dd, J=10 Hz, 16
Hz, 1H, ArCHHCH), 2.71-2.78 (overlapping m, 3H, ArCHHCHH,
ArCHHCH), 3.25 (m, 2H, NCH₂), 3.94 (t, J=6 Hz, 2H, OCH₂),
10 6.63 (d, J=2 Hz, 1H, ArH), 6.66 (dd, J=2 Hz, 8.5 Hz, 1H,
ArH), 6.70-7.50 (broad, 4H, [C(NH₂)₂]⁺), 6.94 (d, J=8.5 Hz,
1H, ArH), 7.57 (t, J=6 Hz, 1H, NHCH₂), 12.1 (s, 1H, CO₂H).
MS (-FAB) m/e (rel. intensity): 304 (M-H, 17).
Analysis calc. for C₁₆H₂₃N₃O₃•CF₃COOH: C, 51.55; H, 5.77;
15 N, 10.03;
Found: C, 51.60; H, 5.75; N, 9.98

Example 38

[6-(2-Guanidino-ethoxy)-1,2,3,4-tetrahydro-napthalen-
2-yl]-acetic acid trifluoroacetate

20 The title compound is prepared according to the
procedure of Example 37 except that [6-(2-guanidino-
ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid
ethyl ester is used in place of [6-(3-guanidino-propoxy)-
1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester.

25 Example 39

[6-(4-Guanidino-butoxy)-1,2,3,4-tetrahydro-napthalen-
2-yl]-acetic acid trifluoroacetate

30 The title compound is prepared according to the
procedure of Example 37 except that [6-(4-guanidino-
butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid
ethyl ester is used in place of [6-(3-guanidino-propoxy)-
1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester.

Example 40

[7-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-
35 yll]-acetic acid trifluoroacetate

The title compound was prepared according to the
procedure of Example 37 except that [7-(3-guanidino-
propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid
ethyl ester was used in place of [6-(3-guanidino-propoxy)-
40 1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester.

- 5 Mp. 148-50 °C.
IR (KBr): 3410 (s), 3210 (s), 1695 (s), 1660 (s), 1630 (s), 1426 (m), 1248 (s), 1180 (s), 1135 (s), 838 (m), 815 (m), 795 (m), 720 (m) cm⁻¹.
¹H NMR (DMSO-d₆, 400 MHz): δ 1.36 (m, 1H, ArCHHCHH), 1.84-
10 1.92 (overlapping m, 3H, ArCHHCHH, NCH₂CH₂), 2.05 (m, 1H, CH), 2.26 (d, J=7 Hz, 2H, CHHCO₂), 2.39 (dd, J=10 Hz, 16.5 Hz, 1H, ArCHHCH), 2.68 (m, 2H, ArCHHCHH), 2.79 (dd, J=5 Hz, 16.5 Hz, 1H, ArCHHCH), 3.25 (m, 2H, NCH₂), 3.94 (t, J=6 Hz, 2H, OCH₂), 6.61 (d, J=2.5 Hz, 1H, ArH), 6.67 (dd, J=2.5 Hz,
15 8 Hz, 1H, ArH), 6.70-7.50 (broad, 4H, [C(NH₂)₂]⁺), 6.96 (d, J=8 Hz, 1H, ArH), 7.58 (t, J=5 Hz, 1H, NHCH₂), 12.1 (s, 1H, CO₂H).
MS (+FAB) m/e (rel. intensity): 306 (M+H, 40).
Analysis calc. for C₁₆H₂₃N₃O₃•CF₃COOH: C, 51.55; H, 5.77;
20 N, 10.02;
Found: C, 51.57; H, 5.72; N, 10.03

Example 41

- 25 [7-(2-Guanidino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-
acetic acid trifluoroacetate

- The title compound is prepared according to the procedure of Example 37 except that [7-(2-guanidino-ethoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester is used in place of [6-(3-guanidino-propoxy)-
30 1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester.

Example 42

- [7-(4-Guanidino-butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-
acetic acid trifluoroacetate

- 35 The title compound is prepared according to the procedure of Example 37 except that [7-(4-guanidino-butoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester is used in place of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester.

Example 43

5 [2-(2-tert-Butoxycarbonylamino-ethoxy)-6,7,8,9-
tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl
 ester

The title compound was prepared according to the
procedure of Example 19 except that (2-bromo-ethyl)-
10 carbamic acid tert-butyl ester was used in place of (3-
bromo-propyl)-carbamic acid tert-butyl ester and (2-
hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic
acid ethyl ester was used in place of (7-hydroxy-1,2,3,4-
tetrahydro-napthalen-2-yl)-acetic acid ethyl ester and the
15 title compound was isolated as a pale yellow oil.

5

Example 44

[2-(3-tert-Butoxycarbonylamino-propoxy)-6,7,8,9-
tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl
10 ester

The title compound was prepared according to the procedure of Example 19 except that (2-hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-1H-
15 naphthalen-2-yl)-acetic acid ethyl ester and the title compound was isolated as a clear yellow oil.

Example 45

[2-(4-tert-Butoxycarbonylamino-butoxy)-6,7,8,9-
tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl
20 ester

The title compound was prepared according to the procedure of Example 19 except that (4-bromo-butyl)-carbamic acid tert-butyl ester was used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester and (2-
25 hydroxy-6,7,8,9-tetrahydro-5H-benzo-cyclohepten-6-yl)-acetic acid ethyl ester was used in place of (7-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid ethyl ester. The title compound was isolated as a clear yellow oil.

Example 46

[3-(2-tert-Butoxycarbonylamino-ethoxy)-6,7,8,9-
tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl
30 ester

The title compound is prepared according to the procedure of Example 19 except that (2-bromo-ethyl)-carbamic acid tert-butyl ester is used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester and (3-hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-naphthalene-2-yl)-acetic acid ethyl ester.
35
40

5

Example 47

[3-(3-tert-Butoxycarbonylamino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester

10

The title compound is prepared according to the procedure of Example 19 except that (3-hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-napthalene-2-yl)-acetic acid ethyl ester.

15

Example 48

[3-(4-tert-Butoxycarbonylamino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester

20

The title compound is prepared according to the procedure of Example 19 except that (4-bromo-butyl)-carbamic acid tert-butyl ester is used in place of (3-bromo-propyl)-carbamic acid tert-butyl ester and (3-hydroxy-6,7,8,9-tetrahydro-5H-benzo-cyclohepten-6-yl)-acetic acid ethyl ester is used in place of (7-hydroxy-1,2,3,4-tetrahydro-napthalen-2-yl)-acetic acid ethyl ester.

25

Example 49

[2-(2-Amino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate

30

The title compound is prepared according to the procedure of Example 25 except that [2-(2-tert-butoxycarbonylamino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

35

5

Example 50

[2-(3-Amino-propoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
trifluoroacetate

10

The title compound is prepared according to the procedure of Example 25 except that [2-(3-tert-butoxycarbonylamino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-

15

tetrahydro-naphtalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

Example 51

[2-(4-Amino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-
6-yl]-acetic acid ethyl ester trifluoroacetate

20

The title compound is prepared according to the procedure of Example 25 except that [2-(4-tert-butoxycarbonylamino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-

25

tetrahydro-naphtalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

Example 52

[3-(2-Amino-ethoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
trifluoroacetate

30

The title compound is prepared according to the procedure of Example 25 except that [3-(2-tert-butoxycarbonylamino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-

35

tetrahydro-naphtalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

40

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Example 53

[3-(3-Amino-propoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
10 trifluoroacetate

The title compound is prepared according to the procedure of Example 25 except that [3-(3-tert-butoxycarbonylamino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in
15 place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

Example 54

[3-(4-Amino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-
20 6-yl]-acetic acid ethyl ester trifluoroacetate

The title compound is prepared according to the procedure of Example 25 except that [3-(4-tert-butoxycarbonylamino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester is used in
25 place of [6-(3-tertbutoxycarbonylamino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester and the title compound is isolated as the trifluoroacetate salt.

Example 55

[2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-
30 benzocyclohepten-6-yl]-acetic acid ethyl ester
trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [2-(2-Amino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-amino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.
35

5

Example 56

[2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
10 trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [2-(3-amino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-
15 amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.

Example 57

[2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
20 trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [2-(4-amino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-
25 amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.

Example 58

[3-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester.
30 trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [3-(2-amino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-
35 amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.

40

5

Example 59

[3-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
10 trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [3-(3-amino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-
15 amino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.

Example 60

[3-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid ethyl ester
20 trifluoroacetate

The title compound is prepared according to the procedure of Example 31 except that [3-(4-amino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate is used in place of [6-(3-
25 amino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate.

Example 61

[2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid hydrochloride

30 The title compound was prepared according to the procedure of Example 37 except that [2-(2-guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate was used in place of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-
35 acetic acid ethyl ester trifluoroacetate. The title compound was isolated as the hydrochloride salt.

IR (KBr): 3400 (s), 3150 (s), 1695 (s), 1650 (s), 1265 (m), 1251 (m), 1175 (m), 800 (w), 720 (w) cm⁻¹.

40 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.37 (m, 1H, CHCH₂HCHH), 1.51 (m, 1H, CHCH₂HCHH), 1.72 (m, 1H, CH), 1.85 (m, 2H,

5 CHCHHCHH), 2.04 (dd, J=7 Hz, 15.5 Hz, 1H, CHHCO₂), 2.13
(dd, J=7 Hz, 15.5 Hz, 1H, CHHCO₂), 2.61-2.72 (overlapping
m, 4H, ArCHH), 3.49 (m, 2H, NCH₂), 4.00 (t, J=5 Hz, 2H,
OCH₂), 6.63 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.70 (d, J=2.5
Hz, 1H, ArH), 6.94 (d, J=8 Hz, 1H, ArH), 6.97-7.66 (broad,
10 4H, [C(NH₂)₂⁺]), 7.75 (t, J=5.5 Hz, 1H, NHCH₂), 11.8-12.4
(broad, 1H, CO₂H).

MS (-FAB) m/e (rel. intensity): 306 (M-H, 100).

Analysis calc. for C₁₆H₂₃N₃O₃•HCl•H₂O: C, 53.40; H, 7.28;
N, 11.68;

15 Found: C, 53.38; H, 6.84; N, 11.32.

Example 62

[2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H- benzocyclohepten-6-yl]-acetic acid trifluoroacetate

The title compound was prepared according to the
20 procedure of Example 37 except that [2-(3-guanidino-
propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-
acetic acid ethyl ester trifluoroacetate was used in place
of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
2-yl]-acetic acid ethyl ester trifluoroacetate. The title
25 compound was isolated as the trifluoroacetate.

Mp. 109-14 °C.

IR (KBr): 3465 (s), 3370 (s), 3200 (m), 1715 (s), 1680
(s), 1615 (s), 1249 (m), 1195 (s), 1130 (s), 820 (w), 720
30 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.37 (m, 1H, CHCHHCHH), 1.51
(m, 1H, CHCHHCHH), 1.72 (m, 1H, CH), 1.83-1.92 (overlapping
m, 4H, CHCHHCHH, NCH₂CH₂), 2.04 (dd, J=7 Hz, 15.5 Hz, 1H,
CHHCO₂), 2.13 (dd, J=7 Hz, 15.5 Hz, 1H, CHHCO₂), 2.60-2.72
35 (overlapping m, 4H, ArCHH), 3.25 (m, 2H, NCH₂), 3.94 (t,
J=6 Hz, 2H, OCH₂), 6.62 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.68
(d, J=2.5 Hz, 1H, ArH), 6.75-7.55 (broad, 4H, [C(NH₂)₂⁺]),
6.92 (d, J=8 Hz, 1H, ArH), 7.65 (t, J=5 Hz, 1H, NHCH₂),
12.0 (s, 1H, CO₂H).

40 MS (+FAB) m/e (rel. intensity): 320 (M+H, 100).

- 5 Analysis calc. for $C_{17}H_{25}N_3O_3 \cdot CF_3COOH$: C, 52.65; H, 6.05;
N, 9.70;
Found: C, 52.59; H, 6.05; N, 9.61.

10

Example 63

[2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate

- 15 The title compound was prepared according to the procedure of Example 37 except that [2-(4-guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid ethyl ester trifluoroacetate was used in place of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester trifluoroacetate. The title
20 compound was isolated as the trifluoroacetate salt as a white solid.

Mp. Shrinks from 72-89 °C, then melts from 89-96 °C.

- IR (KBr): 3400 (s), 3180 (s), 1699 (s), 1630 (s), 1251
25 (m), 1201 (s), 1130 (s), 840 (m), 799 (m), 725 (m) cm^{-1} .
 1H NMR (DMSO- d_6 , 400 MHz): δ 1.37 (m, 1H, CHCHHCHH), 1.47-1.76 (overlapping m, 6H, NCH₂CH₂CH₂, CHCHHCHH), 1.84 (m, 2H, CHCHHCHH), 2.04 (dd, J=7 Hz, 15.5 Hz, 1H, CHHCO₂), 2.13 (dd, J=7 Hz, 15.5 Hz, 1H, CHHCO₂), 2.59-2.71 (overlapping
30 m, 4H, ArCHHCH, ArCHHCHH), 3.25 (m, 2H, NCH₂), 3.92 (t, J=6 Hz, 2H, OCH₂), 6.60 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.66 (d, J=2.5 Hz, 1H, ArH), 6.70-7.50 (broad, 4H, [C(NH₂)₂⁺]), 6.91 (d, J=8 Hz, 1H, ArH), 7.59 (t, J=5 Hz, 1H, NHCH₂), 12.0 (s, 1H, CO₂H).

- 35 MS (+FAB) m/e (rel. intensity): 334 (M+H, 100).
Analysis calc. for $C_{18}H_{27}N_3O_3 \cdot CF_3COOH$: C, 53.69; H, 6.31;
N, 9.39;
Found: C, 53.54; H, 6.31; N, 9.89; 10.03.

Example 64

- 40 [3-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid hydrochloride

5 The title compound is prepared according to the
procedure of Example 37 except that [3-(2-guanidino-
ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic
acid ethyl ester trifluoroacetate is used in place of [6-
10 (3-guanidino-propoxy)-1,2,3,4-tetrahydronaphthalen-2-yl]-
acetic acid ethyl ester trifluoroacetate. The title
compound is isolated as the hydrochloride salt.

5

Example 65[3-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate

The title compound is prepared according to the
10 procedure of Example 37 except that [3-(3-guanidino-
propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-
acetic acid ethyl ester trifluoroacetate is used in place
of [6-(3-guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
2-yl]-acetic acid ethyl ester trifluoroacetate. The title
15 compound is isolated as the trifluoroacetate salt.

Example 66[3-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate

The title compound is prepared according to the
20 procedure of Example 37 except that [3-(4-guanidino-
butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic
acid ethyl ester trifluoroacetate is used in place of [6-
(3-guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid ethyl ester trifluoroacetate. The title
25 compound is isolated as the trifluoroacetate salt as a
white solid.

Example 672-(5-Hydroxy-2-nitro-benzylidene)-succinic acid diethyl
ester

30 Triphenylphosphine (12.2 g, 46.5 mmol) and diethyl
maleate (8.0 g, 46.5 mmol) were combined in glacial acetic
acid (7 mL) at 25°C and the slurry was stirred for 6.5 h
and the resulting solution was treated with 5-hydroxy-2-
nitrobenzaldehyde (5.2 g, 31.1 mmol). Benzene (250 mL) was
35 added and the solution heated to reflux. After 18 h, the
solution was concentrated in vacuo to give a clear orange
oil (27.6 g). Flash chromatography (700 g silica; 5%, then
10%, then 20%, then 40% EtOAc-hexane) gives the title
compound (6.9 g; 69% yield) as a pale yellow solid.
40 ¹H NMR: (DMSO-d₆, 300 MHz): δ 1.15 (t, J=7.5 Hz, 3H, CH₃),
1.22 (t, J=7.5 Hz, 3H, CH₃), 3.25 (s, 2H, CH₂CO₂), 4.05 (q,

5 J=7.5 Hz, 2H, CO₂CH₂), 4.20 (q, J=7.5 Hz, 2H, CO₂CH₂), 6.70
(s, 1H, ArH), 6.95 (d, J=9 Hz, 1H, ArH), 7.99 (s, 1H, CH=),
8.13 (d, J=9 Hz, 1H, ArH), 11.2 (s, 1H, ArOH).

Example 68

10 2-(4-Hydroxy-2-nitro-benzylidene)-succinic acid diethyl
ester

The title compound is prepared according to the
procedure of Example 67 except that 4-hydroxy-2-
nitrobenzaldehyde is used in place of 5-hydroxy-2-
nitrobenzaldehyde.

15 Example 69

(6-Hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic
acid ethyl ester

A solution of 2-(5-hydroxy-2-nitro-benzylidene)-
succinic acid diethyl ester (3.8 g, 12 mmol) in ethanol (35
20 mL) was hydrogenated over 10% Pd-C (0.8 g) at 25°C and 1
atm. After 20 h, the catalyst was filtered through
diatomaceous earth and washed with ethanol (3 x 35 mL).
The filtrate was concentrated giving a mixture of solid and
foam (2.8 g). Flash chromatography (190 g silica; 20%,
25 then 40% EtOAc-hexane) gives the title compound (1.3 g, 45%
yield) as a pale yellow solid.

¹H NMR: (DMSO-d₆, 300 MHz): δ 1.18 (t, J=7.5 Hz, 3H, CH₃),
2.15-2.80 (overlapping m, 5H, ArCHH, CHCHH), 4.05 (q, J=7.5
Hz, 2H, CO₂CH₂), 6.53 (overlapping s, d, 2H, ArH), 6.66 (d,
30 J=9 Hz, 1H, ArH), 9.03 (s, 1H, ArOH), 9.95 (s, 1H, ArNH).

Example 70

(7-Hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic
acid ethyl ester

35 The title compound is prepared according to the
procedure of Example 69 except that 2-(4-hydroxy-2-nitro-
benzylidene)-succinic acid diethyl ester is used in place
of 2-(5-hydroxy-2-nitro-benzylidene)-succinic acid diethyl
ester.

40

5

Example 71(7-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid
methyl ester

10

A suspension of 3-(2-chloro-7-methoxy-quinolin-3-yl)-acetic acid methyl ester prepared from the 7-methoxy-2-chloro-3-formylquinoline (O. Meth-Cohn et al, Tetrahedron Letters, 33, 3111-3114 (1979) and O. Meth-Cohn et al, J.Chem.Soc. Perkin I, 1520-1530 (1981)) 30.4 g (114 mmol) was refluxed with 12N aqueous hydrochloric acid for 12 hours forming a solution. The mixture was cooled to 0-5°C for 2 hours and filtered. The filter cake was washed with cold methyl alcohol and air dried to give the title compound (25.6 g, 90% yield).

20

Mp. 195.0-96.5 °C.

¹H NMR (DMSO-d₆, 300 MHz): δ 3.49 (s, 2H, CH₂), 3.59 (s, 3H, CO₂CH₃), 3.79 (s, 3H, OCH₃), 6.77-6.81 (overlapping m, 2H, ArH), 7.53 (d, J=9 Hz, 1H, ArH), 7.76 (s, 1H, ArCH=), 11.7 (s, 1H, ArNH).

25

Example 72(7-Methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester

A solution of (7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester (8.2 g, 33.2 mmol) in 450 ml of acetic acid in the presence of 8.2 g of 10% Pd/C was hydrogenated at 50 psi of hydrogen for 2.5 days. The mixture was filtered through diatomaceous earth and the filter cake washed with hot acetic acid (2 x 200 ml). The filtrate was evaporated in vacuo to give 8.4 g of a tan solid which was crystallized from methyl alcohol (250 ml) to afford 5.4 g of the title compound as off-white crystals after washing with ice-cold methyl alcohol, ether and hexane, mp 152-155°C.

40

¹H NMR (DMSO-d₆, 300 MHz): δ 2.44 (m, 1H, ArCHH), 2.68-2.87 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.59 (s, 3H,

5 CO₂CH₃), 3.68 (s, 3H, OCH₃), 6.44 (d, J=2.5 Hz, 1H, ArH),
6.49 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 7.05 (d, J=8 Hz, 1H,
ArH), 10.1 (s, 1H, ArNH).

5

Example 73(7-Hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester

A suspension of (7-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester (5.4 g, 21.7 mmol) in 50 ml of methylene chloride at 0°C was treated with 1.0 M BBr₃-CH₂Cl₂ (200 ml, 200 mmol) under inert gas for 1 hour. The reaction mixture was allowed to warm to room temperature over an additional 2 hours. The volatiles were evaporated in vacuo to a brown oil which was treated with ice-cold methyl alcohol (400 ml x 2) and evaporated after each treatment to a residue. The residue was refluxed with 5 ml of 12 N HCl and 100 ml of methyl alcohol for 2 hours and evaporated to a residue which was crystallized from methyl alcohol (25 ml) to give the title compound, (3.9 g) as fluffy tan needles, mp 178-179.5°C.

¹H NMR (DMSO-d₆, 300 MHz): δ 2.43 (m, 1H, ArCH_H), 2.59-2.81 (overlapping m, 4H, ArCH_H, CH, CH_HCO₂), 3.59 (s, 3H, CH₃), 6.28-6.33 (overlapping m, 2H, ArH), 6.90 (d, J=8 Hz, 1H, ArH), 9.27 (s, 1H, ArOH), 10.0 (s, 1H, ArNH).

25

Example 74(7-Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester

Treatment of (7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester with boron tribromide in dichloromethane using the conditions of Example 73 gives the title compound (3.5 g, 58% yield).

Mp. 221-23 °C (dec).

¹H NMR (DMSO-d₆, 300 MHz): δ 3.46 (s, 2H, CH₂), 3.58 (s 3H, CH₃), 6.62 (dd, J=2 Hz, 8.5 Hz, 1H, ArH), 6.69 (d, J=2 Hz, 1H, ArH), 7.42 (d, J=8.5 Hz, 1H, ArH), 7.70 (s, 1H, ArCH=), 10.1 (broad s, 1H, ArOH), 11.6 (s, 1H, ArNH).

40

5

Example 75[7-(2-tert-Butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

10 A solution of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester (2.6 g, 11.1 mmol) in N,N-dimethylformamide (20 mL) was treated with a solution of sodium ethoxide (25 wt%) in methanol (2.5 mL, 10.9 mmol) at 25°C and after 10 min, (2-bromoethyl)-
15 carbamic acid tert-butyl ester (2.5 g, 11.2 mmol) was added. After 3 days, the solution was treated with water (100 mL) and the resulting gum was briskly stirred at 0°C. The precipitated solid was filtered and dried to give crude product (2.9 g). Flash chromatography (90 g silica; CHCl₃,
20 then 1% MeOH (saturated with NH₃)-CHCl₃) gives the title compound (2.0 g) as a white solid.

Example 76[7-(4-tert-Butoxycarbonylamino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

25 The title compound is prepared according to the procedure of Example 75 except that (4-bromobutyl)-carbamic acid tert-butyl ester is used in place of (2-bromoethyl)-carbamic acid tert-butyl ester.

30

Example 77[7-(3-tert-Butoxycarbonylamino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

The title compound is prepared according to the procedure of Example 75 except that (3-bromopropyl)-
35 carbamic acid tert-butyl ester is used in place of (2-bromoethyl)-carbamic acid tert-butyl ester.

Example 78[7-(2-Amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

40 [7-(2-tert-Butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester (2.5 g,

- 5 6.6 mmol) and trifluoroacetic acid (5.1 mL, 66 mmol) were combined in methylene chloride (25 mL) at 25°C. After 18 h, the solution was concentrated in vacuo to give the title compound as a tan solid (2.6 g).

5

Example 79[7-(4-amino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

The title compound is prepared according to the procedure of Example 78 except that [7-(4-tert-butoxycarbonylamino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is used in place of [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester.

15

Example 80[7-(3-amino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

The title compound is prepared according to the procedure of Example 78 except that [7-(3-tert-butoxycarbonylamino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is used in place of [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester.

25

Example 81[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

A suspension of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate (1.49 g, 3.8 mmol), 3,5-dimethylpyrazole carboxamide nitrate (0.84 g, 4.18 mmol) and diisopropylethylamine (1.45 mL, 8.32 mmol) in 3:1 dioxane-water (11 mL) were heated at reflux for 22 h. The cooled solution was concentrated in vacuo to yield a viscous yellow syrup. Washing the syrup with ice-cold water (3x5ml) gives the title compound as a dried white solid (1.04 g).

35

Example 82[7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate

The title compound is prepared according to the procedure of Example 81 except that [7-(2-amino-ethoxy)-2-

40

5 oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [7-(4-amino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

Example 83

10 [7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate

The title compound is prepared according to the procedure of Example 81 except that [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [7-(3-amino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

Example 84

20 [7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

A solution of [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate (0.75 g, 1.6 mmol) in methanol (7 mL) was treated with 0.5 N aqueous NaOH (7.1 ml, 3.6 mmol) and heated at reflux for 1.5 h. The cooled solution was treated with trifluoroacetic acid (2.0 mL x 5) and the solution thus formed concentrated in vacuo to give 1.5 g of a clear colorless oil. The oil was dissolved in 1:1 water:N,N-dimethylformamide and purified by reverse phase HPLC giving the title compound (0.57g) as a white fluffy solid.

Mp. 189-91°C.

IR (KBr): 3435 (m), 3350 (m), 3170 (m), 1695 (s), 1660 (s), 1197 (s), 1180 (s), 1122 (m), 832 (m), 788 (m), 712 (m) cm⁻¹.
1H NMR (DMSO-d₆, 400 MHz): δ 1.60 (m, 2H, NCH₂CH₂), 1.71 (m, 2H, OCH₂CH₂), 2.34 (m, 1H, ArCHH), 2.65-2.87 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.15 (m, 2H, NCH₂), 3.91 (t, J=6 Hz, 2H, OCH₂), 6.42 (d, J=2.5 Hz, 1H, ArH), 6.49 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.60-7.50 (broad, 4H [C(NH₂)₂]⁺), 7.05 (d, J=8 Hz, 1H,

5 ArH), 7.59 (t, J=5.5 Hz, 1H, NHCH₂), 10.1 (s, 1H, ArNH), 12.2 (s, 1H, CO₂H).

MS (+DCI) m/e (rel. intensity): 335 (M+H, 21).

Analysis calc. for C₁₆H₂₂N₄O₄•CF₃COOH C, 48.21; H, 5.17; N, 12.50

10 Found C, 48.17; H, 4.97; N, 12.47

Example 85

[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride

The product of the example was obtained using the
15 conditions of Example 84 and [7-(2-guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate. Following reverse phase chromatography the crude mixture was dissolved in 5 ml of 0.5 N sodium hydroxide, warmed slightly to effect solution and cooled at
20 0°C. The resulting solid was collected by filtration, dissolved in 4 ml of water and treated with 12 N hydrochloric acid, warmed to effect a solution, cooled to 0°C and the resulting solid collected and dried giving a white solid, as the hydrochloride salt.

25 IR (KBr): 3430 (s), 3350 (s), 3162 (s), 1730 (s), 1665 (s), 1615 (s), 1445 (m), 1400 (m), 1278 (s), 1228 (m), 1160 (s), 1132 (s), 850 (m), 815 (m), 805 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 2.34 (m, 1H, ArCHH), 2.66-2.87 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.55 (m, 2H, NCH₂), 3.97
30 (t, J=5 Hz, 2H, OCH₂), 6.46 (d, J=2.5 Hz, 1H, ArH), 6.51 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.80-7.50 (broad, 4H, [C(NH₂)₂]⁺), 7.07 (d, J=8 Hz, 1H, ArH), 7.80 (t, J=5.5 Hz, 1H, NHCH₂), 10.1 (s, 1H, ArNH), 12.2 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 307 (M+H, 11).

35 Analysis calc. for C₁₄H₁₈N₄O₄•HCl•H₂O C, 46.61; H, 5.86; N, 15.53

Found C, 46.80; H, 5.70; N, 15.53

Example 86

40 [7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride

- 5 Using the conditions of Example 85 and [7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate the product of the example was obtained and isolated as the hydrochloride salt.
- 10 Mp. 227-29°C.
IR (KBr): 3438 (s), 3360 (s), 3190 (m), 1715 (s), 1673 (s), 1662 (s), 1618 (s), 1470 (m), 1404 (m), 1262 (m), 1232 (s), 1188 (s), 1156 (s), 834 (m), 810 (w), 798 (w) cm^{-1} .
 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.90 (m, 2H, NCH_2CH_2), 2.34 (m, 1H, ArCHH), 2.66-2.87 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.25 (m, 2H, NCH_2), 3.95 (t, J=6 Hz, 2H, OCH₂), 6.45 (d, J=2.5 Hz, 1H, ArH), 6.50 (dd, J=2.5 Hz, 8Hz, 1H, ArH), 6.70-7.50 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.06 (d, J=8Hz, 1H, ArH), 7.79 (t, J=5.5 Hz, 1H, NHCH₂), 10.1 (s, 1H, ArNH), 12.2 (broad s, 1H, CO₂H).
- 20 MS (+FAB) m/e (rel. intensity): 321 (M+H, 100).
Analysis calc. for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_4 \cdot \text{HCl}$ C, 50.49; H, 5.93; N, 15.70
Found C, 50.35; H, 5.85; N, 15.96

Example 87

- 25 [2-Oxo-7-(trifluoro-methanesulfonyloxy)-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester
- A solution of (7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester (5.5 g, 23 mmol) and triethylamine (16.3 mL, 117 mmol) in 1,4-dioxane (200 mL) was cooled to 0°C and the resulting slurry treated dropwise with trifluoromethanesulfonic anhydride (7.9 mL, 47 mmol). The reaction mixture was warmed to 25°C and after 1.5 h was concentrated in vacuo to an oily residue. The oily residue was taken up in methylene chloride (600 mL) and washed successively with water, 5% aqueous NaHCO_3 and brine (300 mL each). The organic phase was dried (MgSO_4) and concentrated to give a dark brown solid. Flash chromatography (220 g silica; 20%, then 40% EtOAc-hexane) gives the title compound (6.7 g, 78% yield) as a fluffy, pale yellow solid.
- 40

5 ^1H NMR (CDCl_3 , 300 MHz): δ 2.54 (dd, $J=7$ Hz, 17 Hz, 1H, ArCHH), 2.87-3.15 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.74 (s, 3H, CH₃), 6.74 (d, $J=2.5$ Hz, 1H, ArH), 6.91 (dd, $J=2.5$ Hz, 8 Hz, 1H, ArH), 7.23 (d, $J=8$ Hz, 1H, ArH), 8.78 (s, 1H, ArNH).

10

Example 88

15 N-But-3-ynyl-imidodicarbonic acid di-tert-butyl ester

A solution of di-tert-butyliminodicarboxylate (17.4 g, 80.1 mmol) and triphenylphosphine (21.0 g, 80.1 mmol) in tetrahydrofuran (100 mL) was treated dropwise simultaneously with 3-butyn-1-ol (6.0 mL, 79 mmol) and diethylazodicarboxylate (12.6 mL, 80.0 mmol) during 5-10 min. The solution was heated to reflux for 24 h, cooled to room temperature and concentrated in vacuo to give a yellow oil (57.4 g, incomplete reaction). Flash chromatography (500 g silica; 0.5%, then 1%, then 2%, then 4% EtOAc-
20 hexane) gave the title compound (5.3 g, 25% yield based on starting 3-butyn-1-ol) as a white solid.

25 ^1H NMR (CDCl_3 , 300 MHz): δ 1.49 (s, 18 H, CH₃), 1.93 (t, $J=3$ Hz, 1H, $\equiv\text{CH}$), 2.46 (td, $J=3$ Hz, 7 Hz, 2H, NCH₂CH₂), 3.75 (t, $J=7$ Hz, 2H, NCH₂).

Example 89

30 N-Pent-4-ynylimidodicarbonic acid di-tert-butyl ester

Using the conditions of Example 88 and replacing 3-butyn-1-ol with 4-pentyn-1-ol the product of the example was obtained.

35 ^1H NMR (CDCl_3 , 300 MHz): δ 1.49 (s, 18 H, CH₃), 1.79 (m, 2H, NCH₂CH₂), 1.94 (t, $J=3$ Hz, 1H, $\equiv\text{CH}$), 2.20 (td, $J=3$ Hz, 7 Hz, 2H, $\equiv\text{CCH}_2$), 3.65 (t, $J=7$ Hz, 2H, NCH₂).

Example 90

5 N-Hex-5-ynylimidodicarbonic acid di-tert-butyl ester

Using the conditions of Example 88 and replacing 3-butyn-1-ol with 5-hexyn-1-ol the product of the example is obtained.

Example 9110 (7-{4-[Bis-(tert-butoxycarbonyl)-amino]-but-1-ynyl}-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester

A suspension of N-but-3-ynyl-imidodicarbonic acid di-tert-butyl ester (4.65 g, 17.3 mmol), [2-oxo-7-(trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester (6.36 g, 17.3 mmol), tetrakis (triphenylphosphine)palladium (2.0 g, 1.7 mmol) and copper (I) iodide (0.49 g, 2.6 mmol) in N-methylpyrrolidine (50 mL; purged with N₂) was heated to 60°C. The resulting solution was treated with the original amounts of both catalysts, two additional times, at 1.5 h intervals. After 22h, the reaction mixture was filtered and concentrated. The resulting dark oil was treated with saturated aqueous NH₄Cl (250 mL), extracted with chloroform (3 x 250 mL), dried (MgSO₄) and concentrated to give a dark mixture of oil and foam (16.2 g). Flash chromatography (260 g silica; 5%, then 10%, then 20%, then 40% EtOAc-hexane) gave the title compound (5.2 g, 62% yield) as an impure yellow foam. ¹H NMR (CDCl₃, 300 MHz): δ 1.51 (s, 18 H, C(CH₃)₃), 2.50 (dd, J=7 Hz, 16 Hz, 1H, ArCH₂H), 2.69 (t, J=7 Hz, 2H, NCH₂CH₂), 2.81-3.13 (overlapping m, 4H, ArCH₂H, CH, CH₂CO₂), 3.74 (s, 3H, CO₂CH₃), 3.83 (t, J=7 Hz, 2H, NCH₂), 6.80 (d, J=1 Hz, 1H, ArH), 7.02 (dd, J=1 Hz, 8 Hz, 1H, ArH), 7.06 (d, J=8 Hz, 1H, ArH), 8.25 (s, 1H, ArNH).

Example 9235 {7-[5-Bis(tert-butylcarbonyloxy)amino-pent-1-ynyl]-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-acetic acid methyl ester

Using the conditions of Example 91 and replacing N-but-3-ynyl-imidodicarbonic acid di-tert-butyl ester with N-pent-4-ynyl imidodicarbonic acid di-tert-butyl ester, the product of the example is obtained.

Example 93

5 {7-[6-Bis(tert-butylcarbonyloxy)amino-hex-1-ynyl]-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-acetic acid methyl ester

Using the conditions of Example 91 and replacing N-but-3-ynyl-imidodicarbonic acid di-tert-butyl ester with N-hex-5-ynylimidodicarbonic acid di-tert-butyl ester, the product of the example is obtained.

Example 94

[7-(4-Amino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

A solution of (7-{4-[bis-(tert-butoxycarbonyl)-amino]-but-1-ynyl}-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester (5.2 g, 10.7 mmol) and trifluoroacetic acid (8.2 mL, 106 mmol) were combined in methylene chloride (40 mL) at 25°C under nitrogen and stirred for 2h. The solution was concentrated in vacuo to give a cloudy orange oil (6.8 g) which was stirred vigorously with saturated sodium bicarbonate (100 ml). The aqueous phase was extracted with chloroform (3 x 100 ml), dried (K₂CO₃) and evaporated in vacuo to give 3.2 g of a residue. The residue was purified by flash chromatography (90 g silica; CHCl₃, then 1% MeOH (saturated with NH₃)-CHCl₃) to give the title compound as a yellow solid (2.1 g).

Example 95

[7-(5-Amino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 94 and replacing (7-{4-[bis-(tert-butoxycarbonyl)-amino]-but-1-ynyl}-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester with {7-[5-bis(tert-butylcarbonyloxy)amino-pent-1-ynyl]-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-acetic acid methyl ester, the product of the example is obtained.

Example 96

[7-(6-Amino-hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 94 and replacing (7-{4-[bis-(tert-butoxycarbonyl)-amino]-but-1-ynyl}-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester

5 with {7-[6-bis(tert-butylcarbonyloxy)amino-hex-1-ynyl]-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester, the product of the example is obtained.

Example 97

10 [7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Methyl Ester

Using the conditions of Example 81 and [7-(4-amino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate the product of the example is
15 obtained.

Example 98

20 [7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 81 and [7-(5-amino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate the product of the example is obtained.

25 Example 99

[7-(6-Guanidino-hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 81 and [7-(6-amino-hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate the product of the example is obtained.

Example 100

35 [7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride

[7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester was converted to the title compound in a manner analogous to that described for compound 84 and converted to the hydrochloride using the method
40 described in Example 85.

Mp. 130-80 °C (slowly degasses).

- 5 IR (KBr): 3375 (s), 3250 (s), 3190 (s), 1710 (s), 1670 (s),
1620 (s), 1480 (m), 1230 (m), 1155 (m), 840 (w), 775 (m), 740
(m) cm^{-1} .
 ^1H NMR (DMSO- d_6 , 400 MHz): δ 2.36 (m, 1H, ArCH $\underline{\text{H}}$), 2.63 (t, J=7
Hz, 2H, NCH $\underline{2}$ CH $\underline{2}$), 2.68-2.94 (overlapping m, 4H, ArCH $\underline{\text{H}}$, CH,
10 CH $\underline{\text{H}}$ CO $\underline{2}$), 3.35 (m, 2H, NCH $\underline{2}$), 6.75-7.64 (broad, 4H, [C(NH $\underline{2}$) $\underline{2}$] $^+$),
6.88 (d, J=1.5 Hz, 1H, Ar $\underline{\text{H}}$), 6.95 (dd, J=1.5 Hz, 8 Hz, 1H, Ar $\underline{\text{H}}$),
7.14 (d, J=8 Hz, 1H, Ar $\underline{\text{H}}$), 7.73 (t, J=6 Hz, 1H, NHCH $\underline{2}$), 10.2 (s,
1H, ArNH), 12.2 (s, 1H, CO $\underline{2}$ H).
MS (-FAB) m/e (rel. intensity): 313 (M-H, 31).
15 Analysis calc. for $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_3 \cdot \text{HCl} \cdot 1.5 \text{H}_2\text{O}$ C, 50.86; H, 5.87; N,
14.83
Found C, 50.77; H, 5.86; N, 14.56

Example 101

20 [7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate

- Using the conditions of Examples 84 and 85 and [7-(5-guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(4-guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl
25 ester, the product of the example was obtained.

Mp. Shrinks noticeably from 98-99 °C, then melts with degassing from 103-11 °C.

IR (KBr): 3410 (s), 3350 (s), 3170 (s), 1670 (s), 1660 (s), 1200 (s), 1140 (s), 840
(m), 800 (m), 720 (m) cm^{-1} .

- ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.74 (m, 2H, NCH $\underline{2}$ CH $\underline{2}$), 2.36 (m, 1H,
30 ArCH $\underline{\text{H}}$), 2.45 (t, J=7 Hz, 2H, \equiv CCH $\underline{2}$), 2.66-2.94 (overlapping m, 4H, ArCH $\underline{\text{H}}$,
CH, CH $\underline{\text{H}}$ CO $\underline{2}$), 3.20 (m, 2H, NCH $\underline{2}$), 6.60-7.58 (broad, 4H, [C(NH $\underline{2}$) $\underline{2}$] $^+$), 6.83 (d,
J=1.5 Hz, 1H, Ar $\underline{\text{H}}$), 6.93 (dd, J=1.5 Hz, 8 Hz, 1H, Ar $\underline{\text{H}}$), 7.13 (d, J=8 Hz, 1H,
Ar $\underline{\text{H}}$), 7.62 (t, J=5.5 Hz, 1H, NHCH $\underline{2}$), 10.2 (s, 1H, ArNH), 12.2 (s, 1H, CO $\underline{2}$ H).

- 35 MS (-FAB) m/e (rel. intensity): 327 (M-H, 27).

Analysis calc. for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_3 \cdot \text{CF}_3\text{COOH} \cdot 0.6 \text{H}_2\text{O}$

C, 50.35; H, 4.94;

N, 12.36

Found

C, 50.04; H, 4.67;

N, 12.25

40

Example 102

5 [7-(6-Guanidino-hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid hydrochloride

 Using the conditions of Examples 84 and 85 and [7-(6-guanidino-hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(4-guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester, the product of the example is obtained.

Example 103

[7-(4-tert-Butoxycarbonylamino-but-1-ynyl)-2-oxo-1,2,3,4-
 tetrahydro-quinolin-3-yl]-acetic acid methyl ester

15 A suspension of [7-(4-amino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester (0.48 g, 1.7 mmol), di-tert-butyl dicarbonate (0.37 g, 1.7 mmol) and potassium carbonate (0.47 g, 3.4 mmol) in 1:1 MeOH: (3:1) dioxane-water (17 mL) was stirred at 25°C.

20 After 2 h, the mixture was concentrated and the resulting solid partitioned between water and chloroform (25 mL each). The layers were separated and the aqueous phase re-extracted with chloroform (2 x 25 mL). The combined extracts were dried (MgSO₄) and concentrated to give the

25 title compound (0.61 g, 94% yield) as a white foam.
 ¹H NMR (CDCl₃, 300 MHz): δ 1.46 (s, 18H, C(CH₃)₃), 2.46-2.62 (overlapping m, 3H, ArCH₂, CH₂), 2.82-3.13 (overlapping m, 4H, ArCH₂, CH, CH₂CO₂), 3.36 (m, 2H, NCH₂), 3.84 (s, 3H, CO₂CH₃), 4.87 (broad s, 1H, NHCH₂), 6.80 (s, 1H, ArH), 7.02-7.10 (overlapping m, 2H, ArH), 7.94 (s, 1H, ArNH).

Example 104

[7-(5-tert-Butoxycarbonylamino-pent-1-ynyl)-2-oxo-1,2,3,4-
 tetrahydro-quinolin-3-yl]-acetic acid methyl ester

35 Using the conditions of Example 103 and [7-(5-amino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(4-amino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester the product of the example is obtained.

40

Example 105

5 [7-(6-tert-Butoxycarbonylamino-hex-1-ynyl)-2-oxo-1,2,3,4-
 tetrahydro-quinolin-3-yl]-acetic acid methyl ester

 Using the conditions of Example 103 and [7-(6-amino-
hex-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic
acid methyl ester in place of [7-(4-amino-but-1-ynyl)-2-
10 oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl
ester the product of the example is obtained.

Example 106

[7-(4-Amino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-
 3-yl]-acetic acid methyl ester

15 A solution of [7-(4-tert-butoxycarbonylamino-but-1-
ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid
methyl ester (1.10 g, 2.85 mmol) in 2:1 methanol-dioxane
(70 mL) containing quinoline (1.1 mL) was hydrogenated over
Lindlar's catalyst (5% Pd-CaCO₃ poisoned with lead, 0.21 g)
20 at 25°C and 1 atm. After 2 h, the catalyst was removed by
filtration and the filtrate concentrated to give a pale
yellow oil (1.50 g) which was treated with trifluoroacetic
acid in dichloromethane. The resulting crude
trifluoroacetate salt was treated with saturated aqueous
25 NaHCO₃ (25 mL) and extracted with chloroform (3 x 25 mL).
The extracts were dried (MgSO₄) and concentrated to give a
cloudy, yellow oil (0.89 g). Flash chromatography (20 g
silica; 0.5%, then 1%, then 2%, then 4%, then 8%, then 10%
MeOH (saturated with NH₃)-CHCl₃) gives the title compound
30 (0.46 g; 56% yield) as a pale yellow oil.

¹H NMR (CDCl₃, 300 MHz): δ 1.24 (broad s, 2H, NH₂), 2.44-
2.55 (overlapping m, 3H, ArCH₂, =CHCH₂), 2.82-3.14
(overlapping m, 6H, ArCH₂, CH, CH₂CO₂, NCH₂), 3.74 (s, 3H,
CO₂CH₃), 5.67 (dt, J=7 Hz, 12 Hz, 1H, =CHCH₂), 6.46 (d,
35 J=12 Hz, 1H, =CHAr), 6.74 (s, 1H, ArH), 6.92 (dd, J=1 Hz, 8
Hz, 1H, ArH), 7.11 (d, J=8 Hz, 1H, ArH), 8.69 (broad s, 1H,
ArNH).

Example 107

40 [7-(5-Amino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-
 3-yl]-acetic acid methyl ester

5 Using the conditions of Example 106 and [7-(5-
tert-butoxycarbonylamino-pent-1-ynyl)-2-oxo-1,2,3,4-tetra-
hydro-quinolin-3-yl]-acetic acid methyl ester in place of
[7-(4-amino-but-1-enyl)-2-oxo-1,2,3,4-tetra-hydro-quinolin-
3-yl]-acetic acid methyl ester, the product of the example
10 is obtained.

Example 108

[7-(6-Amino-hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid methyl ester

15 Using the conditions of Example 106 and [7-(6-
tert-butoxycarbonylamino-hex-1-ynyl)-2-oxo-1,2,3,4-tetra-
hydro-quinolin-3-yl]-acetic acid methyl ester in place of
[7-(4-tert-butoxy-carbonylamino-but-1-enyl)-2-oxo-1,2,3,4-
tetra-hydro-quinolin-3-yl]-acetic acid methyl ester, the
product of the example is obtained.

20 Example 109

[7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Methyl Ester

25 Using the conditions of Example 81 and [7-(4-amino-
but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic
acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-
1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester
trifluoroacetate the product of the example is obtained.

30

Example 110

[7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Methyl Ester

35 Using the conditions of Example 81 and [7-(5-amino-
pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic
acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-
1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester
trifluoroacetate, the product of the example is obtained.

Example 111

40 [7-(6-Guanidino-hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Methyl Ester

5 Using the conditions of Example 81 and [7-(6-amino-hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate, the product of the example is obtained.

10

Example 112

[7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

 [7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester was converted to
15 the title compound in a manner analogous to that described for Example 84.

Mp. 173-76 °C.

IR (KBr): 3430 (s), 3330 (s), 3220 (s), 1680 (s), 1660 (s), 1625 (s), 1490 (m), 1425 (m), 1400 (s), 1250 (s), 1180
20 (s), 1135 (s), 870 (m), 830 (m), 799 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 2.36 (m, 1H, ArCH₂H), 2.47 (m, 2H, =CHCH₂), 2.69-2.97 (overlapping m, 4H, ArCH₂H, CH₂CH₂CO₂), 3.22 (m, 2H, NCH₂), 5.57 (dt, J=7 Hz, 12 Hz, 1H, =CHCH₂), 6.45 (d, J=12 Hz, 1H, ArCH=), 6.60-7.45 (broad, 25 4H, [C(NH₂)₂]⁺), 6.79 (d, J=1Hz, 1H, ArH), 6.84 (dd, J=1 Hz, 8 Hz, 1H, ArH), 7.15 (d, J=8 Hz, 1H, ArH), 7.52 (t, J=6 Hz, 1H, NHCH₂), 10.1 (s, 1H, ArNH), 12.2 (s, 1H, CO₂H).

MS (+ESI) m/e (rel. intensity): 317 (M+H, 100).

Analysis calc. for C₁₆H₂₀N₄O₃•CF₃COOH C, 50.23; H, 4.92;
30 N, 13.02

Found C, 49.93; H, 4.87; N, 12.84

Example 113

[7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

35

 [7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester was converted to the title compound in a manner analogous to that described for Example 112.

40 Mp. 162-65 °C.

- 5 IR (KBr): 3440 (s), 3350 (s), 3200 (m), 1710 (s), 1675 (s), 1430 (m), 1400 (m),
1250 (m), 1180 (s), 1132 (s), 830 (m), 795 (m), 725 (m) cm^{-1} .
 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.60 (m, 2H, NCH_2CH_2), 2.26-2.39
(overlapping m, 3H, ArCHH , $\text{CH}_2\text{CH}=\text{}$), 2.69-2.96 (overlapping m, 4H, ArCHH ,
 CH , CHHCO_2), 3.11 (m, 2H, NCH_2), 5.62 (dt, $J=7$ Hz, 12 Hz, 1H, $\text{CH}_2\text{CH}=\text{}$),
10 6.35 (d, $J=12$ Hz, 1H, $\text{ArCH}=\text{}$), 6.60-7.45 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 6.79 (d, $J=1$
Hz, 1H, ArH), 6.83 (dd, $J=1$ Hz, 8 Hz, 1H, ArH), 7.14 (d, $J=8$ Hz, 1H, ArH), 7.53
(t, $J=6$ Hz, 1H, NHCH_2), 10.1 (s, 1H, ArNH), 12.2 (s, 1H, CO_2H).
MS (+ESI) m/e (rel. intensity): 331 (M+H, 34).
Analysis calc. for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_3 \cdot \text{CF}_3\text{COOH}$ C, 51.35; H, 5.22; N,
15 12.61
Found C, 50.95; H, 5.19;
N, 12.32

Example 114

- 20 [7-(6-Guanidino-hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate

[7-(6-Guanidino-hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester is converted to the
title compound in a manner analogous to that described for
Example 112.

- 25 Example 115

[7-(4-Amino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-
acetic acid methyl ester

- A solution of [7-(4-amino-but-1-enyl)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetic acid methyl ester (0.41 g,
30 1.43 mmol) and 86 mg of 10% palladium-on-carbon in 40 ml of
acetic acid was hydrogenated under 55 psi of hydrogen for 3
hours. The reaction mixture was filtered through
diatomaceous earth and the filter cake washed with acetic
acid (2 x 20 ml). The filtrate was evaporated in vacuo to
35 a residue of oil and crystalline solid (0.57 g) which was
partitioned between saturated sodium bicarbonate (20 ml)
and chloroform and extracted (3 x 20 ml). The combined
extracts were dried (K_2CO_3) and evaporated in vacuo to give
0.24 g (free base, 57% crude yield) of a pale yellow solid.
40 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.32 (m, 2H, NCH_2CH_2), 1.51
(m, 2H, ArCH_2CH_2), 2.43-2.88 (m, 9H, ArCHHCH , CHHCO_2 ,

5 ArCH₂CH₂, NCH₂), 3.32 (broad, 2H, NH₂), 3.60 (s, 3H, CH₃),
6.66 (d, J=1.5 Hz, 1H, ArH), 6.73 (dd, J=1.5 Hz, 7.5 Hz,
1H, ArH), 7.03 (d, J=7.5 Hz, 1H, ArH), 10.1 (broad s, 1H,
ArNH).

Example 116

10 [7-(5-Amino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]-acetic acid methyl ester

Using the conditions of Example 115 and [7-(5-amino-
pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic
acid methyl ester in place of [7-(4-amino-but-1-enyl)-2-
15 oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl
ester, the product of the example is obtained.

Example 117

[7-(6-Amino-hexyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-
acetic acid methyl ester

20 Using the conditions of Example 115 and [7-(6-amino-
hex-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic
acid methyl ester in place of [7-(4-amino-but-1-enyl)-2-
oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl
ester, the product of the example is obtained.

Example 118

25 [7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]-acetic acid Methyl Ester

Using the conditions of Example 81 and [7-(4-amino-
butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid
methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-
30 1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester
trifluoroacetate the product of the example is obtained.

35

Example 119

40 [7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid Methyl Ester

5 Using the conditions of Example 81 and [7-(5-amino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate, the product of the example is obtained.

10 Example 120

[7-(6-Guanidino-hexyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Methyl Ester

Using the conditions of Example 81 and [7-(6-amino-hexyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate, the product of the example is obtained.

Example 121

20 [7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

[7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester was converted to the title compound in a manner analogous to that described for Example 84.

25 Mp. 157-60 °C.

IR (KBr): 3405 (s), 3180 (s), 1680 (s), 1625 (s), 1480 (m), 1430 (m), 1400 (m), 1295 (m), 1250 (m), 1190 (s), 1140 (s), 840 (m), 800 (m), 725 (m) cm^{-1} .

30 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.42-1.58 (overlapping m, 4H, NCH_2CH_2 , ArCH_2CH_2), 2.31-2.92 (overlapping m, 7H, ArCH_2CH_2 , CH_2CO_2 , ArCH_2CH_2), 3.09 (m, 2H, NCH_2). 6.56-7.40 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 6.65 (d, $J=1.5$ Hz, 1H, ArH), 6.74 (dd, $J=1.5$ Hz, 8Hz, 1H, ArH), 7.06 (d, $J=8$ Hz, 1H, ArH), 7.46 (t, $J=5$ Hz, 1H, NHCH_2), 10.1 (s, 1H, ArNH), 12.2 (s, 1H, CO_2H).

MS (-FAB) m/e (rel. intensity): 317 (M-H, 34).

Analysis calc. for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_3 \cdot \text{CF}_3\text{COOH} \cdot 0.3 \text{H}_2\text{O}$ C, 49.38; H, 5.43; N, 12.80

Found C, 49.12; H, 5.23; N, 12.72

5

Example 122[7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

10 [7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester was converted to the title compound in a manner analogous to that described for Example 84.

Mp. 148-51 °C.

IR (KBr): 3380 (s), 3180 (s), 1700 (s), 1675 (s), 1475 (m), 1435 (m), 1400 (m),
15 1199 (s doublet), 1135 (s), 840 (m), 795 (m), 725 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.27 (m, 2H, NCH₂CH₂CH₂), 1.43-1.56 (overlapping m, 4H, NCH₂CH₂, ArCH₂CH₂), 2.31-2.91 (overlapping m, 7H, ArCHHCH, CHHCO₂, ArCH₂CH₂), 3.06 (m, 2H, NCH₂), 6.56-7.42 (broad, 4H, [C(NH₂)₂]⁺), 6.65 (d, J=1 Hz, 1H, ArH), 6.73 (dd, J=1 Hz, 7.5 Hz, 1H, ArH),
20 7.05 (d, J=7.5 Hz, 1H, ArH), 7.49 (t, J=5 Hz, 1H, NHCH₂), 10.1 (s, 1H, ArNH), 12.2 (s, 1H, CO₂H).

MS (-FAB) m/e (rel. intensity): 331 (M-H, 14).

Analysis calc. for C₁₇H₂₄N₄O₃•CF₃COOH C, 51.12; H, 5.64; N,
12.55

25 Found C, 51.33; H, 5.70;
N, 12.65

Example 123[7-(6-Guanidino-hexyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

30 [7-(6-Guanidino-hexyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is converted to the title compound in a manner analogous to that described for Example 84.

Example 124(1-Ethyl-7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester

A slurry of (7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester (5.0 g, 20 mmol) in tetrahydrofuran (40 mL) was treated with potassium
40 bis(trimethylsilyl)amide (0.5 M in toluene, 41 mL, 21 mmol) at 25°C and the mixture heated to reflux. After 1 h at

5 reflux, ethyl iodide (16 mL, 200 mmol) was added. After an additional 3 h at reflux, the cooled mixture was quenched with 0.1N aqueous HCl (50 mL) and concentrated in vacuo. Water (200 mL) was added and the aqueous phase extracted with chloroform (3 x 200 mL). The extracts were dried
10 (K₂CO₃) and concentrated in vacuo to give the crude product (5.3 g). Flash chromatography (225 g silica; 2:1, then 1:1 hexane-ether, then 100% ether) gave the title compound (4.4 g, 79% yield) as a white solid.
¹H NMR (DMSO-d₆, 300 MHz): δ 1.19 (t, J=7 Hz, 3H, CH₂CH₃),
15 3.53 (s, 2H, CH₂CO₂), 3.60 (s, 3H, CO₂CH₃), 3.89 (s, 3H, OCH₃), 4.25 (q, J=7 Hz, 2H, NCH₂), 6.90 (d, J=9 Hz, 1H, ArH), 6.96 (s, 1H, ArH), 7.61 (s, J=9 Hz, 1H, ArH), 7.78 (s, 1H, ArCH=).

Example 125

20 (1-Benzyl-7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester

The title compound (5.2 g, 76% yield) was prepared in essentially the same manner as described for the preparation of Example 124 using benzyl bromide in place of
25 ethyl iodide.

Mp. 118.0 -119.5 °C.

¹H NMR (DMSO-d₆, 300 MHz): δ 3.61 (s, 5H, CO₂CH₃, CH₂CO₂),
3.73 (s, 3H, OCH₃), 5.52 (s, 2H, CH₂Ph), 6.82-6.88
(overlapping m, 2H, ArH), 7.20 (m, 3H, ArH), 7.30 (m, 2H,
30 ArH), 7.62 (d, J=8.5 Hz, 1H, ArH), 7.87 (s, 1H, ArCH=).

Example 126

(1-Ethyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid

A suspension of (1-ethyl-7-methoxy-2-oxo-1,2-dihydro-
35 quinolin-3-yl)-acetic acid methyl ester (4.0g, 14.5 mmol) in 1:1 48% aqueous HBr-HOAc (30 mL) was heated at reflux for 48 h. The resulting solution was cooled to 25°C and the resulting crystalline solid was stored at 0-5°C for 2 h, then vacuum filtered, washed with water and air-dried to
40 give the title compound (3.2 g, 89% yield) as tan needles.
Mp. 226-29 °C.

5 ^1H NMR (DMSO- d_6 , 300 MHz): δ 1.18 (t, $J=7$ Hz, 3H, CH_3),
3.41 (s, 2H, CH_2CO_2), 4.17 (q, $J=7$ Hz, 2H, NCH_2), 6.73 (dd,
 $J=2$ Hz, 8.5 Hz, 1H, ArH), 6.83 (d, $J=2$ Hz, 1H, ArH), 7.49
(d, $J=8.5$ Hz, 1H, ArH), 7.70 (s, 1H, ArCH=), 10.2 (s, 1H,
 ArOH), 12.2 (broad s, 1H, CO_2H).

10

Example 127(1-Ethyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic
acid methyl ester

A suspension of (1-ethyl-7-hydroxy-2-oxo-1,2-dihydro-
quinolin-3-yl)-acetic acid (2.9 g, 12 mmol) in methanol (30
15 mL) was treated with 12 N aqueous HCl (3 mL, 36 mmol) and
the mixture heated to reflux. After 5 h, the resulting
solution was cooled to room temperature, filtered and left
standing overnight. The resulting solid was vacuum
filtered, washed with ice-cold methanol and air-dried to
20 give the title compound (1.8 g, 58% yield) as white
needles.

Mp. 175.5-78.0 °C.

^1H NMR (DMSO- d_6 , 300 MHz): δ 1.18 (t, $J=7$ Hz, 3H, CH_2CH_3),
3.50 (s, 2H, CH_2CO_2), 3.59 (s, 3H, CO_2CH_3), 4.17 (q, $J=7$
25 Hz, 2H, NCH_2), 6.73 (dd, $J=2$ Hz, 8.5 Hz, 1H, ArH), 6.83 (d,
 $J=2$ Hz, 1H, ArH), 7.50 (d, $J=8.5$ Hz, 1H, ArH), 7.72 (s, 1H,
 ArCH=), 10.2 (s, 1H, ArOH).

Example 128(1-Benzyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic
30 acid

The title compound (4.1 g, 89% yield) was prepared in
essentially the same manner as described for the
preparation of Example 126 using (1-benzyl-7-methoxy-2-oxo-
1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester
35 in place of (1-ethyl-7-methoxy-2-oxo-1,2-dihydro-quinolin-
3-yl)-acetic acid methyl ester.

^1H NMR (DMSO- d_6 , 300 MHz): δ 3.49 (s, 2H, CH_2CO_2), 5.42
(broad s, 2H, CH_2Ph), 6.67-6.70 (overlapping m, 2H, ArH),
7.15-7.33 (overlapping m, 5H, ArH), 7.49 (d, $J=8$ Hz, 1H,

5 ArH), 7.78 (s, 1H, ArCH=), 10.1 (s, 1H, ArOH), 12.2 (s, 1H, CO₂H).

Example 129

(1-Benzyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester

10 The title compound (2.4 g, 56% yield) was prepared in essentially the same manner as described for the preparation of Example 127 using (1-benzyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid in place of (1-ethyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic
15 acid.

¹H NMR (DMSO-d₆, 300 MHz): δ 3.58 (s, 2H, CH₂CO₂), 3.60 (s, 3H, CH₃), 5.42 (broad s, 2H, CH₂Ph), 6.67-6.70 (overlapping m, 2H, ArH), 7.14-7.34 (overlapping m, 5H, ArH), 7.51 (d, J=8 Hz, 1H, ArH), 7.82 (s, 1H, ArCH=), 10.1 (s, 1H, ArOH).

20 Example 130

[7-(3-tert-Butoxycarbonylamino-propoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

The title compound was prepared using the procedure of Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester in place of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid methyl ester and (3-bromopropyl)carbamic acid tert-butyl ester in place of (2-bromoethyl)carbamic acid tert-butyl ester.

30 Example 131

[7-(2-tert-Butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared using the procedure of Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester in place of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid methyl ester

Example 132

40 [7-(4-tert-Butoxycarbonylamino-butoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

5 The title compound is prepared using the conditions of
Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2-dihydro-
quinolin-3-yl)-acetic acid methyl ester in place of 7-
hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid
methyl ester and (4-bromobutyl)carbamic acid tert-butyl
10 ester in place of (2-bromoethyl) carbamic acid tert-butyl
ester.

15

Example 133

[1-Benzyl-7-(3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3-
yllacetic acid methyl ester

The title compound is prepared according to the
procedure of Example 78 except that [7-(2-tert-
20 butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester is replaced with
[7-(3-tert-butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 134

25 [1-Benzyl-7-(2-aminoethoxy)-2-oxo-1,2-dihydro-quinolin-3-
yllacetic acid methyl ester

The title compound is prepared according to the
procedure of Example 78 except that [7-(2-tert-
butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
30 quinolin-3-yl]-acetic acid methyl ester is replaced with
[7-(2-tert-butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 135

35 [1-Benzyl-7-(4-aminobutoxy)-2-oxo-1,2-dihydro-quinolin-3-
yllacetic acid methyl ester

The title compound is prepared according to the
procedure of Example 78 except that [7-(2-tert-
butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester is replaced with
40 [7-(4-tert-butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester.

5 Example 136[1-Benzyl-7-(3-amino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid

The title compound was prepared according to the procedure of Example 84 except that [7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate was replaced with [1-benzyl-7-(3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Mp. 126-28 °C.

15 IR (KBr): 3420 (m), 3050 (m), 1673 (s), 1642 (s), 1585 (s), 1240 (m), 1196 (s), 1125 (s), 838 (m), 820 (m), 795 (m), 720 (m), 700 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.96 (m, 2H, NCH_2CH_2), 2.92 (m, 2H, NCH_2CH_2), 3.52 (s, 2H, CH_2CO_2), 4.06 (t, J=6 Hz, 2H, OCH_2), 5.51 (broad s, 2H, CH_2Ph), 6.82 (d, J=2 Hz, 1H, ArH), 6.88 (dd, J=2 Hz, 9 Hz, 1H, ArH), 7.19-7.25 (overlapping m, 3H, ArH), 7.31 (m, 2H, ArH), 7.64 (d, J=9 Hz, 1H, ArH), 7.71 (broad s, 3H, NH_3^+), 7.85 (s, 1H, ArCH=), 12.2 (broad s, 1H, CO_2H).

25 MS (+FAB) m/e (rel. intensity): 367 (M+H, 60).

Analysis calc. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 1.2 \text{H}_2\text{O}$ C,

55.02; H, 5.10; N, 5.58.

Found

C, 54.97; H,

4.95; N, 5.54

30 Example 137[1-Benzyl-7-(2-aminoethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid

The title compound is prepared according to the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [1-benzyl-7-(2-aminoethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 13840 [1-Benzyl-7-(4-aminobutoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid

5 The title compound is prepared according to the
procedure of Example 84 except that [7-(4-guanidino-
butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid
methyl ester trifluoroacetate is replaced with [1-benzyl-7-
(4-aminobutoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid
10 methyl ester.

Example 139

[7-(3-tert-Butoxycarbonylamino-propoxy)-1-ethyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester

 The title compound is prepared using the
15 procedure of Example 75 and (1-ethyl-7-hydroxy-2-oxo-1,2-
dihydro-quinolin-3-yl)-acetic acid methyl ester in place of
7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic
acid methyl ester and (3-bromo-propyl)carbamic acid tert-
butyl ester in place of (2-bromoethyl)carbamic acid tert-
20 butyl ester.

Example 140

[7-(2-tert-Butoxycarbonylaminoethoxy)-1-ethyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester

 The title compound is prepared using the
25 procedure of Example 75 and (1-ethyl-7-hydroxy-2-oxo-1,2-
dihydro-quinolin-3-yl)-acetic acid methyl ester in place of
7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic
acid methyl ester.

Example 141

30 [7-(4-tert-Butoxycarbonylamino-butoxy)-1-ethyl-2-oxo-1,2-
dihydro-quinolin-3-yl]acetic acid methyl ester

 The title compound is prepared using the
procedure of Example 75 and (1-ethyl-7-hydroxy-2-oxo-1,2-
dihydro-quinolin-3-yl)-acetic acid methyl ester in place of
35 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic
acid methyl ester and (4-bromobutyl)carbamic acid tert-
butyl ester in place of (2-bromoethyl)carbamic acid tert-
butyl ester.

Example 142

40 [1-Ethyl-7-(3-amino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-
yl]acetic acid Trifluoroacetate

5 The title compound was prepared according to the
procedure of Example 84 except that [7-(3-tert-butoxy-
carbonylamino-propoxy)-1-ethyl-2-oxo-1,2-dihydro-quinolin-3-
yl]acetic acid methyl ester was used in place of [7-(4-
10 guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]acetic acid methyl ester trifluoroacetate.

Mp. 182-84 °C.

IR (KBr): 3410 (m), 3130 (m), 3060 (m), 1715 (s), 1648
(s), 1600 (s), 1235 (m), 1202 (s), 1178 (s), 1126 (s), 1105
(m), 852 (m), 792 (m), 788 (m), 720 (m) cm⁻¹.

15 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.20 (t, J=7 Hz, 3H, CH₃),
2.05 (m, 2H, NCH₂CH₂), 3.01 (m, 2H, NCH₂CH₂), 3.45 (s, 2H,
CH₂CO₂), 4.21 (t, J=6 Hz, 2H, OCH₂), 4.26 (q, J=7 Hz, 2H,
NCH₂CH₃), 6.91 (dd, J=2 Hz, 9 Hz, 1H, ArH), 6.97 (d, J=2
20 Hz, 1H, ArH), 7.63 (d, J=9 Hz, 1H, ArH), 7.77 (overlapping
s, broad s, 4H, ArCH=, NH₃⁺), 12.2 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 305 (M+H, 100).

Analysis calc. for C₁₆H₂₀N₂O₄•CF₃COOH.

C,

51.67; H, 5.06; N, 6.70

Found

C, 51.69; H,

25 4.96; N, 6.77

Example 143

[1-Ethyl-7-(2-aminoethoxy)-2-oxo-1,2-dihydro-quinolin-3- yl]acetic acid methyl ester

30 The title compound is prepared according to the
procedure of Example 78 except that [7-(2-tert-
butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]acetic acid methyl ester is replaced with [7-
(2-tert-butoxycarbonylaminoethoxy)-1-ethyl-2-oxo-1,2-
35 dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 144

[1-Ethyl-7-(3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3- yl]acetic acid methyl ester

40 The title compound is prepared according to the
procedure of Example 78 except that [7-(2-tert-butoxy-
carbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-3-
yl]acetic acid methyl ester is replaced with [7-(3-tert-

5 butoxycarbonylamino-propoxy)-1-ethyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 145

[1-Ethyl-7-(4-aminobutoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

10 The title compound is prepared according to the procedure of Example 78 except that [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester is replaced with [7-(4-tert-butoxycarbonylamino-butoxy)-1-ethyl-2-oxo-1,2-
15 dihydro-quinolin-3-yl]acetic acid methyl ester.

5

Example 146[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Methyl Ester

The title compound is prepared according to the procedure of Example 81 except that [1-ethyl-7-(3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

15

Example 147[1-Ethyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [7-(2-amino-ethoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

25

Example 148[1-Ethyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [7-(4-amino-butoxy)-1-ethyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

35

Example 149[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate

The title compound was prepared using the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate was replaced with [1-ethyl-7-(3-guanidino-

40

5 propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester.

Mp. 131°C (degasses).

IR (KBr): 3515 (m), 3460 (m), 3300 (m), 1720 (m), 1645 (s), 1599 (s), 1410 (m), 1222 (s), 1190 (s), 1140 (s), 822 (m), 800 (m), 792 (m), 725 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.20 (t, J=7 Hz, 3H, CH_3), 1.98 (m, 2H, NCH_2CH_2), 3.31 (m, 2H, NCH_2CH_2), 3.45 (s, 2H, CH_2CO_2), 4.17 (t, J=6 Hz, 2H, OCH_2), 4.26 (q, J=7 Hz, 2H, NCH_2CH_3), 6.60-7.50 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 6.91 (dd, J=2 Hz, 8.5 Hz, 1H, ArH), 6.96 (d, J=2 Hz, 1H, ArH), 7.61-7.65 (overlapping m, 2H, ArH , NHCH_2), 7.76 (s, 1H, $\text{ArCH}=\text{}$), 12.2 (broad s, 1H, CO_2H).

MS (+FAB) m/e (rel. intensity): 347 (M+H, 100).

Analysis calc. for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot \text{H}_2\text{O}$ C,

20 47.70; H, 5.27; N, 11.71

Found C, 47.73; H, 5.25; N, 11.70

Example 150

25 [1-Ethyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid Trifluoroacetate

The title compound is prepared using the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate is replaced with [1-ethyl-7-30 (2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 151

35 [1-Ethyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid Trifluoroacetate

The title compound is prepared using the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate is replaced with [1-ethyl-7-40 (4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 152

5 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 153

15 [1-Benzyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(2-aminoethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 154

25 [1-Benzyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(4-aminobutoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 155

35 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]-acetic acid

The title compound was prepared according to the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate was replaced with [1-benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

40 Mp. 132-34 °C.

- 5 IR (KBr): 3342 (m), 3190 (m), 1715 (s), 1670 (s), 1645 (s), 1594 (s), 1408 (m), 1199 (s), 1133 (m), 840 (m), 799 (m), 723 (m) cm^{-1} .
- ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.88 (m, 2H, NCH_2CH_2), 3.23 (m, 2H, NCH_2CH_2), 3.52 (s, 2H, CH_2CO_2), 4.01 (t, $J=6$ Hz, 2H, OCH_2), 5.52 (broad s, 2H, CH_2Ph), 6.60-7.50 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 6.81 (s, 1H, ArH), 6.88 (d, $J=9$ Hz, 1H, ArH), 7.19-7.35 (overlapping m, 5H, ArH), 7.60 (t, $J=5$ Hz, 1H, NHCH_2), 7.63 (d, $J=9$ Hz, 1H, ArH), 7.85 (s, 1H, $\text{ArCH}=\text{}$), 12.2 (broad s, 1H, CO_2H),
- 15 MS (+FAB) m/e (rel. intensity): 409 (M+H, 100).
Analysis calc. for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH}$ C, 55.17; H, 4.82; N, 10.72
Found C, 55.07; H, 4.74; N, 10.80

20

Example 156[1-Benzyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid

The title compound is prepared according to the procedure of Example 84 except that [7-(4-guanidino-
25 butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate is replaced with [1-benzyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 157

30

[1-Benzyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid

The title compound is prepared according to the procedure of Example 84 except that [7-(4-guanidino-
35 butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate is replaced with [1-benzyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

Example 158

40

[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate

5 A solution of [1-ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid trifluoroacetate (400 mg, 0.87 mmol) in 20 ml of methyl alcohol and 0.4 g of 10% Pd/C was hydrogenated under 50 psi of hydrogen for 3 days. The reaction mixture was filtered through diatomaceous
10 earth and the filtrate concentrated in vacuo to a residue which was dissolved in 10 ml of hot acetic acid and hydrogenated over 0.4 g of 10% Pd/C for 3 days. The reaction mixture was filtered through diatomaceous earth and the filter cake washed with hot methyl alcohol. The
15 combined filtrates were evaporated in vacuo to a residue of oil and solid. The residue was purified by chromatography on a reverse phase column to afford 57 mg of the title compound as a pale yellow solid.

Mp. 165-66 °C.

20 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.10 (t, J=7 Hz, 3H, CH₃), 1.92 (m, 2H, NCH₂CH₂), 2.33 (dd, J=6 Hz, 16 Hz, 1H, ArCHH), 2.64-2.84 (overlapping m, 4H, CH, ArCHH, CHHCO₂), 3.28 (m, 2H, NCH₂CH₂), 3.88 (overlapping m, 2H, NCHHCH₃), 4.02 (t, J=6 Hz, 2H, OCH₂), 6.60 (dd, J=2 Hz, 8 Hz, 1H, ArH), 6.65 (d, J=2 Hz, 1H, ArH),
25 6.70-7.50 (broad, 4H, [C(NH₂)₂]⁺), 7.12 (d, J=8 Hz, 1H, ArH), 7.58 (t, J=6 Hz, 1H, NHCH₂), 12.1 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 349 (M+H, 20).

Analysis calc. for C₁₇H₂₄N₄O₄•CF₃COOH C, 49.35; H, 5.45; N, 12.12

30 Found C, 49.05; H, 5.40; N, 11.89

Example 159

[1-Ethyl-7-(2-guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid Trifluoroacetate

The title compound is prepared using the
35 procedure of Example 158 except that [1-ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid trifluoroacetate is replaced with [1-ethyl-7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid trifluoroacetate.

40

Example 160

5 [1-Ethyl-7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]acetic acid Trifluoroacetate

The title compound is prepared using the procedure of Example 158 except that [1-ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid trifluoroacetate is replaced with [1-ethyl-7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid trifluoroacetate.

Example 161

15 [1-Benzyl-7-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
 yl]acetic acid methyl ester

The title compound (4.3 g, 88% yield) was prepared using the conditions of Example 124 using (7-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester in place of (7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)acetic acid methyl ester and benzyl bromide in place of ethyl iodide.

¹H NMR (DMSO-d₆, 300 MHz): δ 2.57 (dd, J=6Hz, 16Hz, ArCH_H), 2.78-3.06 (overlapping m, 4H, ArCH_H, CH, CH_HCO₂), 3.61 (s, 6H, OCH₃, CO₂CH₃), 5.05 (d, J=17 Hz, 1H, CH_HPh), 5.17 (d, J=17 Hz, 1H, CH_HPh), 6.44 (s, 1H, ArH), 6.55 (d, J=9 Hz, 1H, ArH), 7.11 (d, J=9 Hz, 1H, ArH), 7.18-7.33 (overlapping m, 5H, ArH).

Example 162

30 (1-Benzyl-7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
 yl)-acetic acid methyl ester

The title compound (3.9 g, 100% yield) was prepared using the conditions of Example 209 using [1-benzyl-7-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester in place of (1-ethyl-7-methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)acetic acid methyl ester.

¹H NMR (DMSO-d₆, 300 MHz): δ 2.54 (dd, J=6 Hz, 16.5 Hz, 1H, ArCH_H), 2.77-2.86 (overlapping m, 3H, ArCH_H, CH_HCO₂), 3.00 (m, 1H, CH), 3.61 (s, 3H, CH₃), 4.97 (d, J=17 Hz, 1H, CH_HPh), 5.13 (d, J=17 Hz, 1H, CH_HPh), 6.35-6.39 (overlapping m, 2H, ArH), 6.98 (d, J=8 Hz, 1H, ArH), 7.17-7.34 (overlapping m, 5H, ArH), 9.33 (s, 1H, ArOH).

5

Example 163

[7-(3-tert-Butoxycarbonylamino-propoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared using the procedure of Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester in place of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid and (3-bromopropyl)carbamic acid tert-butyl ester in place of (2-bromoethyl)carbamic acid tert-butyl ester.

15

Example 164

[7-(2-tert-Butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared using the procedure of Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester in place of [7-(3-tert-butoxycarbonylamino-propoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester.

20

Example 165

[7-(4-tert-Butoxycarbonylamino-butoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared using the conditions of Example 75 and (1-benzyl-7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester in place of [7-(3-tert-butoxycarbonylamino-propoxy)-1-benzyl-2-oxo-1,2-dihydro-quinolin-3-yl]acetic acid methyl ester and (4-bromobutyl)carbamic acid tert-butyl ester in place of (2-bromoethyl) carbamic acid tert-butyl ester.

25

Example 166

[1-Benzyl-7-(3-aminopropoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 78 except that [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is replaced with [7-(3-tert-butoxycarbonylamino-propoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester.

35

40

5

Example 167

[1-Benzyl-7-(2-aminoethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 78 except that [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is replaced with [7-(2-tert-butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester.

Example 168

15

[1-Benzyl-7-(4-aminobutoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 78 except that [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester is replaced with [7-(4-tert-butoxycarbonylaminoethoxy)-1-benzyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester.

Example 169

25

[1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Methyl Ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(3-aminopropoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 170

35

[1-Benzyl-7-(2-guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(2-aminoethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 171

40

5 [1-Benzyl-7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [1-benzyl-7-(4-aminobutoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester is used in place of [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate.

Example 172

15 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetic acid

The title compound was prepared according to the procedure of Example 84 except that [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester trifluoroacetate was replaced with [1-benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester.

Mp. 172-73 °C.

IR (KBr): 3380 (m), 3180 (m), 1702 (s), 1672 (s), 1618 (s), 1288 (s), 1207 (s), 1188 (s), 1140 (s), 842 (m), 799 (m), 725 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.83 (m, 2H, NCH₂CH₂), 2.45 (dd, J=6 Hz, 16 Hz, 1H, ArCH₂), 2.74-3.00 (overlapping m, 4H, ArCH₂, CH₂, CH₂CO₂), 3.19 (m, 2H, NCH₂CH₂), 3.88 (t, J=6 Hz, 2H, OCH₂), 5.09 (d, J=16 Hz, 1H, CH₂Ph), 5.16 (d, J=16 Hz, 1H, CH₂Ph), 6.48 (d, J=2 Hz, 1H, ArH), 6.56 (dd, J=2 Hz, 8 Hz, 1H, ArH), 6.64-7.44 (broad, 4H, [C(NH₂)₂]⁺), 7.13 (d, J=8 Hz, 1H, ArH), 7.19-7.33 (overlapping m, 5H, ArH), 7.52 (t, J=6 Hz, 1H, NHCH₂), 12.2 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 411 (M+H, 20).

35 Analysis calc. for C₂₂H₂₆N₄O₄•CF₃COOH C,

54.96; H, 5.19; N, 10.68

Found C, 54.56; H,

4.78; N, 10.62

Example 173

40 [1-Benzyl-7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]acetic acid

5 The title compound is prepared according to the
procedure of Example 84 except that [7-(4-guanidino-butoxy-
2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid methyl
ester trifluoroacetate is replaced with [1-benzyl-7-(4-
10 guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]acetic acid methyl ester.

Example 174

[1-Benzyl-7-(2-guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]acetic acid

15 The title compound is prepared according to the
procedure of Example 84 except that [7-(4-guanidinobutoxy-
2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid methyl
ester trifluoroacetate is replaced with [1-benzyl-7-(2-
20 guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]acetic acid methyl ester.

20

25

Example 175

[7-(2-tert-Butoxycarbonylamino-ethoxy)-2-oxo-1,2-
dihydro-quinolin-3-yl]-acetic acid methyl ester

30 The title compound is prepared according to the
procedure of Example 75 except that (7-hydroxy-2-oxo-1,2-
dihydro-quinolin-3-yl)-acetic acid methyl ester is used in
place of (7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
35 yl)-acetic acid methyl ester.

Example 176

35 [7-(4-tert-Butoxycarbonylamino-butoxy)-2-oxo-1,2-
dihydro-quinolin-3-yl]-acetic acid methyl ester

40 The title compound is prepared according to the
procedure of Example 75 except that (4-bromobutyl)-carbamic
acid tert-butyl ester is used in place of (3-bromopropyl)-
carbamic acid tert-butyl ester and that (7-hydroxy-2-oxo-
40 1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester is used

5 in place of (7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester.

Example 177

10 [7-(3-tert-Butoxycarbonylamino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester

The title compound is prepared according to the procedure of Example 75 except that (3-bromopropyl)-carbamic acid tert-butyl ester is used in place of (2-bromoethyl)-carbamic acid tert-butyl ester and that (7-
15 hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid methyl ester is used in place of (7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid methyl ester.

Example 178

20 [7-(2-Amino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

The title compound is prepared according to the procedure of Example 78 except that [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester is used in place of [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
25 quinolin-3-yl]-acetic acid methyl ester.

Example 179

30 [7-(4-Amino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

The title compound is prepared according to the procedure of Example 78 except that [7-(4-tert-butoxycarbonylamino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester is used in place of [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
35 quinolin-3-yl]-acetic acid methyl ester.

Example 180

40 [7-(3-Amino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester Trifluoroacetate

The title compound is prepared according to the procedure of Example 78 except that [7-(3-tert-

5 butoxycarbonylamino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester is used in place of [7-(2-tert-butoxycarbonylamino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester.

Example 181

10 [7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [7-(4-amino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

Example 182

20 [7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester

The title compound is prepared according to the procedure of Example 81 except that [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [7-(4-amino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

5

Example 183[7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester

The title compound is prepared according to the
10 procedure of Example 81 except that [7-(2-amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate is replaced with [7-(3-amino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

15

Example 184[7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Hydrochloride

The product of the example was obtained using the
conditions of Example 84 and replacing [7-(4-guanidino-
20 butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate with [7-(4-guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester.
Mp. 216.5-19.0 °C.

IR (KBr): 3400 (m), 3310 (m), 1700 (m), 1645 (s), 1408 (m), 1290 (w), 1250 (m),
25 1222 (m), 1172 (m), 837 (w), 773 (w) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.62 (m, 2H, NCH_2CH_2), 1.77 (m, 2H, OCH_2CH_2), 3.17 (m, 2H, NCH_2), 4.03 (t, $J=6$ Hz, 2H, OCH_2), 6.78-6.81 (overlapping m, 2H, ArH), 6.84-7.48 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.53 (d, $J=8.5$ Hz, 1H, ArH), 7.74-7.76 (overlapping s, t, $J=6$ Hz, 2H, $\text{ArCH}=\text{NCH}_2$), 11.7 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).
30

MS (+FAB) m/e (rel. intensity): 333 (M+H, 100).

Analysis calc. for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_4 \cdot \text{HCl}$

C, 52.11; H, 5.74;

N, 15.19

Found

C, 52.05; H, 5.72;

35 N, 15.15

Example 185[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid

The product of the example was obtained using the
40 conditions of Example 84 and [7-(2-guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester

5 trifluoroacetate in place of [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

Mp. 219-20 °C.

IR (KBr): 3490 (s), 3140 (s), 1718 (s), 1685 (s), 1630 (s), 1468 (m), 1449 (m), 1290 (m), 1230 (s), 1178 (s), 1117 (s), 828 (m), 808 (w), 782 (m), 710 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 3.41 (s, 2H, CH_2CO_2), 3.55 (m, 2H, NCH_2), 4.10 (t, $J=5$ Hz, 2H, OCH_2), 6.80-6.83 (overlapping m, 2H, ArH), 6.86-7.52 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.56 (d, $J=8.5$ Hz, 1H, ArH), 7.71 (t, $J=5.5$ Hz, 1H, NHCH_2), 7.75 (s, 1H, $\text{ArCH}=\text{}$), 11.7 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).

15 MS (+FAB) m/e (rel. intensity): 305 (M+H, 100).

Analysis calc. for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH}$ C, 45.94; H, 4.10; N, 13.39

Found C, 45.86; H, 3.80; N, 13.24

20 Example 186

[7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate

The product of the example was obtained using the conditions of Example 84 and [7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate in place of [7-(4-guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester trifluoroacetate.

Mp. 195-98°C (degasses).

30 IR(KBr): 3440 (s), 1712 (s), 1655 (s), 1627 (s), 1611 (s), 1493 (m), 1419 (m), 1240 (s), 1200 (s), 1180 (s), 1122 (s), 838 (m), 810 (w), 798 (m), 723 (w) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.96 (m, 2H, NCH_2CH_2), 3.29 (m, 2H, NCH_2), 3.41 (s, 2H, CH_2CO_2), 4.04 (t, $J=6$ Hz, 2H, OCH_2), 6.79-6.82 (overlapping m, 2H, ArH), 6.84-7.45 (broad, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.54 (d, $J=8$ Hz, 1H, ArH), 7.61 (t, $J=5$ Hz, 1H, NHCH_2), 7.74 (s, 1H, $\text{ArCH}=\text{}$), 11.7 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).

MS (+FAB) m/e (rel. intensity): 319 (M+H, 100).

Analysis calc. for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 0.3 \text{H}_2\text{O}$ C, 46.64; H, 4.52; N, 12.80

40 Found C, 46.60; H, 4.34; N, 12.57

5

Example 1874-Formyl-3-nitro-benzoic acid tert-butyl ester

A solution of tert-butyl 3-nitro-4-bromomethyl
10 benzoate (Kashman, Y.; Edwards J.A. *J. Org. Chem.* 43, 1538,
(1978), (20g, 63.3 mmol) and pyridine (5.6 mL, 69.6 mmol)
in ethanol (50 mL) was heated at reflux for 45 min. The
solution was allowed to cool to 25°C and the resulting
precipitate was collected and washed with ethanol to give a
15 white solid. The filtrate was concentrated to give
additional precipitate. To the combined solids and ethanol
(70 mL) was added p-nitrosodimethylaniline (9.5 g, 63.3
mmol) and 2.0 N aqueous sodium hydroxide (39.5 mL, 79 mmol)
at 0°C according to the procedure described in Organic
20 Synthesis, Collective Volume V, p. 825. After 1 h a dark
solid was collected and washed with water. The solid was
treated with 6N aqueous sulfuric acid (100 mL). After 15
min, ice was added and the resulting beige solid filtered
and washed with water. Drying in vacuo gave the title
25 compound as a beige powder (9.08 g, 57%). NMR (dms_o-d₆,
200 MHz) : δ 1.6 (s, 9H, C(CH₃)₃), 8 - 8.5 (m, 3H, ArH),
10.3 (s, 1 H, CHO).

Example 188

30 2-(4-tert-Butoxycarbonyl-2-nitro-benzylidene)-succinic acid
dimethyl ester

Triphenylphosphine (13.3 g, 50.7 mmol) and dimethyl
maleate (7.31 g, 50.7 mmol) were combined in glacial acetic
acid (62 mL) at 25°C and stirred for 6 h whereupon benzene
35 (164 mL) and 4-formyl-3-nitro-benzoic acid tert-butyl
ester (8.5 g, 33.8 mmol) was added. The dark solution was
heated at reflux for 18 h then cooled to 25°C.
Concentration in vacuo gave a dark oil. Flash
chromatography (silica gel, hexane/ethyl acetate) affords
40 the title compound as an amber oil (11.1 g, 87%). NMR
(dms_o-d₆, 300 MHz) : δ 1.6 (s, 9H, tert-butyl), 3.3 (s, 2H,

5 CH₂), 3.6 (s, 3H, CH₃), 3.8 (s, 3H, CH₃), 7.5 - 8.6 (m, 4H, ArH, ArCH).

Example 189

10 3-Methoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-carboxylic acid tert-butyl ester

A solution of 2-(4-tert-butoxycarbonyl-2-nitro-benzylidene)-succinic acid dimethyl ester (5.0 g, 13.2 mmol) in methanol (40 mL) with 10% Pd/C was hydrogenated at 50 psi and 25°C for 20 h. The reaction mixture was
15 filtered to afford after evaporation in vacuo the title compound as a gray solid (3.56 g, 85%). NMR (dms_o-d₆, 200 MHz) : δ 1.5 (s, 9H, tert-butyl), 2.7 - 3.4 (m, 5H, CH₂CHCH₂), 3.6 (s, 3H, CH₃), 7.2 - 7.5 (m, 3H, ArH), 10.3 (s, 1 H, NH).

20

Example 190

3-Methoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-7-carboxylic acid

A suspension of 3-methoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-7-carboxylic acid tert-butyl ester (3.5
25 g, 13.2 mmol) in dioxane (40 mL) was treated with 10 mL of 4N hydrochloric acid in dioxane and heated to 40 - 50°C. Evaporation of the volatiles in vacuo gave the title compound (3.35 g, 97%). NMR (dms_o-d₆, 200 MHz) : δ 2.7 - 3.4 (m, 5H, CH₂CHCH₂), 3.6 (s, 3H, CH₃), 7.2 - 7.5 (m, 3H, ArH), 10.3 (s, 1 H, NH).
30

Example 191

[7-(3-tert-Butoxycarbonylamino-propylcarbonyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

To a solution of 3-methoxycarbonylmethyl-2-oxo-
35 1,2,3,4-tetrahydro-quinoline-7-carboxylic acid (1.0 g, 3.8 mmol) in DMF (20 mL) at 25°C was added 1-hydroxy-benzotriazole hydrate (HOBT) (0.565 g, 4.18 mmol). The solution was cooled to 0°C and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DAEC) (0.801 g, 4.18
40 mmol) was added. After 10 min the reaction mixture was allowed to warm to 25°C. After 2 h triethylamine (1.3 mL)

5 was added and tert-butyl-N(3-aminopropyl)carbamate (0.66 g,
3.8 mmol) added after 30 minutes. After 20 h ethyl acetate
was added and the mixture washed with 0.1 N aqueous
hydrochloric acid (3X), aqueous sodium bicarbonate (3X) and
brine. The organic layer was dried over anhydrous
10 magnesium sulfate and concentrated in vacuo to give the
title compound as a light brown powder. NMR (dms_o-d₆, 200
MHz) : δ 1.4 (s, 9H, tert-butyl), 1.6 (m, 2H, CH₂), 2.7 -
3.3 (m, 9H, CH₂CHCH₂, NCH₂, NCH₂), 3.6 (s, 3H, CH₃), 6.8
(t, 1H, NH), 7.2 - 7.4 (m, 3H, ArH), 8.3 (t, 1H, NH), 10.3
15 (s, 1 H, NH).

Example 192

[7-(2-tert-Butoxycarbonylamino-ethylcarbamoyl)-2-oxo-
20 1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 191 and tert-butyl-
N(2-aminoethyl)carbamate in place of tert-butyl-N(3-
aminopropyl)carbamate the product of the example is
obtained.

25 Example 193

[7-(4-tert-Butoxycarbonylamino-butylcarbamoyl)-2-oxo-
1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester

Using the conditions of Example 191 and tert-butyl-
N(4-aminobutyl)carbamate in place of tert-butyl-N(3-
30 aminopropyl)carbamate the product of the example is
obtained.

Example 194

[7-(2-Amino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester

35 Using the conditions of Example 78 and [7-(2-tert-
butoxycarbonylamino-ethylcarbamoyl)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place
of [7-(2-tert-butoxycarbonylaminoethoxy)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]acetic acid methyl ester, the
40 product of the example is obtained.

Example 195

5 [7-(3-Amino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid methyl ester

 Using the conditions of Example 78 and [7-(3-tert-
butoxycarbonylamino-propylcarbamoyl)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place
10 of [7-(2-tert-butoxycarbonylaminoethoxy)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]acetic acid methyl ester, the
product of the example is obtained.

Example 196

15 [7-(4-Amino-butylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid methyl ester

 Using the conditions of Example 78 and [7-(4-tert-
butoxycarbonylamino-butylcarbamoyl)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place
of [7-(2-tert-butoxycarbonylaminoethoxy)-2-oxo-1,2,3,4-
20 tetrahydro-quinolin-3-yl]acetic acid methyl ester, the
product of the example is obtained.

Example 197

[7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid methyl ester

25 Using the conditions of Example 81 and [7-(2-amino-
ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-
acetic acid methyl ester in place of [7-(2-aminoethoxy)-2-
oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl
ester, the product of the example is obtained.

30 Example 198

[7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid methyl ester

 Using the conditions of Example 81 and [7-(3-amino-
propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-
35 acetic acid methyl ester in place of [7-(2-aminoethoxy)-2-
oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl
ester, the product of the example is obtained.

Example 199

40 [7-(4-Guanidino-butylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-acetic acid methyl ester

- 5 Using the conditions of Example 81 and [7-(4-amino-butylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-aminoethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester, the product of the example is obtained.

5

Example 200[7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride

Using the conditions of Example 85 and [7-(2-
10 guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-
guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]acetic acid methyl ester, the product of the example was
obtained as a white powder.

15

^1H NMR (D₂O, 400 MHz): δ 2.4-2.9 (overlapping m, 5H, ArCH₂CH₂CH₂CO₂), 3.24 (t, 2H, J = 5.7 Hz, NCH₂), 3.37 (t, 2H, J = 5.7 Hz, NCH₂), 7.03 (d, 1H, J = 1.8 Hz, ArH), 7.13 (d, 1H, J = 7.9 Hz, ArH), 7.20 (dd, 1H, J = 1.8, 7.9 Hz, ArH).

20

MS (+FAB) m/e (rel. intensity): 334 (M+H, 75).
Analysis calc. for C₁₅H₁₉N₅O₄•HCl•1.3H₂O C, 45.82; H, 5.79 N,
17.81

Found C, 45.45; H, 5.85; N, 18.13

25

Example 201[7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride

Using the conditions of Example 85 and [7-(3-
30 guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-
guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]acetic acid methyl ester, the product of the example was
obtained as a white powder.

^1H NMR (D₂O, 400 MHz): δ 1.70 (p, 2H, J = 6.8 Hz, -CH₂-) J = 2.4-
35 2.9 (overlapping m, 5H, ArCH₂CH₂CH₂CH₂CO₂), 3.06 (t, 2H, J = 6.8 Hz, NCH₂), 3.25 (t, 2H, J = 6.8 Hz, NCH₂), 7.01 (d, 1H, J = 1.8 Hz, ArH), 7.11 (d, 1H, J = 7.9 Hz, ArH), 7.19 (dd, 1H, J = 1.8, 7.9 Hz, ArH).

MS (+FAB) m/e (rel. intensity): 348 (M+H, 37).

40 Analysis calc. for C₁₆H₂₁N₅O₄•HCl•0.4H₂O C, 49.15; H, 5.88 N,
17.91

5 FoundC, 48.79; H, 5.73; N, 18.28

Example 202

10 [7-(4-Guanidino-butylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid hydrochloride

Using the conditions of Example 85 and [7-(4-guanidino-butylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid methyl ester in place of [7-(2-guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]acetic acid methyl ester, the product of the example was
15 obtained as a white powder.

IR (KBr): 3395 (s), 3350 (s), 1720 (s), 1670 (s), 1570 (s), 1410 (s), 1240 (s), 1160 (s), 875 (m), 7000 (s) cm^{-1} .

^1H NMR (D_2O , 400 MHz): δ 1.45 (bd s, 4H, $-\text{CH}_2\text{CH}_2-$), 2.4-2.9
20 (overlapping m, 5H, $\text{ArCH}_2-\text{CH}-\text{CH}_2\text{CO}_2$), 3.01 (bd s, 2H, NCH_2), 3.19 (bd s, 2H, NCH_2), 7.02 (s, 1H, ArH), 7.12 (m, 1H, ArH), 7.19 (m, 1H, ArH).

Analysis calc. for $\text{C}_{17}\text{H}_{23}\text{N}_5\text{O}_4 \cdot \text{HCl}$ C, 51.32; H, 6.08 N, 17.60
Found C, 50.46; H, 6.07; N, 16.93

25

Example 203

[7-(4-Amino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
yl]-acetic acid

The product of the example was obtained using the
30 conditions of Example 84 and the product of Example 79.

Mp. 229-30 $^\circ\text{C}$.

IR (KBr): 3530 (m), 3140 (m), 1714 (s), 1692 (s), 1640 (s), 1611 (s), 1464 (m), 1240 (s), 1183 (s), 1158 (m), 1118 (s), 848 (m), 825 (m), 807 (m), 787 (m), 710 (m) cm^{-1} .

35 ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 1.70 (m, 2H, NCH_2CH_2), 1.79 (m, 2H, OCH_2CH_2), 2.86 (m, 2H, NCH_2), 3.41 (s, 2H, CH_2CO_2), 4.03 (t, $J=6$ Hz, 2H, OCH_2), 6.78-6.80 (overlapping m, 2H, ArH), 7.54 (d, $J=9$ Hz, 1H, ArH), 7.58-7.82 (overlapping broad s, s, 4H, NH_3^+ , $\text{ArCH}=\text{}$), 11.7 (s, 1H, ArNH), 12.2
40 (broad s, 1H, CO_2H).

MS (+FAB) m/e (rel. intensity): 291 (M+H, 30).

5 Analysis calc. for $C_{15}H_{18}N_2O_4 \cdot CF_3COOH \cdot 0.25 H_2O$ C,
49.94; H, 4.81; N, 6.85
Found C, 49.67; H,
5.02; N, 7.10

10

Example 204

[7-(2-Amino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

Using the conditions of Example 84 and the
15 product of Example 78 the title compound was obtained.
Mp. 205-08 °C (degasses).
IR (KBr): 3110 (m), 1678 (s), 1642 (m), 1600 (m), 1290
(s), 1238 (m), 1200 (s), 1177 (s), 1157 (s), 1130 (s), 842
(m), 822 (m), 800 (m), 722 (m) cm^{-1} .
20 1H NMR (DMSO- d_6 , 400 MHz): δ 2.35 (m, 1H, ArCHH), 2.67-
2.88 (overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.21 (t, J=5
Hz, 2H, NCH₂), 4.08 (t, J=5 Hz, 2H, OCH₂), 6.49 (d, J=2.5
Hz, 1H, ArH), 6.54 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 7.09 (d,
J=8 Hz, 1H, ArH), 7.99 (broad s, 3H, NH₃⁺), 10.2 (s, 1H,
25 ArNH), 12.9 (broad s, 1H, CO₂H).
MS (+DCI) m/e (rel. intensity): 265 (M+H, 100).
Analysis calc. for $C_{13}H_{16}N_2O_4 \cdot CF_3 \cdot COOH$ C,
47.62; H, 4.53; N, 7.40
Found C, 47.84; H,
30 4.48; N, 7.43

Example 205

[7-(3-Amino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

35 Using the conditions of Example 84 and the
product of Example 80 the title compound was obtained.
Mp. 194-96 °C.
IR (KBr): 3410 (m), 3090 (m), 1743 (m), 1722 (s), 1672
(s), 1630 (m), 1287 (m), 1185 (s), 1130 (s), 862 (m), 832
40 (m), 798 (m), 778 (m), 720 (m) cm^{-1} .

- 5 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.97 (m, 2H, NCH_2CH_2), 2.34 (m, 1H, ArCHH), 2.66-2.87 (overlapping m, 4H, ArCHH , CH , CHHCO_2), 2.94 (broad, 2H, NCH_2), 3.98 (t $J=6$ Hz, 2H, OCH_2), 6.43 (d, $J=2.5$ Hz, 1H, ArH), 6.50 (dd, $J=2.5$ Hz, 8 Hz, 1H, ArH), 7.07 (d, $J=8$ Hz, 1H, ArH), 7.74 (broad s, 3H, NH_3^+),
 10 10.0 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).
 MS (+FAB) m/e (rel. intensity): 279 (M+H, 14).
 Analysis calc. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4 \cdot \text{CF}_3\text{COOH}$ C,
 48.98; H, 4.88; N, 7.14
 Found C, 49.09; H,
 15 4.54; N, 7.16

Example 206[7-(4-Amino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

- Using the conditions of Example 84 and the
 20 product of Example 79 the title compound was obtained.
 Mp. 152.5-55.0°C.
 IR (KBr): 3490 (m), 3225 (m), 3130 (m), 1700 (s), 1615 (s), 1622 (m), 1593 (s), 1434 (m), 1260 (m), 1188 (s), 1127 (s), 849 (m), 832 (m), 808 (m), 792 (m), 718 (m) cm^{-1} .
 25 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.63-1.78 (overlapping m, 4H, NCH_2CH_2 , OCH_2CH_2), 2.34 (m, 1H, ArCHH), 2.66-2.87 (overlapping m, 6H, ArCHH , CH , CHHCO_2 , NCH_2), 3.91 (t, $J=6$ Hz, 2H, OCH_2), 6.42 (d, $J=2$ Hz, 1H, ArH), 6.49 (dd, $J=2$ Hz, 8 Hz, 1H, ArH), 7.06 (d, $J=8$ Hz, 1H, ArH), 7.70 (broad s, 3H, NH_3^+), 10.1 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).
 30 MS (+FAB) m/e (rel. intensity): 293 (M+H, 17).
 Analysis calc. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 0.5 \text{H}_2\text{O}$ C,
 49.15; H, 5.35; N, 6.75
 Found C, 48.95; H,
 35 5.41; N, 6.60

Example 207(6-Methoxy-3,4-dihydro-1H-naphthalen-2-ylidene)-acetic acid ethyl ester

- 40 A suspension of 2,6-dimethoxynaphthalene (20.0 g, Aldrich) in 200 mL of anhydrous EtOH was heated to reflux

5 under a stream of nitrogen. Sodium spheres (18 g, Aldrich)
were added gradually to the hot suspension over a period of
2 hours. Additional EtOH (50 mL) was added and the reaction
was heated until all of the sodium had dissolved. The
solution was cooled to room temperature and placed in an
10 ice bath. The addition of 6 N HCl brought the solution to
pH 6, and additional HCl (10 mL) was added. The solution
was heated to reflux for 0.5 h. The golden mixture was
cooled to room temperature, H₂O (200 mL) was added, and the
solution was extracted with Et₂O. The combined Et₂O
15 extracts were dried (Na₂SO₄), filtered, and concentrated to
afford 6-methoxy-2-tetra-lone as a red oil (23.5 g).
Triethyl phosphono-acetate (29 mL, Aldrich) was added
dropwise to a suspension of hexane-washed sodium hydride
(5.8 g of 60 % dispersion) in benzene (80 mL) cooled in an
20 ice bath. The phos-phonate solution was stirred at room
temperature for 0.5 h, and the ice bath was replaced. A
solution of 6-methoxy-2-tetralone (23.5 g) in benzene (20
mL) was added to the phosphonate solution over 10 minutes,
and the reaction was allowed to stir at room temperature
25 overnight. The reaction was poured into H₂O and extracted
with EtOAc (3 x 150 mL). The combined extracts were dried
(Na₂SO₄), filtered, and concentrated to afford a brown oil
which was purified using silica gel chromatography. Elution
with 10 % EtOAc / hexane afforded the title compound (27 g)
30 as a yellow oil. NMR (300 MHz, CDCl₃) δ 6.98 (d, J = 9.03
Hz, 1 H), 6.79 - 6.70 (m, 2H), 6.35 (s, 1H), 3.94 (q, J =
7.11 Hz, 2H), 3.58 (s, 3H), 2.99 (s, 2H), 2.61 (t, J = 8.11
Hz, 2H), 2.14 (t, J = 8.07 Hz, 2H), 1.08 (t, J = 7.14 Hz, 3
H).

35

Example 208

(6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid
ethyl ester

40

A mixture of 6-methoxy-3,4-dihydro-1H-naphthalen-
2-ylidene)-acetic acid ethyl ester

5 (27 g) in EtOH (200 mL) and 10 % Pd/C (0.3 g) was
hydrogenated at 40 psi over 5 h. The mixture was filtered
through diatomaceous earth and washed with EtOH (50 mL).
The filtrate was concentrated under reduced pressure to
give the product of the example as a yellow oil (27 g).
10 NMR (300 MHz, CDCl₃) δ 7.02 (d, J = 8.34 Hz, 1H), 6.74 (dd,
J = 8.34, 2.67 Hz, 1H), 6.67 (d, J = 2.52 Hz, 1H), 4.22 (q,
J = 7.12 Hz, 2H), 3.82 (s, 3H), 2.93 - 2.85 (m, 3H), 2.52 -
2.40 (m, 3H), 2.33 - 2.28 (m, 1H), 2.03 - 1.97 (m, 1H),
1.55 - 1.51 (m, 1H), 1.33 (t, J = 7.11 Hz, 3H).

15

Example 209

(6-Hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid
methyl ester

To a solution of (6-methoxy-1,2,3,4-tetrahydro-
20 naphthalen-2-yl)-acetic acid ethyl ester
(6.2 g) in CH₂Cl₂ (50 mL) cooled to -78°C under N₂ was
added dropwise boron tribromide in CH₂Cl₂ (1.0 M, 100 mL,
Aldrich). The solution was stirred for 1 h at -78°C and 2 h
at 0°C, then cooled again to -78°C. Methanol (25 mL) was
25 added and the solution was allowed to warm to room
temperature overnight. The brown solution was concentrated
under reduced pressure and the resulting oil was purified
using silica gel chromatography. Elution with a gradient of
20 % EtOAc/hexane to 60 % EtOAc/hexane afforded the product
30 of the example as a tan powder (3.4 g). NMR (300 MHz,
CDCl₃) δ 6.89 (d, J = 8.15 Hz, 1H), 6.59 (d of d, J = 8.10,
2.66 Hz, 1H), 6.55 (d, J = 2.44 Hz, 1H), 5.37 (s, 1H),
3.71 (s, 3H), 2.79 - 2.74 (m, 3H), 2.41 - 2.36 (m, 3H),
2.28 - 2.17 (m, 1H), 1.94 - 1.88 (m, 1H), 1.49 - 1.35 (m,
35 1H).

Example 210

{6-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxyl]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl
ester

40 To a solution of (6-hydroxy-1,2,3,4-tetrahydro-
naphthalen-2-yl)-acetic acid methyl ester,

5 (11.9 g) in DMF (45 mL) was added sodium hydride (2.2 g, 60
% dispersion) in portions over 0.5 h. The solution was
stirred at room temperature for 1h, and N-(3-
bromopropyl)phthalimide (14.6 g) was added in one portion.
The solution was stirred at room temperature for 1h, then
10 concentrated under reduced pressure. The resulting material
was suspended in EtOAc and filtered to remove the salt. The
filtrate was concentrated to a brown oil and applied to a
silica gel column. Elution with 2 % acetone in CHCl₃
afforded the product of the example also containing (6-
15 hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid
methyl ester.
A solution of the combined material in CH₂Cl₂ was washed
sequentially with 1 N NaOH solution and brine. The solution
was dried (Na₂SO₄), filtered, and concentrated to afford
20 the product of the example as a yellow powder (17.7 g). NMR
(300 MHz, CDCl₃) δ 7.70 (dd, J = 5.47, 3.03 Hz, 2H), 7.57
(dd, J = 5.43, 3.05 Hz, 2H), 6.77 (d, J = 8.36 Hz, 1H),
6.43 (dd, J = 8.32, 2.62 Hz, 1H), 6.37 (d, J = 2.45 Hz,
1H), 3.85 (t, J = 6.06 Hz, 2H), 3.76 (t, J = 6.89 Hz, 2H),
25 3.56 (s, 3H), 2.70 - 2.60 (m, 3H), 2.47 - 2.33 (m, 3H), 2.26
- 2.14 (m, 3H), 2.02 - 1.91 (m, 1H), 1.51 - 1.38 (m, 1H);
MS (+APCI) m/z 408 (M+H)⁺; Calculated for C₂₄H₂₅NO₅: C,
70.75; H, 6.18; N, 3.44. Found: C, 70.35; H, 6.15; N, 3.25.

30

Example 211[6-(3-Amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-
acetic acid methyl ester

To a suspension of {6-[3-(1,3-dioxo-1,3-dihydro-
isoindol-2-yl)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-
35 yl}-acetic acid methyl ester, (17.7 g) in isopropyl alcohol
(350 mL) heated at 55°C was added hydrazine (3 mL). The
mixture was heated to reflux for 1.5 h, then the reaction
mixture was allowed to stand at room temperature overnight.
Concentrated HCl (7.8 mL) was added, the mixture was
40 stirred for 10 minutes, and filtered. The white solid was
washed with isopropyl alcohol. The filtrate was

5 concentrated under reduced pressure and applied to a silica
gel column. Elution with 2 % NH₄OH/10 % MeOH/CH₂Cl₂
afforded the product of the example as a golden oil which
solidified on standing (8.0 g). NMR (300 MHz, CDCl₃) δ
6.95 (d, J = 8.34 Hz, 1H), 6.67 (dd, J = 8.30, 2.55 Hz,
10 1H), 6.62 (d, J = 2.16 Hz, 1H), 4.01 (t, J = 6.07 Hz, 2H),
3.69 (s, 3H), 2.93 (broad s, 2H), 2.86 - 2.77 (m, 3H), 2.46
- 2.36 (m, 3H), 2.26 - 2.18 (m, 1H), 2.12 - 1.98 (broad s,
2H), 1.93 (m, 3H), 1.51 -1.38 (m, 1H).

5

Example 212{6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester

A solution of [6-(3-amino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid methyl ester, (5.8 g), 2-bromopyrimidine (3.5 g), chlorotrimethyl-silane (21.5 mL), and diisopropylethyl amine (29 mL) in 1,4-dioxane (100 mL) was heated to reflux for 72 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with H₂O, dried (Na₂SO₄), filtered, and concentrated. The dark oil was purified by silica gel chromatography. Elution with a gradient of CH₂Cl₂ to 1 % MeOH/CH₂Cl₂ to 2 % MeOH/ CH₂Cl₂ gave the product of the example as a slightly yellow solid (4.68 g). NMR (300 MHz, CDCl₃) δ 8.26 (d, J = 4.79 Hz, 2H), 6.95 (d, J = 8.35 Hz, 1H), 6.67 (dd, J = 8.29, 2.62 Hz, 1H), 6.62 (d, J = 2.37 Hz, 1H), 6.50 (t, J = 4.82 Hz, 1H), 5.49 (broad s, 1H), 4.04 (t, J = 5.93 Hz, 2H), 3.70 (s, 3H), 3.61 (q, J = 6.46 Hz, 2H), 2.86 - 2.77 (m, 3H), 2.46 - 2.36 (m, 3H), 2.27 - 2.20 (m, 1H), 2.08 (dt, J = 12.53, 6.31 Hz, 2H), 1.96 - 1.89 (m, 1H), 1.51 - 1.40 (m, 1H); Calculated for C₂₀H₂₅N₃O₃•0.20 CH₂Cl₂: C, 65.15; H, 6.87; N, 11.28. Found: C, 65.11; H, 6.89; N, 10.81.

Example 213{6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid

To a solution of {6-[3-(pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester (0.09 g) in 1,4-dioxane (5 mL) was added a solution of LiOH•H₂O (0.04 g) in H₂O (2 mL) and the reaction was heated to 100°C for 1h. The reaction was cooled to room temperature and concentrated under reduced pressure. Water was added to the residue and the mixture was cooled in an ice bath. The mixture was brought to pH 5 by the addition of 1N HCl. The aqueous suspension was extracted with CH₂Cl₂ and CHCl₃. The combined organic

5 layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography. Elution with 10% MeOH/CH₂Cl₂ gave the title compound as a white solid (14 mg). NMR (300 MHz, MeOH-d₄) δ 8.24 (broad s, 2H), 7.32
10 (broad s, 1H), 6.82 (d, J = 8.25 Hz, 1H), 6.68 - 6.63 (m, 2H), 6.52 (t, J = 4.76 Hz, 1H), 4.08 (t, J = 6.11 Hz, 2H), 3.63 (d, J = 5.59 Hz, 2H), 2.83 (dd, J = 15.90, 3.70 Hz, 1H), 2.71 (d, J = 3.32 Hz, 2H), 2.42 - 2.34 (m, 3H), 2.11 (dd, J = 11.82, 5.88 Hz, 3H), 1.90 (d, J = 11.76 Hz, 1H),
15 1.46 - 1.32 (m, 1H); MS (+ESI) m/z 342 (M+H)⁺; Calculated for C₁₉H₂₃N₃O₃•0.5 H₂O: C, 64.94; H, 6.88; N, 11.96. Found: C, 65.43; H, 6.72; N, 11.48.

Example 214

20 {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid

A mixture of {6-[3-(pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester (0.29 g), 10% Pd/C (0.03 g), acetic acid (5 mL), and 1N HCl (2 mL) was stirred under H₂ atmosphere
25 (balloon) for 7 days. The mixture was filtered through diatomaceous earth and washed with 1N HCl. The filtrate was concentrated under reduced pressure and azeotroped with toluene. The residue was dissolved in 1% ammonium hydroxide/10 % MeOH/CH₂Cl₂ and eluted from a silica gel
30 column with this solution. The product was further purified using reverse phase silica gel, eluting with 20 % and 40 % CH₃CN/H₂O, and reverse phase HPLC, eluting with 37 % CH₃CN/H₂O, to provide the title compound as a hygroscopic ivory powder (66 mg). NMR (300 MHz, MeOH-d₄) δ 6.93 (d, J =
35 5.52 Hz, 1H), 6.68 - 6.65 (m, 2H), 4.01 (t, J = 5.35 Hz, 2H), 3.33 - 3.32 (m, 4H), 2.80 (s, 2H), 2.42 - 2.31 m, 3H), 2.42 - 2.31 (m, 3H), 2.29 - 2.16 (m, 1H), 2.03 - 1.92 (m, 3H), 1.46 - 1.33 (m, 1H); MS (+ESI) m/z 346 (M+H)⁺.

5

Example 215

{6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester bis(hydrochloride)

10 To a solution of {6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid (25 mg) in MeOH (2 mL) was added HCl in MeOH and the solution was heated to reflux for 3h. The reaction was cooled to room temperature and
15 concentrated under reduced pressure to afford a tan oil. Ether was added, the contents were swirled and the solvent decanted. Lyophilization of the oily residue gave the title compound as a hygroscopic, ivory solid (29 mg). NMR (300 MHz, MeOH-d₄) δ 6.84 (d, J = 8.20 Hz, 1H), 6.61 - 6.56 (m, 2H), 3.92 (t, J = 5.75 Hz, 2H), 3.59 (s, 3H), 3.28 - 3.21 (m, 5H), 2.72 - 2.68 (m, 3H), 2.33 - 2.24 (m, 3H), 2.09 - 2.06 (m, 1H), 1.92 (t, J = 7.09 Hz, 2H), 1.87 - 1.77 (m, 3H), 1.37 - 1.19 (m, 2H); MS (+ESI) m/z 360 (M+H)⁺; Calculated for C₂₀H₂₉N₃O₃•2 HCl: C, 55.56; H, 7.23; N, 9.72. Found: C, 55.15; H, 7.10; N, 9.88.
25

Example 216

{6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid ethyl ester, acetic acid salt

30 To a solution of {6-[3-(pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester (4.68 g) in 1,4-dioxane (170 mL) was added a solution of LiOH•H₂O (1.66 g) in H₂O (25 mL) and the
35 reaction was heated to 100°C for 0.5 h. The reaction was cooled to room temperature and concentrated under reduced pressure. Water (250 mL), EtOAc (150 mL), and Et₂O (100 mL) were added to the residue and the mixture was filtered to obtain a white solid. The aqueous layer of the filtrate was
40 combined with the collected solid and the suspension was concentrated under reduced pressure. Water (15 mL),

5 concentrated HCl (10 mL), acetic acid (5 mL), EtOH (50 mL),
and 10% Pd/C (0.04 g) were added to the residue. The
mixture was stirred under H₂ pressure (balloon) overnight.
The mixture was filtered through diatomaceous earth and
washed with EtOH. The filtrate was concentrated under
10 reduced pressure. Absolute EtOH (120 mL) and 1M HCl in Et₂O
(20 mL) were added to the syrup and the solution was heated
to reflux for 1.5 h. The reaction was cooled to room
temperature and concentrated under reduced pressure. The
residue was adsorbed onto silica gel and purified by silica
15 gel chromatography, eluting with 2% acetic acid/2%
MeOH/CHCl₃ and 5% acetic acid/5% MeOH/CHCl₃. After a pass
through a second silica gel column using the same
conditions, the residue was lyophilized to give the title
compound as a hygroscopic, beige solid (2.56 g). NMR (300
20 MHz, MeOH-d₄) δ 6.99 (d, J = 10.98 Hz, 1H), 6.68 - 6.61 (m,
2H), 4.12 (q, J = 7.12 Hz, 2H), 3.96 (t, J = 5.71 Hz, 2H),
3.33 - 3.25 (m, 8H), 2.76 - 2.73 (m, 3H), 2.39 - 2.31 (m,
3H), 2.15 - 2.00 (m, 1H), 1.95 (dd, J = 12.23, 6.31 Hz, 2H),
1.90 - 1.82 (m, 5H), 1.47 - 1.36 (m, 1H), 1.23 (t, J = 7.13
25 Hz, 3H); MS (+ESI) m/z 374 (M+H)⁺.

Example 217

4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-
propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-
30 benzenesulfonamide, trifluoroacetic acid salt

To {6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid (0.39 g) was added paratoluenesulfonamide (0.29 g), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide
35 hydrochloride (0.33 g), dimethylaminopyridine (0.02 g), and DMF (20 mL) and the resulting solution was stirred under N₂ at room temperature for 48 h. The DMF was removed by vacuum distillation. Water (25 mL) was added, and saturated NaHCO₃ solution was used to bring the pH of the suspension to 10. The solution was washed with CH₂Cl₂ (25
40 mL). The pH of the aqueous layer was adjusted to 3.5 by

5 the addition of 6M HCl. The acidic solution was extracted
with EtOAc (3X25 mL). The combined EtOAc layers were dried
(Na₂SO₄), filtered and concentrated. The resulting oil was
adsorbed onto magnesium silicate and purified by silica gel
10 chromatography, eluting with a gradient of 0.5% acetic
acid/2% MeOH/CH₂Cl₂ to 5% acetic acid/10% MeOH/CH₂Cl₂ to
afford the title compound as a white powder (17 mg). The
compound was dissolved in a solution of 5% trifluoroacetic
acid/20% CH₃CN/H₂O and eluted through a reverse phase C18
15 column with the same solution to afford the title compound
(11 mg) as a beige gum.
NMR (300 MHz, DMSO-d₆) δ 7.64 (d, J=8.05 Hz, 2H), 7.22 (d,
J=8.03 Hz, 2H), 6.85 (d, J=8.35 Hz, 1H), 6.67-6.61 (m, 2H),
3.96-3.92 (m, 2H), 3.24-3.16 (m, 6H), 2.76-2.61 (m, 3H),
2.33 (s, 3H), 2.23-2.11 (m, 1H), 1.98-1.86 (m, 5H), 1.83-
20 1.74 (m, 3H), 1.24 (s, 1H); MS(+ESI) m/z 499 (M+H)⁺.

Example 218

3-(2-Chloro-6-methoxy-quinolin-3-yl)-acrylic acid ethyl ester

A suspension of 2-chloro-6-methoxy-quinoline-3-
25 carbaldehyde (22.6 g, 102 mmol) and sodium hydride (4.5 g,
113 mmol, 60% dispersion in mineral oil) in tetrahydrofuran
(450 mL) was treated dropwise with triethyl
phosphonoacetate (20.2 mL, 102 mmol) during 10-15 min at
0°C. After 30 min, the mixture was warmed to rt. After 15
30 h, the reaction was quenched with water (4.5 mL) and
concentrated in vacuo. The resulting wet solid was
partitioned between water (1 L) and chloroform (1 L), the
phases separated, and the aqueous phase extracted once more
with chloroform (1 L). The combined extracts were washed
35 with water (1 L), dried (K₂CO₃) and concentrated to give a
soft, pale yellow solid (30.8 g). Recrystallization from
hot 5:2 ether-methylene chloride (700 mL) gave the title
compound (20.2 g, 68% yield) as fluffy, pale yellow
needles.
40 Mp. 113-14°C.

5 ^1H NMR (DMSO- d_6 , 300 MHz): δ 1.27 (t, $J=7$ Hz, 3H, CH_2CH_3),
3.90 (s, 3H, OCH_3), 4.24. (q, $J=7$ Hz, 2H, CH_2), 6.82 (d,
 $J=17$ Hz, 1H, $=\text{CHCO}_2$), 7.38 (s, 1H, ArH), 7.49 (d, $J=9$ Hz,
1H, ArH), 7.84-7.94 (overlapping d, $J=9$ Hz, 17Hz, 2H, ArH ,
 ArCH=), 8.90 (s, 1H, ArH).

10

Example 219

3-(6-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acrylic acid
ethyl ester

15 A suspension of 3-(2-chloro-6-methoxy-quinolin-3-yl)-
acrylic acid ethyl ester (20.2 g, 69.2 mmol) in ethanol
(175 mL) was treated with 12 N aqueous HCl and heated to
reflux to form a solution. After 21 h, the resulting
precipitate was cooled to 0°C for 1 h. Vacuum filtration
20 gave the title compound (18.0 g, 95% yield) as a yellow
crystalline solid.

Mp. $209-11^\circ\text{C}$.

^1H NMR (DMSO- d_6 , 300 MHz): δ 1.25 (t, $J=7$ Hz, 3H, CH_2CH_3),
3.78 (s, 3H, OCH_3), 4.16 (q, $J=7$ Hz, 2H, CH_2), 7.11 (d,
25 $J=16$ Hz, 1H, $=\text{CHCO}_2$), 7.18-7.28 (overlapping m, 3H, ArH),
7.64 (d, $J=16$ Hz, 1H, ArCH=), 8.34 (s, 1H, ArH), 12.0 (s,
1H, ArNH).

Example 220

30 3-(6-Methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-
propionic acid ethyl ester

A suspension of 3-(6-methoxy-2-oxo-1,2-dihydro-
quinolin-3-yl)-acrylic acid ethyl ester (9.0 g, 33 mmol) in
acetic acid (900 mL) was hydrogenated over 10% Pd-C (9.0 g)
35 at 50 psi. After 6 days, the catalyst was filtered through
diatomaceous earth and washed with acetic acid (2 x 500
mL). Concentration of the filtrate gave a tan crystalline
solid (9.5 g). Recrystallization from hot ethanol (100 mL)
gave the title compound (5.0 g, 55% yield) as white
40 needles.

- 5 Mp. 106-07°C.
1H NMR (DMSO-d₆, 300 MHz): δ 1.16 (t, J=7 Hz, 3H, CH₂CH₃),
1.57 (m, 1H, CHHCHHCO₂), 1.92 (m, 1H, CHHCHHCO₂), 2.32-2.44
(overlapping m, 3H, CH, CHHCO₂), 2.63 (m, 1H, ArCHH), 2.90
(m, 1H, ArCHH), 4.03 (q, J=7 Hz, 2H, CO₂CH₂), 6.68-6.78
10 (overlapping m, 3H, ArH), 9.94 (s, 1H, ArNH).

Example 221

- 15 3-(6-Hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-
propionic acid ethyl ester

Using the conditions of Example 73 and 3-(6-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid ethyl ester in place of (7-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)acetic acid methyl ester and in the presence
20 of ethyl alcohol the title compound was prepared.

Mp. 138.0-38.5°C.

- 1H NMR (DMSO-d₆, 300 MHz): δ 1.16 (t, J=7Hz, 3H, CH₃),
25 1.57 (m, 1H, CHHCHHCO₂), 1.91 (m, 1H, CHHCHHCO₂), 2.26-2.43
(overlapping m, 3H, CH, CHHCO₂), 2.56 (m, 1H, ArCHH), 2.83
(m, 1H, ArCHH), 4.04 (q, J= 7 Hz, 2H, CO₂CH₂), 6.50-6.64
(overlapping m, 3H, ArH), 9.01 (s, 1H, ArOH), 9.82 (s, 1H,
ArNH).

30

Example 222

3-[6-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-propionic acid

- 35 Starting with 3-(6-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid ethyl ester and using the conditions of Examples 75, 78, 81 and 84 the title compound was synthesized.

Mp. 119-22 °C.

- 5 IR (KBr): 3440 (s), 3360 (s), 1692 (s), 1655 (s), 1428 (m), 1410 (m), 1247 (s), 1200 (s), 1168 (s), 1134 (s), 843 (m), 800 (m), 721 (m) cm^{-1} .
 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.54 (m, 1H, CHHCHHCO_2), 1.89 (m, 1H, CHHCHHCO_2), 2.32-2.41 (overlapping m, 3H, CH , CHHCO_2), 2.64 (dd, $J=10$ Hz, 16 Hz, 1H, ArCHH), 2.92 (dd, $J=6$ Hz, 16 Hz, 1H, ArCHH), 3.48 (m, 2H, NCH_2), 4.00 (t, $J=5$ Hz, 2H, OCH_2), 6.73-6.82 (overlapping m, 3H, ArH), 6.82-7.55 (broad s, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.65 (t, $J=6$ Hz, 1H, NHCH_2), 9.96 (s, 1H, ArNH), 12.1 (s, 1H, CO_2H).
- 10
15 MS (+FAB) m/e (rel. intensity): 321 (M+H, 57).
Analysis calc. for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 0.5 \text{H}_2\text{O}$.
C, 46.05; H, 5.00; N, 12.64
Found C, 46.09; H, 4.93; N, 12.69

20

Example 2233-[6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid

- Starting from 3-(6-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid ethyl ester and using the conditions of Examples 75 (except that (3-bromopropyl)-carbamic acid tert-butyl ester is used in place of (2-bromoethyl)-carbamic acid tert-butyl ester), 78, 81 and 84 the title compound was synthesized.
- 25
30 Mp. 168-72 °C (degasses).
IR (KBr): 3370 (m), 1695 (m), 1625 (m), 1405 (m), 1248 (m), 1197 (m), 1163 (m), 1138 (m), 842 (w), 817 (w), 800 (w), 722 (w) cm^{-1} .
 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.54 (m, 1H, CHHCHHCO_2), 1.85-1.94 (overlapping m, 3H, NCH_2CH_2 , CHHCHHCO_2), 2.33-2.41 (overlapping m, 3H, CHHCO_2 , CH), 2.63 (dd, $J=10$ Hz, 16 Hz, 1H, ArCHH), 2.91 (dd, $J=6$ Hz, 16 Hz, 1H, ArCHH), 3.25 (m, 2H, NCH_2), 3.94 (t, $J=6$ Hz, 2H, OCH_2), 6.71-6.80 (overlapping m, ArH), 6.80-7.45 (broad s, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.56 (t, $J=5$ Hz, 1H, NHCH_2), 9.94 (s, 1H, ArNH), 12.3
- 35
40

- 5 (broad s, 1H, CO₂H). MS (+FAB) m/e (rel. intensity): 335
 (M+H, 100).
 Analysis calc. for C₁₆H₂₂N₄O₄•CF₃COOH C,
 48.21; H, 5.17; N, 12.49
 Found C, 47.91; H,
 10 5.01; N, 12.46

Example 224

3-[6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl]-propionic acid

- 15 Starting from 3-(6-hydroxy-2-oxo-1,2,3,4-tetrahydro-
 quinolin-3-yl)-propionic acid ethyl ester and using the
 conditions of Examples 75 (except that (4-bromobutyl)-
 carbamic acid tert-butyl ester was used in place of (2-
 bromoethyl)-carbamic acid tert-butyl ester), 78, 81 and 84
 20 the title compound was synthesized.
 Mp. 152-55°C.
 IR (KBr): 3370 (m), 1728 (m), 1692 (s), 1632 (s), 1400
 (m), 1268 (m), 1250 (m), 1192 (s), 1158 (m), 1135 (m), 838
 (m), 810 (m), 796 (m), 720 (m) cm⁻¹.
 25 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.49-1.68 (overlapping m,
 3H, CH₂CH₂CO₂, NCH₂CH₂), 1.68 (m, 2H, OCH₂CH₂), 1.89 (m,
 1H, CH₂CH₂CO₂), 2.32-2.40 (overlapping m, 3H, CH₂CO₂, CH),
 2.62 (dd, J=10 Hz, 16 Hz, 1H, ArCH₂), 2.90 (dd, J=6 Hz, 16
 Hz, 1H, ArCH₂), 3.15 (m, 2H, NCH₂), 3.91 (t, J=6 Hz, 2H,
 30 OCH₂), 6.69-6.78 (overlapping m, 3H, ArH), 6.80-7.50 (broad
 s, 4H, [C(NH₂)₂]⁺), 7.56 (t, J=5.5 Hz, 1H, NHCH₂), 9.94 (s,
 1H, ArNH), 12.1 (broad s, 1H, CO₂H).
 MS (+FAB) m/e (rel. intensity): 349 (M+H, 100).
 35 Analysis calc. for C₁₇H₂₄N₄O₄•CF₃COOH C,
 49.35; H, 5.45; N, 12.12
 Found C, 49.08; H,
 5.33; N, 12.05

5

Example 225[6-(3-tert-Butoxycarbonylamino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester

A solution of (6-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester (2.0 g, 8.0 mmol) in N, N-dimethylformamide (16 mL) was treated with a solution of sodium ethoxide (21 wt%) in ethanol (3.0 mL, 8.0 mmol) at rt and after 15 min, (3-bromopropyl)-carbamic acid tert-butyl ester (1.9 g, 8.0 mmol) was added. After 4 days, the solution was treated with water (75 mL) and the resulting gum was briefly heated, then cooled to 0°C. The precipitated solid was triturated for 6 h, to give the crude product (2.7 g). Flash chromatography (90 g silica; CHCl₃, then 1% MeOH (saturated with NH₃)-CHCl₃) gave the title compound (2.6 g, 79% yield) as a white solid.

¹H NMR: (DMSO-d₆, 300 MHz): δ 1.16 (t, J=7.5 Hz, 3H, CH₂CH₃), 1.33 (s, 9H, C(CH₃)₃), 1.75 (m, 2H, NCH₂CH₂), 2.30-2.90 (overlapping m, 5H, ArCH₂, CH, CH₂CO₂), 3.03 (m, 2H, NCH₂), 3.87 (t, J=6 Hz, 2H, OCH₂), 4.05 (q, J=7.5 Hz, 2H, CH₂CH₃), 6.65-6.90 (overlapping m, 4H, ArH, NHCH₂), 9.96 (s, 1H, ArNH).

Example 226[6-(3-Amino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester

[6-(3-tert-Butoxycarbonylamino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester (2.6 g, 6.4 mmol) and trifluoroacetic acid (5.0 mL, 65 mmol) were combined in methylene chloride (25 mL) at rt. After 18 h, the solution was concentrated in vacuo to give a sticky tan solid (2.8 g) which was triturated with 25:1 methylene chloride-methanol (50 mL) for 2 h to give the trifluoroacetate salt of the title compound (2.5 g, 93% yield) as a white powder.

¹H NMR: (DMSO-d₆, 300 MHz): δ 1.17, (t, J= 7.5 Hz, 3H, CH₃), 1.96 (m, 2H, NCH₂CH₂), 2.37-3.00 (overlapping m, 7H,

- 5 ArCH_H, CH, CHHCO₂, NCH₂), 3.98 (t, J=6 Hz, 2H, OCH₂), 4.05 (q, J=7.5 Hz, 2H, CO₂CH₂), 6.76 (overlapping m, 3H, ArH), 7.80 (s, 3H, NH₃⁺), 10.0 (s, 1H, ArNH).

Example 227

- 10 [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester

A suspension of [6-(3-amino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester (0.80 g, 1.9 mmol), 3,5-dimethylpyrazole carboxamide nitrate (0.42 g, 2.1 mmol) and diisopropylethylamine (0.73 mL, 4.2 mmol) in 3:1 dioxane-water (5.5 mL) was heated at reflux for 9 h. The cooled solution was concentrated in vacuo to yield a viscous oil. Purification by reverse phase HPLC gave the title compound (0.76 g, 86%) as a clear, almost colorless oil.

- 20 ¹H NMR: (DMSO-d₆, 300 MHz): δ 1.18 (t, J=7.5 Hz, 3H, CH₂CH₃), 1.94 (m, NCH₂CH₂), 2.37-2.90 (overlapping m, 5H, ArCH_H, CH, CHHCO₂), 3.22 (m, 2H, NCH₂), 3.95 (t, J=6 Hz, 2H, OCH₂), 4.05 (q, J=7.5 Hz, 2H, CO₂CH₂), 6.70-6.78 (overlapping m, 3H, ArH), 6.80-7.50 (broad s, 4H, [C(NH₂)₂]⁺), 7.65 (broad m, 1H, NHCH₂), 10.0 (s, 1H, ArNH).

Example 228

- 30 [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

A solution of [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid ethyl ester (0.76 g, 1.6 mmol) in ethanol (7 mL) was treated with 0.5 N aqueous NaOH and heated at reflux for 3 h. The resulting precipitate was cooled to room temperature, treated with trifluoroacetic acid (1.5 mL) and the solution thus formed concentrated in vacuo to yield a clear, colorless oil. Purification by reverse phase HPLC gave the title compound (0.38 g, 55% yield) as a fluffy white solid.

40 Mp. 178-79°C.

5 IR(KBr): 3400 (m), 1705 (m), 1660 (s), 1605 (s), 1245 (s),
1198 (s), 1180 (s), 1158 (s), 1125 (s), 1025 (m), 790 (m),
715 (m) cm^{-1} .

^1H NMR: (DMSO- d_6 , 400 MHz): δ 1.89 (m, 2H, NHCH_2CH_2), 2.33
(m, 1H, ArCHH), 2.68-2.97 (overlapping m, 4H, ArCHH, CH,
10 CHHCO₂), 3.25 (m, 2H, NCH₂), 3.94 (t, J=6 Hz, 2H, OCH₂),
6.72-6.79 (overlapping m, 3H, ArH), 6.79-7.50 (broad s, 4H,
[C(NH₂)₂]⁺), 7.63 (broad m, 1H, NHCH₂), 10.0 (s, 1H, ArNH),
12.2 (s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 321 (M+H, 100).

15 Analysis calc. for C₁₅H₂N₄O₄•CF₃COOH C,
47.01; H, 4.87; N, 12.99
Found C, 47.03; H,
4.75; N, 12.86

Example 229

20 [6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid

The title compound was synthesized from (6-hydroxy-2-
oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl
ester and (4-bromo-butyl)carbamic acid tert-butyl ester in
25 essentially the same manner as described in Example 225 and
followed by steps in essentially the same manner as
described in Examples 226, 227 and 228.

Mp. 170-73 °C.

IR(KBr): 3420 (s), 1703 (s), 1665 (s), 1432 (m), 1409 (m),
30 1245 (s), 1195 (s), 1160 (s), 1134 (s), 863 (w), 800 (w),
720 (m), 679 (m) cm^{-1} .

^1H NMR: (DMSO- d_6 , 400 MHz): δ 1.60 (m, 2H, NCH₂CH₂), 1.69
(m, 2H, OCH₂CH₂), 2.31 (m, 2H, ArCHH), 2.68-2.91
(overlapping m, 4H, ArCHH, CH, CHHCO₂), 3.15 (m, 2H, NCH₂),
35 3.92 (t, J=6 Hz, 2H, OCH₂), 6.70-6.78 (overlapping m, 3H,
ArH), 6.78-7.54 (broad s, 4H, [C(NH₂)₂]⁺), 7.64 (t, J=6 Hz,
1H, NHCH₂), 9.99 (s, 1H, ArNH), 12.2 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 335 (M+H, 100).

5

Analysis calc. for $C_{16}H_{22}N_4O_4 \cdot CF_3COOH \cdot H_2O$ C,
 46.35; H, 5.40; N, 12.01.
 Found C, 46.09; H,
 5.31; N, 12.02.

10

Example 2303-[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid

15

The title compound was synthesized from 3-(7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid ethyl ester prepared using the conditions of Examples 218, 219, 220 and 221 and (2-bromo-ethyl)carbamic acid tert-butyl ester in essentially the same manner as described in Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.

20

Mp. 193-96 °C.

IR (KBr): 3410 (m), 3190 (m), 1695 (s), 1675 (s), 1620 (s), 1278 (m), 1205 (s), 1183 (s), 1140 (s), 870 (m), 848 (m), 800 (m), 727 cm^{-1} .

25

1H NMR (DMSO- d_6 , 400 MHz): δ 1.54 (m, 1H, $CH_2CH_2CO_2$), 1.91 (m, 1H, $CH_2CH_2CO_2$), 2.32-2.42 (overlapping m, 3H, $CH_2CH_2CO_2$), 2.58 (dd, J=10 Hz, 16 Hz, 1H, Ar CH_2), 2.89 (dd, J=6 Hz, 16 Hz, 1H, Ar CH_2), 3.50 (m, 2H, NCH_2), 3.98 (t, J=5 Hz, 2H, OCH_2), 6.44 (d, J=2.5 Hz, 1H, Ar H), 6.50 (dd, J=2.5 Hz, 8 Hz, 1H, Ar H), 6.66-7.56 (broad, 4H, $[C(NH_2)_2]^+$), 7.08 (d, J=8 Hz, 1H, Ar H), 7.66 (t, J=6 Hz, 1H, $NHCH_2$), 10.1 (s, 1H, Ar NH), 12.1 (broad s, 1H, CO_2H).

30

MS (-FAB) m/e (rel. intensity): 319 (M-H, 22).

35

Analysis calc. for $C_{15}H_{20}N_4O_4 \cdot CF_3COOH$ C,
 47.01; H, 4.87; N, 12.90
 Found C, 47.29; H,
 4.70; N, 13.11

40

5

Example 2313-[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid

10 The title compound was synthesized from 3-(7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid ethyl ester prepared using the conditions of Examples 218, 219, 220 and 221 and (3-bromo-propyl)carbamic acid tert-butyl ester in essentially the same manner as described in
15 Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.

Mp. 157-59°C.

IR (KBr): 3420 (m), 3200 (m), 1718 (s), 1680 (s), 1620 (s), 1275 (m), 1202 (s), 1182 (s), 1139 (s), 868 (m), 842
20 (m), 798 (m), 722 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 1.54 (m, 1H, CH₂CH₂CO₂), 1.87-1.93 (overlapping m, 3H, CH₂CH₂CO₂, NCH₂CH₂), 2.32-2.42 (overlapping m, 3H, CH₂CO₂, CH), 2.57 (dd, J=10 Hz, 16 Hz, 1H, ArCH₂), 2.88 (dd, J=6 Hz, 16 Hz, 1H, ArCH₂), 3.25 (m, 2H, NCH₂), 3.93 (t, J=6 Hz, 2H, OCH₂), 6.42 (d, J=2.5 Hz, 1H, ArH), 6.49 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.60-7.50 (broad, 4H, [C(NH₂)₂]⁺), 7.07 (d, J=8 Hz, 1H, ArH), 7.60 (t, J=5 Hz, NHCH₂), 10.0 (s, 1H, ArNH), 12.1 (broad s, 1H, CO₂H).

30 MS (-FAB) m/e (rel. intensity): 333 (M-H, 18).

Analysis calc. for C₁₆H₂₂N₄O₄•CF₃COOH

C,

48.21; H, 5.17; N, 12.50

Found

C, 48.41; H,

4.98; N, 12.64

35

Example 2323-[7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid

40 The title compound was synthesized from 3-(7-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-propionic acid

- 5 ethyl ester prepared using the conditions of Examples 218, 219, 220 and 221 and (4-bromo-butyl)carbamic acid tert-butyl ester in essentially the same manner as described in Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.
- 10 Mp. 176-77 °C.
 IR (KBr): 3380 (m), 3198 (m), 1718 (s), 1688 (s), 1662 (s), 1629 (s), 1388 (m), 1295 (m), 1286 (m), 1210 (s), 1182 (s), 1138 (s), 872 (m), 847 (m), 800 (m), 730 (m) cm⁻¹.
¹H NMR (DMSO-d₆, 400 MHz): δ 1.49-1.63 (overlapping m, 3H, CHHCHHCO₂, NCH₂CH₂), 1.70 (m, 2H, OCH₂CH₂), 1.91 (m, 1H, CHHCHHCO₂), 2.32-2.42 (overlapping m, 3H, CH, CHHCO₂), 2.57 (dd, J=10 Hz, 16 Hz, 1H, ArCHH), 2.87 (dd, J=6 Hz, 16 Hz, 1H, ArCHH), 3.15 (m, 2H, NCH₂), 3.90 (t, J=6 Hz, 2H, OCH₂), 6.41 (d, J=2.5 Hz, 1H, ArH), 6.48 (dd, J=2.5 Hz, 8 Hz, 1H, ArH), 6.60-7.46 (broad, 4H, [C(NH₂)₂]⁺), 7.05 (d, J=8 Hz, 1H, ArH), 7.55 (t, J=5 Hz, 1H, NHCH₂), 10.0 (s, 1H, ArNH), 12.1 (s, 1H, CO₂H).
- MS (-FAB) m/e (rel. intensity): 347 (M-H, 15).
 Analysis calc. for C₁₇H₂₄N₄O₄•CF₃COOH C,
 25 49.35; H, 5.45; N, 12.12
 Found C, 49.32; H,
 5.36; N, 12.45

Example 233

30 (8-Hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester

- A solution of (8-methoxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester (prepared in essentially the same manner as described for Example 72)
 35 (2.4 g, 9.1 mmol) in methylene chloride (25 mL) was treated with 1.0 M BBr₃-CH₂Cl₂ solution (90 mL, 90 mmol) at 0°C in an oven-dried flask. After 3 h, the resulting mixture was concentrated in vacuo and the residue treated with ice-cold ethanol (200 mL) and concentrated. Ethanol treatment and
 40 concentration were repeated twice more to give a tan foam (3.1 g). Flash chromatography (102 g silica; 2.5% MeOH

5 (saturated with NH_3)- CHCl_3) gave the title compound (2.1 g, 91% yield) as a pale yellow solid.
 ^1H NMR (DMSO- d_6 , 300 MHz): δ 1.18 (t, $J=7$ Hz, 3H, CH_3),
 2.41-2.48 (m 1H, ArCHH), 2.70-2.88 (overlapping m, 4H,
 10 ArCHH , CH , CHHCO_2), 4.07 (t, $J=7$ Hz, 2H, CO_2CH_2), 6.60-6.78
 (overlapping m, 3H, ArH), 8.94 (s, 1H, ArOH), 9.63 (s, 1H,
 ArNH).

Example 234

[8-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

15 The title compound was synthesized from (8-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester prepared using the conditions of Examples 218, 219, 220 and 221 and (3-bromo-propyl)carbamic acid tert-butyl ester in essentially the same manner as described in
 20 Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.

Mp. 151-55 °C.

IR (KBr): 3405 (s), 1750 (m), 1690 (s), 1660 (s), 1630
 25 (s), 1435 (m), 1420 (m), 1400 (m), 1275 (s), 1195 (s), 1145 (s), 835 (m), 780 (m), 725 (s) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.94 (m, 2H, NCH_2CH_2), 2.37
 (m, 1H, ArCHH), 2.69-2.93 (overlapping m, 4H, ArCHH , CH ,
 CHHCO_2), 3.36 (m, 2H, NCH_2), 3.99 (t, $J=6$ Hz, 2H, OCH_2),
 30 6.77 (d, $J=7$ Hz, 1H, ArH), 6.84-6.91 (overlapping m, 2H, ArH), 7.00-7.50 (broad s, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.61 (t, $J=5$ Hz, 1H, NHCH_2), 9.28 (s, 1H, ArNH), 12.2 (s, 1H, CO_2H). MS
 (+FAB) m/e (rel. intensity): 321 (M+H, 100).

Analysis calc. for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH}$ C,
 35 47.01; H, 4.87; N, 12.90
 Found C, 46.61; H,
 4.80; N, 12.64

5

Example 235[8-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

The title compound was synthesized from (8-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester prepared using the conditions of Examples 218, 219, 220 and 221 and (4-bromo-butyl)carbamic acid tert-butyl ester in essentially the same manner as described in Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.

Mp. 207-210 °C.

IR (KBr): 3385 (s), 1700 (s), 1630 (s), 1440 (m), 1425 (m), 1400 (m), 1275 (m), 1205 (s), 1180 (s), 835 (w), 805 (m), 775 (m), 725 (m), 680 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.67 (m, 2H, NCH_2CH_2), 1.75 (m, 2H, OCH_2CH_2), 2.37 (m, 1H, ArCHH), 2.69-2.93 (overlapping m, 4H, ArCHH , CH , CHHCO_2), 3.14 (m, 2H, NCH_2), 3.99 (t, $J=6$ Hz, 2H, OCH_2), 6.76 (d, $J=7$ Hz, 1H, ArH), 6.84-6.91 (overlapping m, 2H, ArH), 7.00-7.46 (broad s, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.54 (t, $J=5$ Hz, 1H, NHCH_2), 9.09 (s, 1H, ArNH), 12.2 (broad s, 1H, CO_2H).

MS (DCI) m/e (rel. intensity): 335 (M+H, 38).

Analysis calc. for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 0.2 \text{H}_2\text{O}$ C, 47.83; H, 5.22; N, 12.40

Found C, 47.76; H, 5.00; N, 12.37

Example 236(6-Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid ethyl ester

A mixture of 2-(5-hydroxy-2-nitro-benzylidene)-succinic acid diethyl ester (9.5 g, 30 mmol) and Zn (5.8 g, 89 mmol) in ethanol (125 mL) was treated with 12 N aqueous HCl at 0°C. After 5 min, the reaction was warmed to room temperature and then heated to reflux after 30 min total.

5 After 3 h, additional Zn (0.2 g, 3 mmol) was added. After
 4 h total at reflux, the cooled solution was filtered and
 concentrated in vacuo. The crude, dark brown residue was
 triturated with water (500 mL) overnight to give a brown
 solid (6.3 g). Recrystallization from hot acetonitrile
 10 gave the title compound (5.3 g, 73% yield) as a tan
 crystalline solid.
¹H NMR: (DMSO-d₆, 300 MHz): δ 1.26 (t, J=7.5 Hz, 3H,
 CH₃), 3.04 (s, 2H, CH₂CO₂), 4.02 (q, J=7.5Hz, 2H, CO₂CH₂),
 6.85 (overlapping m, 2H, ArH), 6.98 (d, J=9Hz, 1H, ArH),
 15 7.67 (s, 1H, ArCH=), 9.53 (s, 1H, ArOH), 10.1 (s, 1H,
 ArNH).

Example 237

20 [6-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
acetic acid

The title compound was prepared according to the
 procedures of Examples 77, 80, 81 and 84 starting from (6-
 hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid ethyl
 ester in place of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-
 25 quinolin-3-yl)-acetic acid methyl ester.

Mp. 207-12 °C (dec).

IR (KBr): 3360 (s), 1680 (broad s), 1435 (m), 1414 (m),
 1400 (m), 1263 (s), 1192 (s), 1168 (s), 1130 (s), 1081 (s),
 842 (m), 798 (m), 720 (m) cm⁻¹.

30 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.92 (m, 2H, NCH₂CH₂), 3.04
 (s, 2H, CH₂CO₂), 3.27 (m, 2H, NCH₂), 4.02 (t, J=6Hz, 2H,
 OCH₂), 6.60-7.60 (overlapping m, broad s, 7H, ArH,
 [C(NH₂)₂]⁺), 7.65 (t, J=5.5 Hz, 1H, NHCH₂), 7.75 (s, 1H,
 ArCH=), 10.2 (s, 1H, ArNH), 12.9 (broad s, 1H, CO₂H).

35 MS (+FAB) m/e (rel. intensity): 319 (M+H, 100).

Analysis calc. for C₁₅H₁₈N₄O₄•CF₃COOH•H₂O C,

45.34; H, 4.70; N, 12.44

Found

C, 45.50; H,

4.58; N, 12.45

5

Example 238[6-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
acetic acid trifluoroacetic acid salt

The title compound was prepared according to the
10 procedures of Examples 76, 79, 81 and 84 starting from (6-
hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)-acetic acid ethyl
ester in place of 7-hydroxy-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl)-acetic acid methyl ester.

IR (KBr): 3380 (s), 1690 (s), 1654 (s), 1615 (s), 1432
15 (m), 1270 (s), 1250 (s), 1208 (s), 1182 (s), 1125 (s), 834
(m), 795 (m), 760 (m), 718 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 1.61 (m, 2H, NCH_2CH_2), 1.73
(m, 2H, OCH_2CH_2), 3.04 (s, 2H, CH_2CO_2), 3.16 (m, 2H, NCH_2),
3.99 (t, $J=6$ Hz, 2H, OCH_2), 6.60-7.50 (overlapping m,
20 broad, 7H, ArH , $[\text{C}(\text{NH}_2)_2]^+$), 7.59 (t, $J=6$ Hz, 1H, NHCH_2),
7.75 (s, 1H, ArCH=), 10.2 (s, 1H, ArNH), 12.9 (broad s, 1H,
 CO_2H).

MS (+FAB) m/e (rel. intensity): 333 (M+H, 26).

Analysis calc. for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot \text{H}_2\text{O}$ C,
25 46.55; H, 4.99; N, 12.06
Found C, 46.54; H,
4.88; N, 12.10

30

Example 239[1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]-acetic acid trifluoroacetic acid salt

The title compound was prepared according to the
procedures of Examples 81 and 84 starting from [1-benzyl-7-
35 (3-aminopropoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]acetic
acid methyl ester in place of 7-hydroxy-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl)-acetic acid methyl ester.

5

Mp. 132-34°C.

IR (KBr): 3342 (m), 3190 (m), 1715 (s), 1670 (s), 1645 (s), 1594 (s), 1408 (m), 1199 (s) 1133 (m), 840 (m), 799 (m), 723 (m) cm⁻¹.

10 ¹H NMR (DMSO-d₆, 400 MHz): δ 1.88 (m, 2H, NCH₂CH₂), 3.23 (m, 2H, NCH₂CH₂), 3.52 (s, 2H, CH₂CO₂), 4.01 (t, J=6 Hz, 2H, OCH₂), 5.52 (broad s, 2H, CH₂Ph), 6.60-7.50 (broad, 4H, [C(NH₂)₂]⁺), 6.81 (s, 1H, ArH), 6.88 (d, J=9 Hz, 1H, ArH), 7.19-7.35 (overlapping m, 5H, ArH), 7.60 (t, J=5 Hz, 1H, NHCH₂), 7.63 (d, J=9 Hz, 1H, ArH), 7.85 (s, 1H, ArCH=), 12.2 (broad s, 1H, CO₂H),

15 MS (+FAB) m/e (rel. intensity): 409 (M+H, 100).

Analysis calc. for C₂₂H₂₄N₄O₄•CF₃COOH C, 55.17; H, 4.82; N, 10.72

20 Found C, 55.07; H, 4.74; N, 10.80

Example 240

(7-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)propionic acid methyl ester

25 The title compound was prepared from 7.0 g 3-(2-chloro-7-methoxy-quinolin-3-yl)propionic acid methyl ester using the conditions of Example 71 gave 4.5 g of the title compound as a white crystalline solid.

Example 241

30 (7-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)butyric acid methyl ester

The title compound was prepared from 3-(2-chloro-7-methoxy-quinolin-3-yl)butyric acid methyl ester using the conditions of Example 71.

35

Example 242

(7-Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)propionic acid methyl ester

40 Treatment of 4.5 g of (7-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)propionic acid methyl ester with boron tribromide in dichloromethane using the conditions of

5 Example 73 gave 2.5 g of the title compound as a yellow crystalline solid.

Example 243 :

7-(Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)butyric acid methyl ester

10 Treatment of (7-Methoxy-2-oxo-1,2-dihydro-quinolin-3-yl)butyric acid methyl ester with boron tribromide in dichloromethane using the conditions of Example 73 gives the title compound.

Example 244

15 [7-(2-tert-Butoxycarbonylaminoethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid methyl ester

The title compound was prepared from 2.5 g of (7-Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)propionic acid methyl ester using the conditions of Example 75 gave 2.2 g
20 of a white crystalline solid.

Example 245

[7-(2-Amino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid methyl ester

The title compound was prepared from 2.2 g of [7-(2-
25 tert-Butoxycarbonylamino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid methyl ester using the conditions of Example 78 gave 2.3 g of the title compound as a light tan crystalline solid.

Example 246

30 [7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid methyl ester

The title compound was prepared from 1.30 g of [7-(2-
amino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid methyl ester using the conditions of Example 81 gave
35 0.79 g of the title compound as a white crystalline solid.

5

Example 2473-[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
propionic acid nitric acid salt

The title compound was prepared from 0.79 g of [7-(2-
10 guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic
acid methyl ester using the conditions of Example 85 gave
0.55 g of the title compound as the nitric acid salt.

Mp. 211 °C (dec).

15 IR (KBr): 3345 (s), 3205 (s), 1703 (s), 1645 (s), 1400
(s), 1248 (s), 1232 (s), 1197 (s), 1176 (m), 842 (m), 830
(m), 810 (m), 785 (m) cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 2.53 (t, J=7.5 Hz, 2H,
CH₂CH₂CO₂), 2.70 (t, J=7.5 Hz, 2H, CH₂CO₂), 3.55 (m, 2H,
20 NCH₂), 4.09 (t, J=5 Hz, 2H, OCH₂), 6.78-6.81 (overlapping
m, 2H, ArH), 6.83-7.48 (broad, 4H, [C(NH₂)₂]⁺), 7.54 (d,
J=9 Hz, 1H, ArH), 7.62 (t, J=5 Hz, 1H, NHCH₂), 7.67 (s, 1H,
ArCH=), 11.7 (s, 1H, ArNH), 12.1 (broad s, 1H, CO₂H).

MS (+FAB) m/e (rel. intensity): 319 (M+H, 100).

25 Analysis calc. for C₁₅H₁₈N₄O₄• HNO₃ C,
47.24; H, 5.02; N, 18.37
Found C, 47.21; H,
4.96; N, 18.04

30

Example 2484-Methyl-N-[[7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-
tetrahydro-quinolin-3-yl]-acetyl]-benzenesulfonamide

To [7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
35 quinolin-3-yl]-acetic acid hydrochloride (0.90g) was added
para-toluenesulfonamide (0.65g), 1-[3-(dimethylamino)-
propyl]-3-ethylcarbodiimide hydrochloride (0.73 g),
dimethylaminopyridine (0.05 g), and DMF (40 mL) and the
resulting slurry formed a solution as it was stirred under
40 N₂ at room temperature for 21 days. The DMF was removed by
vacuum distillation. The golden oil was triturated with

- 5 CH₂Cl₂ (25 mL) followed by EtOAc (25 mL). The resulting oil was dissolved in 10 mL of 25% CH₃CN/H₂O and chromatographed on a C₁₈ reverse phase column, eluting with a gradient of 10% CH₃CN/H₂O to 40% CH₃CN/H₂O to afford the title compound (73 mg) as an ivory solid after lyophilization.
- 10 NMR (300 MHz, DMSO-d₆) δ 9.96 (s, 1H), 7.69 (t, J=8.23 Hz, 1H), 7.61 (d, J=8.07 Hz, 2H), 7.40-7.05 (broad, 4H), 7.17 (d, J=8.11 Hz, 2H), 6.92 (d, J=8.27 Hz, 1H), 6.46 (dd, J=8.23, 2.25 Hz, 1H), 6.41 (d, J=2.19 Hz, 1H), 3.92 (t, J=5.82 Hz, 2H), 3.24 (broad m, 2H), 2.74-2.62 (m, 2H), 2.47-2.37 (m, 2H), 2.32 (s, 3H), 1.90-1.82 (m, 3H); MS(+ESI)m/z 474 (M+H)⁺; Calculated for C₂₂N₂₇N₅O₅S•1.5H₂O: C, 52.79; H, 6.04; N, 13.99. Found: C, 52.79; H, 6.04; N, 13.05.

Example 249

20

(5-Bromo-pentyl)-carbamic acid tert-butyl ester

The title compound is prepared according to the procedure of Example 16 except that 5-amino-1-pentanol is used in place of 2-amino-ethan-1-ol.

25

Example 250

[8-(5-Guanidino-pentoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

30 The title compound was synthesized from (8-hydroxy-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-acetic acid ethyl ester prepared using the conditions of Examples 218, 219, 220, 221 and (5-bromo-pentyl)-carbamic acid tert-butyl ester in essentially the same manner as described in

35 Example 225 and followed by steps in essentially the same manner as described in Examples 226, 227 and 228.

m.p. 126-31°C

40 IR (KBr): 3375 (s, doublet), 1720 (s), 1680 (s), 1645 (s), 1435 (m), 1270 (s), 1200 (s), 1145 (s), 845 (m), 805 (m), 725 (s) cm⁻¹.

- 5 ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.42-1.56 (overlapping m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$), 1.76 (m, 2H, OCH_2CH_2), 2.37 (m, 1H, ArCHH), 2.69-2.92 (overlapping m, 4H, ArCHH , CH , CHHCO_2), 3.11 (m, 2H, NCH_2), 3.97 (t, $J=6.5$ Hz, 1H, OCH_2), 6.76 (d, $J=6.5$ Hz, 1H, ArH), 6.84-6.90 (overlapping m, 2H, ArH), 6.96-7.46 (broad s, 4H, $[\text{C}(\text{NH}_2)_2]^+$), 7.51 (t, $J=5$ Hz, 1H, NHCH_2), 9.01 (s, 1H, ArNH), 12.2 (s, 1H, CO_2H).

MS (DCI) m/e (rel. intensity): 349 ($\text{M}+\text{H}$, 100).

Analysis calc. For $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_4 \cdot \text{CF}_3\text{COOH} \cdot 0.2 \text{H}_2\text{O}$

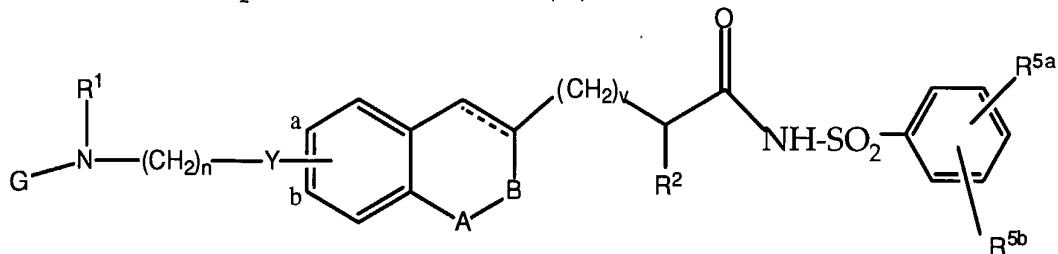
C, 48.97; H, 5.49; N, 12.02

- 15 Found C, 48.75; H, 5.29; N, 12.06

5

We claim:

1. A compound of Formula (I):



10

Formula I

wherein:

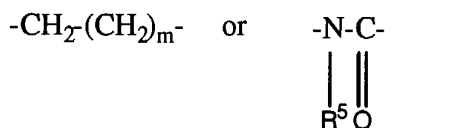
----- represents the presence of an optional double bond;

n is an integer of 2 to 5;

v is an integer of 0 or 1;

15

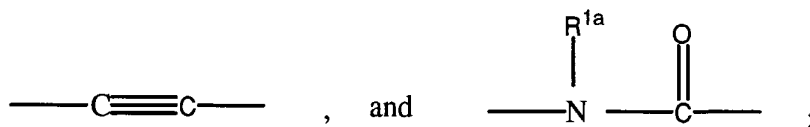
A-B is a diradical of the formulae:



m is an integer of 1 or 2;

Y is selected from the group consisting of -O-,
-CH₂-CH₂-, -CH=CH-,

20



R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more
25 substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;
30 heterocyclylalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocyclyl moiety is selected from a 5- or 6-membered heterocyclic

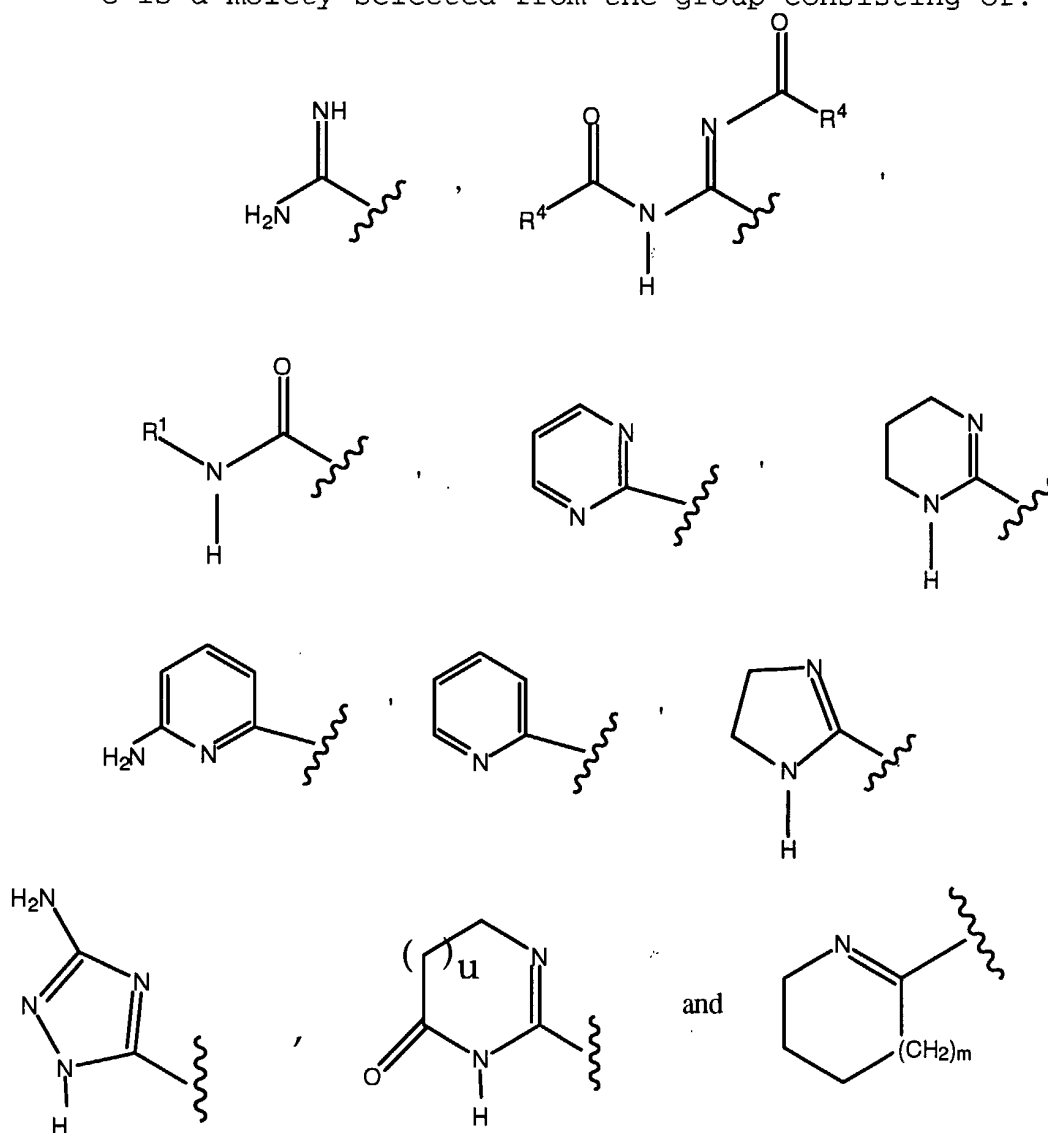
5 ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
which may be the same or different, and are selected from
10 hydroxy, amino, halogen, straight chain alkyl of 1 to 6
carbon atoms, cyano and nitro;

R^{1a} is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
15 substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

20 R^2 is hydrogen, $-NHR^1$, or $-OR^1$, aryl of 6 to 12 carbon
atoms optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
alkoxy of 1 to 6 carbon atoms, $-S$ -alkyl of 1 to 6 carbon
atoms, cyano, nitro, halogen and phenyl; the heterocyclyl
25 moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more
substituents which may be the same or different, and are
30 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, cyano and nitro; phenylalkyl
wherein the alkyl moiety is a straight chain alkyl of 1 to
6 carbon atoms and the phenyl moiety is optionally
substituted with one or more substituents which may be the
35 same or different and are selected from hydroxy, amino,
halogen, straight chain alkyl of 1 to 6 carbon atoms,
branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro,
alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to
6 carbon atoms; heterocyclylalkyl, wherein the alkyl moiety
40 is a straight chain alkyl of 1 to 6 carbon atoms and the
heterocyclyl moiety is selected from a 5- or 6-membered

5 heterocyclic ring which contains 1 to 3 heteroatoms which
 may be the same or different, selected from nitrogen,
 oxygen and sulfur optionally substituted with one or more
 substituents which may be the same or different, and are
 selected from hydroxy, amino, halogen, straight chain alkyl
 10 of 1 to 6 carbon atoms, cyano and nitro;

G is a moiety selected from the group consisting of:



15 u is an integer of 0 or 1;

R^4 is straight chain alkyl of 1 to 6 carbon atoms,
 alkoxy or phenylalkoxy wherein the alkyl moiety is a

5 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
10 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
15 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
20 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms and dialkylamino of 1 to 6 carbon atoms;

R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
25 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
30 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
35 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
40 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

5

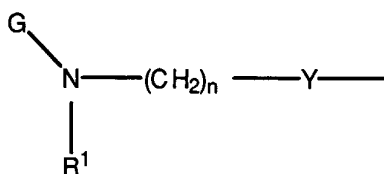
provided that the optional double bond ----- is a single
 bond when A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;
 10 or a pharmaceutically acceptable salt thereof.

2. A compound as defined in claim 1 wherein:

n is an integer of 2 to 4;

the moiety

15



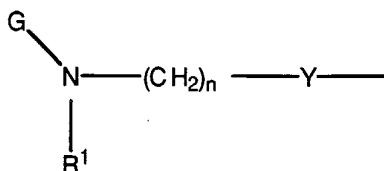
is located at the a or b position of the bicyclic nucleus;

R¹ is hydrogen or straight chain alkyl of 1 to 6
 20 carbon atoms; phenylalkyl wherein the alkyl moiety is a
 straight chain alkyl of 1 to 6 carbon atoms and the phenyl
 moiety is optionally substituted with one or two
 substituents which may be the same or different and are
 selected from halogen, straight chain alkyl of 1 to 6
 25 carbon atoms, and nitro; heterocyclylalkyl, wherein the
 alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 atoms and the heterocyclyl moiety is selected from 2- or 3-
 furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally
 substituted with one or two substituents which may be the
 same or different, and are selected from halogen, straight
 30 chain alkyl of 1 to 6 carbon atoms and nitro;

R² is hydrogen; aryl of 6 to 12 carbon atoms
 optionally substituted with one or more substituents
 selected from straight chain alkyl of 1 to 6 carbon atoms,
 35 alkoxy of 1 to 6 carbon atoms, nitro, and halogen; the
 heterocyclyl moiety is selected from 2- or 3-furyl, 2- or
 3-thienyl, and 2-, 3- or 4-pyridyl; phenylalkyl wherein the
 alkyl moiety is a straight chain alkyl of 1 to 6 carbon

5 atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 10 atoms and the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl; the optional double bond ----- is a single bond; or a pharmaceutically acceptable salt thereof.

15 3. A compound as defined in claim 1 wherein:
 n is an integer of 2 to 4;
 the moiety



20 is located at the a or b position of the bicyclic nucleus;
 A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

R^1 is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl
 25 moiety is optionally substituted with one or two substituents which may be the same or different and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms, and nitro; heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon
 30 atoms and the heterocycl moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl optionally substituted with one or two substituents which may be the same or different, and are selected from halogen, straight chain alkyl of 1 to 6 carbon atoms and nitro;

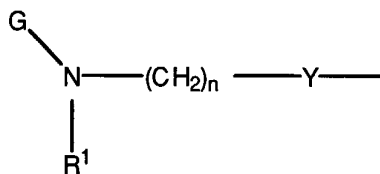
35 R^2 is hydrogen; aryl optionally substituted with one or more substituents selected from straight chain alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, nitro, and halogen; the heterocycl moiety is selected from 2- or

- 5 3-furyl, 2- or 3-thienyl, and 2-, 3- or 4-pyridyl;
 phenylalkyl wherein the alkyl moiety is a straight chain
 alkyl of 1 to 6 carbon atoms and the phenyl moiety is
 optionally substituted with one or more substituents which
 may be the same or different and are selected from halogen,
 10 straight chain alkyl of 1 to 6 carbon atoms, and nitro;
 heterocyclalkyl, wherein the alkyl moiety is a straight
 chain alkyl of 1 to 6 carbon atoms and the heterocycl
 moiety is selected from 2- or 3-furyl, 2- or 3-thienyl, and
 2-, 3- or 4-pyridyl;
 15 the optional double bond ----- is a single bond;
 or a pharmaceutically acceptable salt thereof.

4. A compound as defined in Claim 1 wherein:

20 n is an integer of 2 to 4;

the moiety



25

is located at the a or b position of the bicyclic nucleus;

R¹ is H;

30 R² is H;

R⁵ is H;

the optional double bond ----- is a single bond;
 or a pharmaceutically acceptable salt thereof.

35

5. A compound as defined in Claim 1 wherein:

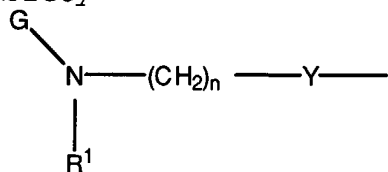
5 n is an integer of 2 to 4;

m is an integer of 1;

v is an integer of 0;

10

the moiety



is located at the a or b position of the bicyclic nucleus;

Y is -O-;

15

R¹ is H;

R² is H;

20

R⁵ is H;

the optional double bond ----- is a single bond;
or a pharmaceutically acceptable salt thereof.

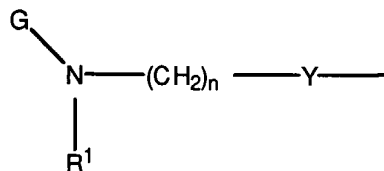
25

6. A compound as defined in Claim 1 wherein:

n is an integer of 2 to 4;

30

the moiety



is located at the a or b position of the bicyclic nucleus;

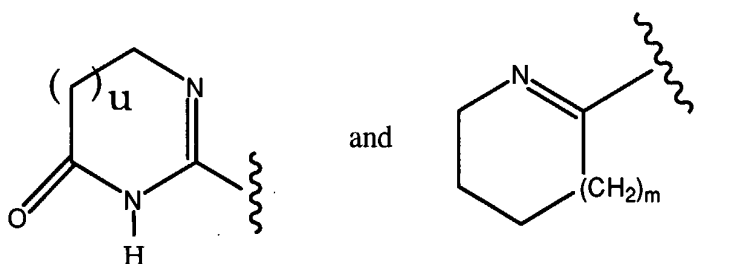
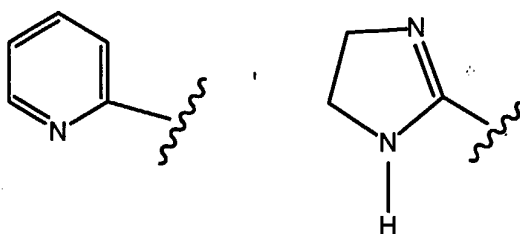
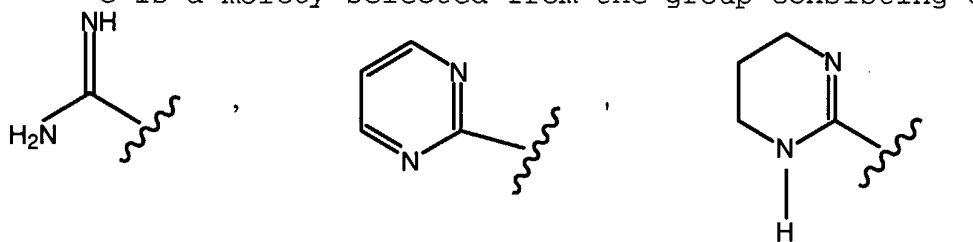
R¹ is H;

35

5 R^2 is H;

R^5 is H;

G is a moiety selected from the group consisting of:



10

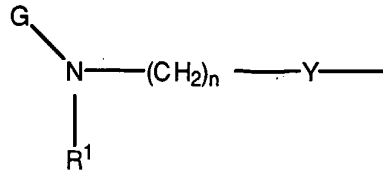
or a pharmaceutically acceptable salt thereof.

15 7. A compound as defined in Claim 1 wherein:

n is an integer of 2 to 4;

5

the moiety



is located at the a or b-position of the bicyclic nucleus;

10

R¹ is H;

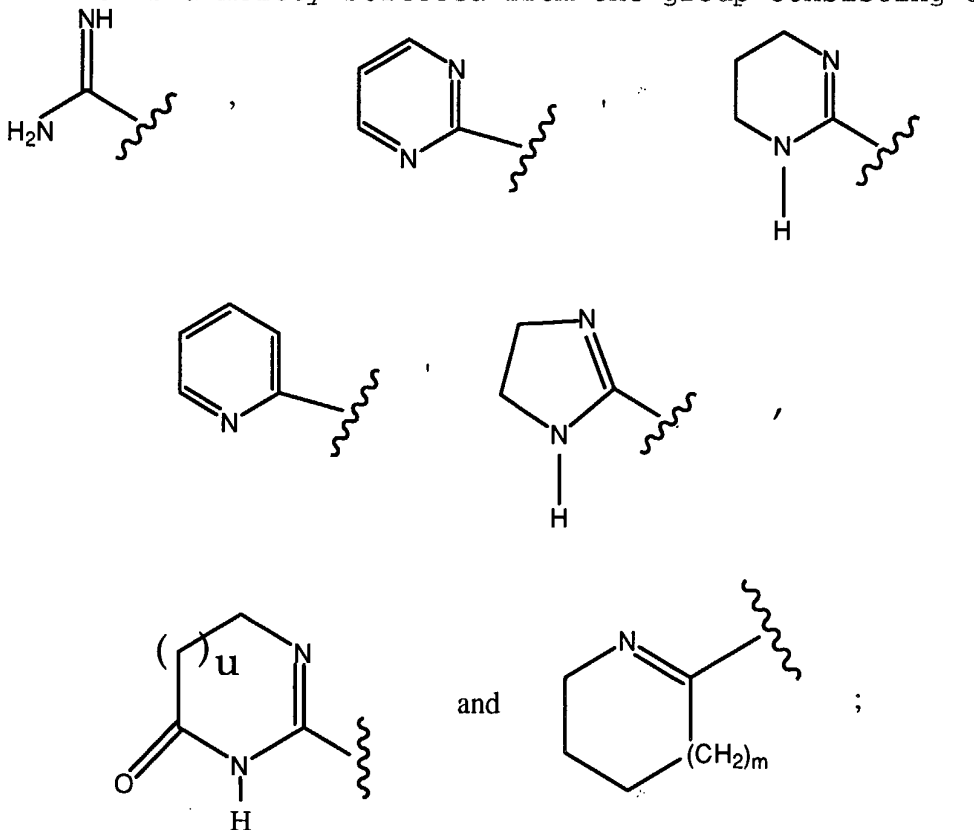
R² is H;

R⁵ is H;

15

Y is -O-;

G is a moiety selected from the group consisting of:

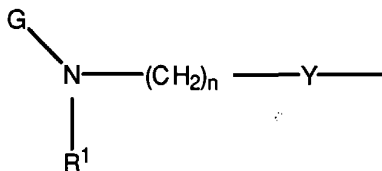


20 or a pharmaceutically acceptable salt thereof.

5 8. A compound as defined in Claim 1 wherein:

n is an integer of 2 to 4;

10 the moiety



is located at the b-position of the bicyclic nucleus;

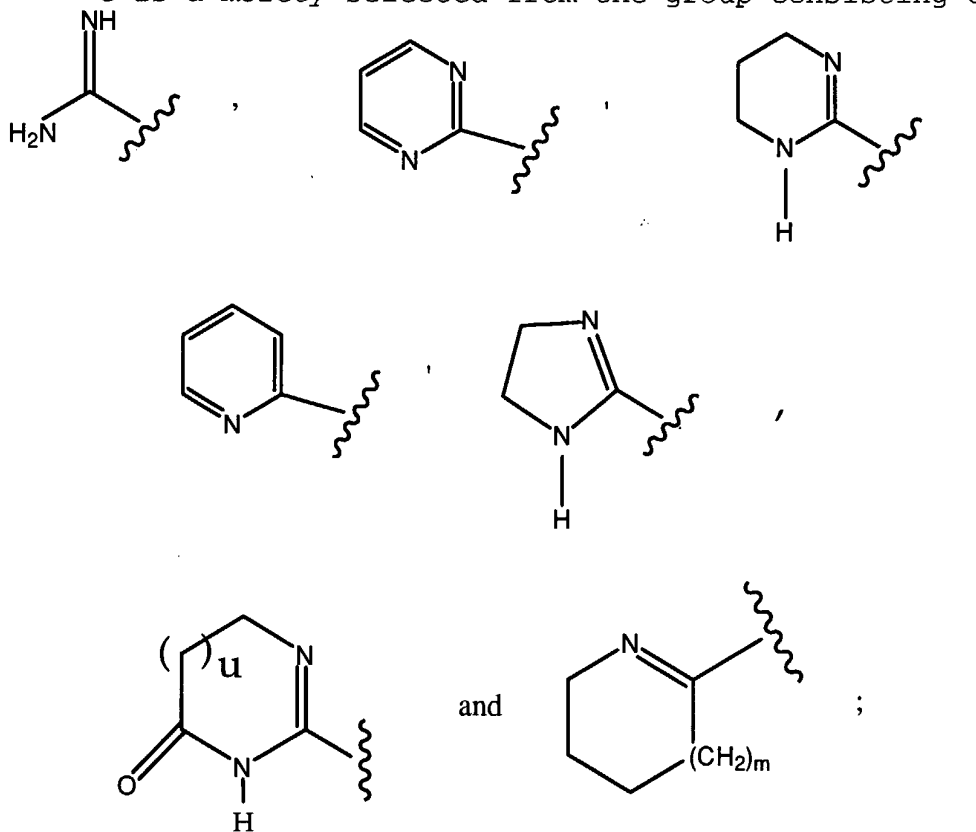
R¹ is H;

15

R² is H;

R⁵ is H;

20 G is a moiety selected from the group consisting of:

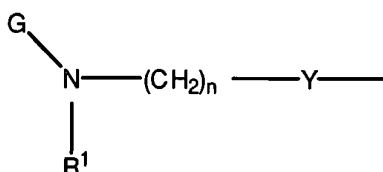


5 or a pharmaceutically acceptable salt thereof.

9. A compound as defined in Claim 1 wherein:

10 n is an integer of 2 to 4;

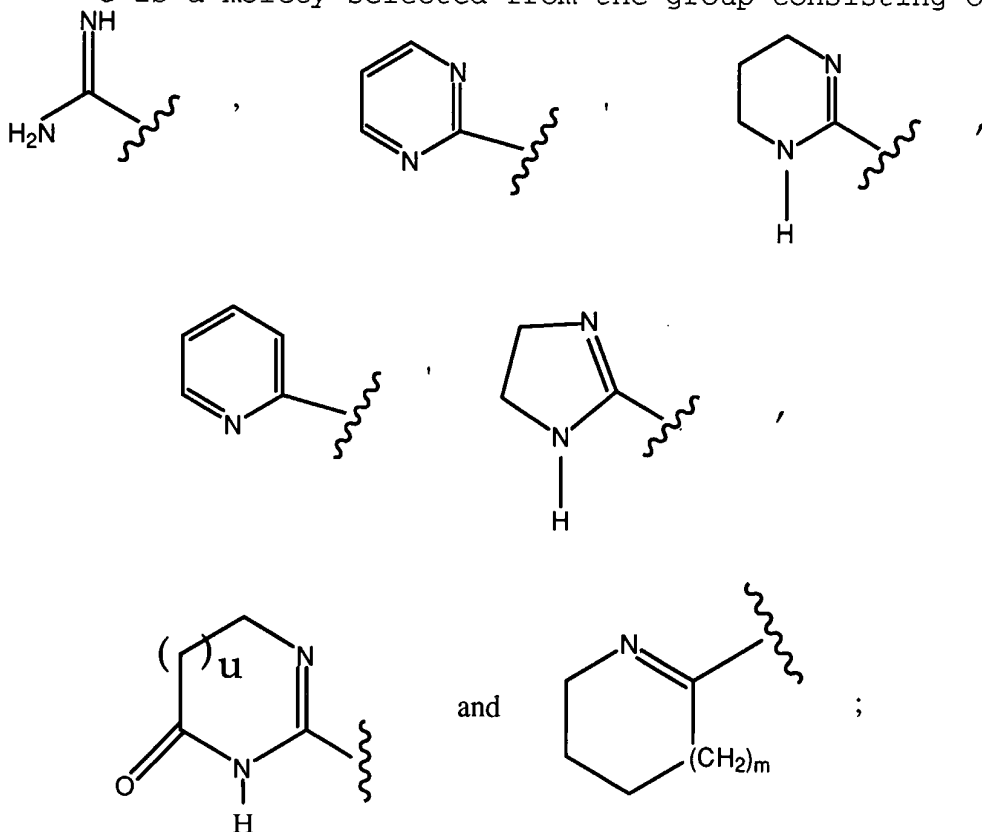
the moiety



is located at the b-position of the bicyclic nucleus;

15

G is a moiety selected from the group consisting of:



20 or a pharmaceutically acceptable salt thereof.

5 10. A compound as defined in Claim 1 wherein:

n is an integer of 2 to 4;

A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

10

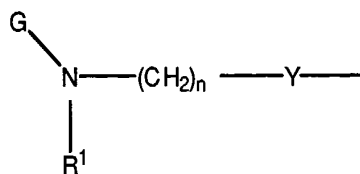
R^1 is H;

R^2 is H;

15

R^5 is H;

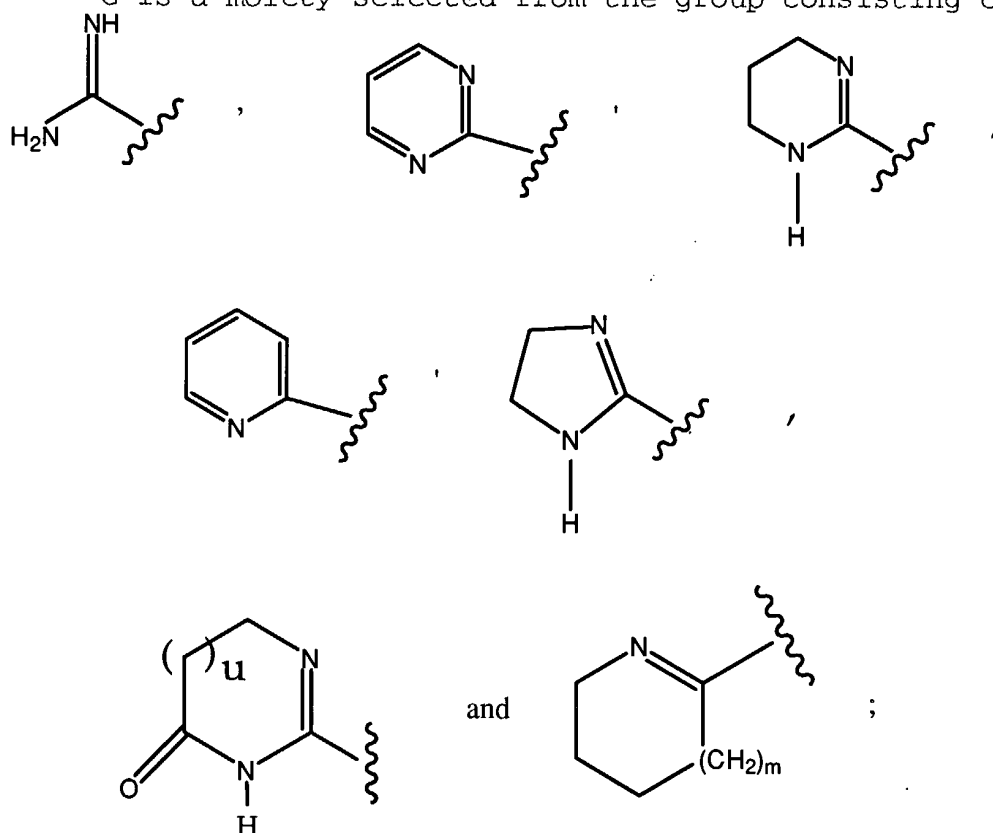
the moiety



is located at the a or b-position of the bicyclic
20 nucleus;

5

G is a moiety selected from the group consisting of:

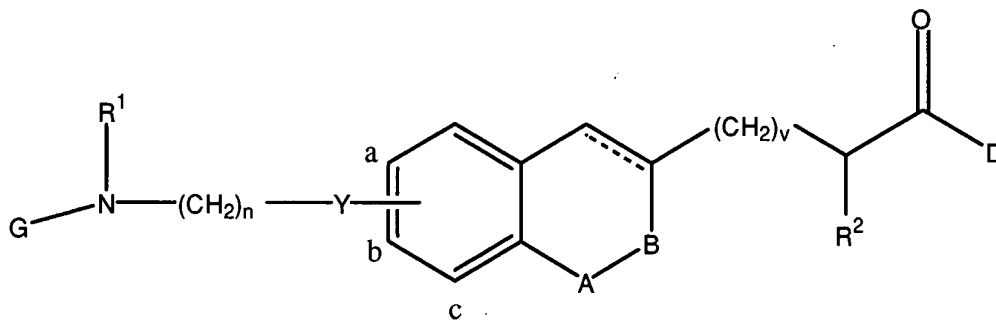


10 the optional double bond ----- is a single bond;
or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1
4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-
propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-
15 benzenesulfonamide, trifluoroacetic acid salt, or a
pharmaceutically acceptable salt thereof.

12. The compound according to claim 1 4-Methyl-N-{{7-(3-
20 guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-
acetyl}-benzenesulfonamide,
or a pharmaceutically acceptable salt thereof.

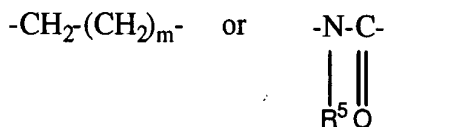
5 13. A pharmaceutical composition useful for blocking
 or inhibiting bone resorption by antagonizing the $\alpha_v\beta_3$
 integrin receptor mediated binding of an osteoclast to a
 bone matrix which comprises administering to a mammal in
 need thereof an effective amount of a compound of general
 10 Formula (II):



Formula II

wherein:

15 ----- represents the presence of an optional double bond;
 n is an integer of 2 to 5;
 v is an integer of 0 or 1;
 A-B is a diradical of the formulae:



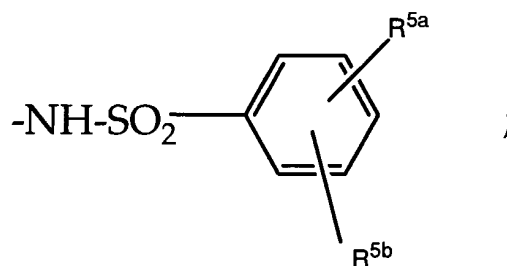
20

m is an integer of 1 or 2;

D is a moiety selected from the group consisting of:

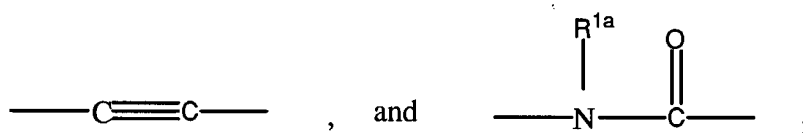
-OR³

and



5

Y is selected from the group consisting of -O-,
-CH₂-CH₂-, -CH=CH-,



10 R^1 is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are
15 selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms; heterocyclylalkyl, wherein the alkyl moiety is a straight
20 chain alkyl of 1 to 6 carbon atoms and the heterocyclyl moiety is selected from a 5- or 6-membered heterocyclic ring which contains 1 to 3 heteroatoms which may be the same or different, selected from nitrogen, oxygen and sulfur optionally substituted with one or more substituents
25 which may be the same or different, and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro;

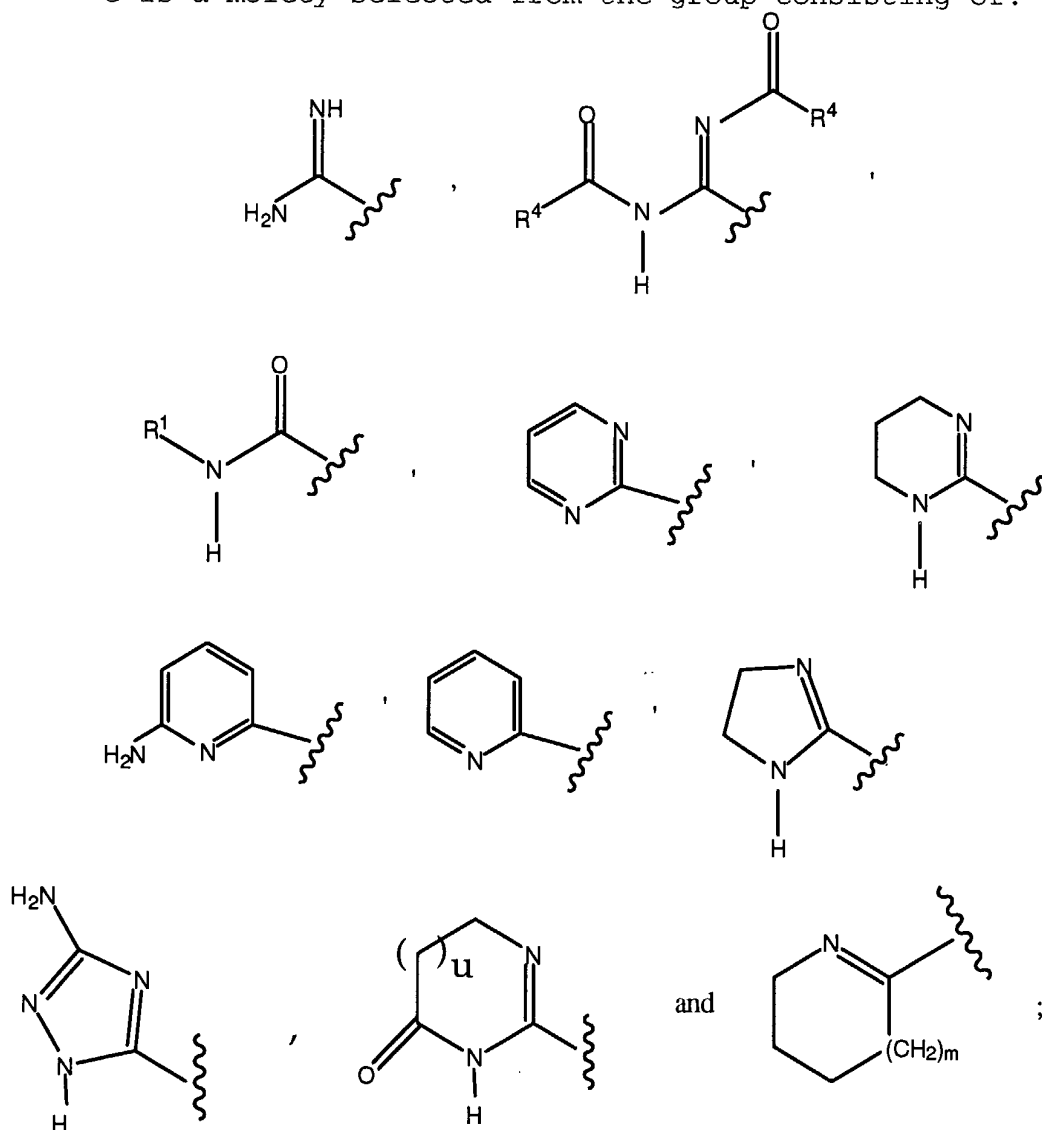
5 R^{1a} is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
10 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

 R² is hydrogen, -NHR¹, or -OR¹, aryl of 6 to 12 carbon
15 atoms optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
alkoxy of 1 to 6 carbon atoms, -S-alkyl of 1 to 6 carbon
atoms, cyano, nitro, halogen and phenyl; the heterocyclyl
moiety is selected from a 5- or 6-membered heterocyclic
20 ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
which may be the same or different, and are selected from
hydroxy, amino, halogen, straight chain alkyl of 1 to 6
25 carbon atoms, cyano and nitro; phenylalkyl wherein the
alkyl moiety is a straight chain alkyl of 1 to 6 carbon
atoms and the phenyl moiety is optionally substituted with
one or more substituents which may be the same or different
and are selected from hydroxy, amino, halogen, straight
30 chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of
3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6
carbon atoms, and dialkylamino of 1 to 6 carbon atoms;
heterocyclylalkyl, wherein the alkyl moiety is a straight
chain alkyl of 1 to 6 carbon atoms and the heterocyclyl
35 moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
which may be the same or different, and are selected from

5 hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro;

10 R^3 is H, straight chain alkyl of 1 to 6 carbon atoms optionally substituted with a group selected from amino, hydroxyl and carboxyl or branched chain alkyl of 3 to 7 carbon atoms optionally substituted with a group selected from amino, hydroxyl and carboxyl;

G is a moiety selected from the group consisting of:



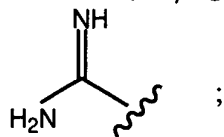
15

u is an integer of 0 or 1;

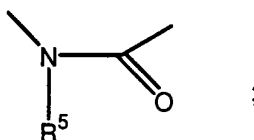
- 5 R⁴ is straight chain alkyl of 1 to 6 carbon atoms,
alkoxy or phenylalkoxy wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
10 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
- 15 R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
20 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms and dialkylamino of 1 to 6 carbon atoms;
- 25 R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
30 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
- 35 R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
40 selected from hydroxy, amino, halogen, straight chain alkyl

5 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;

with the proviso that Y is not -O-; n is not 3 or 4; R¹, R²,
 10 R³ and R⁵ are not H; D is not -OR³; G is not



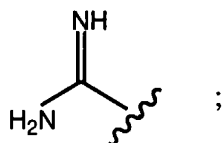
A-B is not



---- is not a single bond;

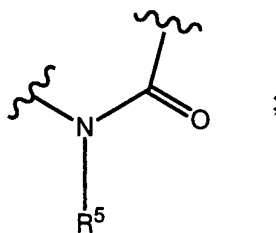
15 a) when v is 0 and substitution is at position a;

with the additional proviso that n is not 2,3 or 4; G is not



20

---- is not a single bond; v is not 1; A-B is not



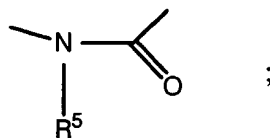
D is not -OR³;

25 a) when Y is O; R¹, R², R³ and R⁵ are H; and substitution is at position a;

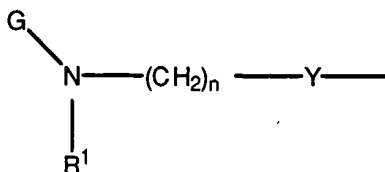
30 with the still further proviso that when A-B is the moiety

229

5



the moiety



10 is located at the a,b or c positions of the bicyclic nucleus;

and with the additional proviso that the optional double bond ----- is a single bond when A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

15 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13 wherein the bone resorption disease in a mammal is selected from the group consisting of osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and the result of glucocorticoid treatment.

25 15. A pharmaceutical composition according to claim 14 wherein the disease in a mammal characterized by bone resorption is osteoporosis.

30 16. The pharmaceutical composition of claim 13 containing a compound which is selected from the group consisting of:

[6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-naphthalen-2-yl]-acetic acid ethyl ester,

35

- 5 [6-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
2-yl]-acetic acid trifluoroacetate,
- [7-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-
yl]-acetic acid trifluoroacetate,
- 10 [2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid hydrochloride,
- [2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-
15 benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- [2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-
benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- 20 [7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid trifluoroacetate,
- [7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Hydrochloride,
- 25 [7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Hydrochloride,
- [7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
30 quinolin-3-yl]-acetic acid Hydrochloride,
- [7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- 35 [7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
40 quinolin-3-yl]-acetic acid Trifluoroacetate,

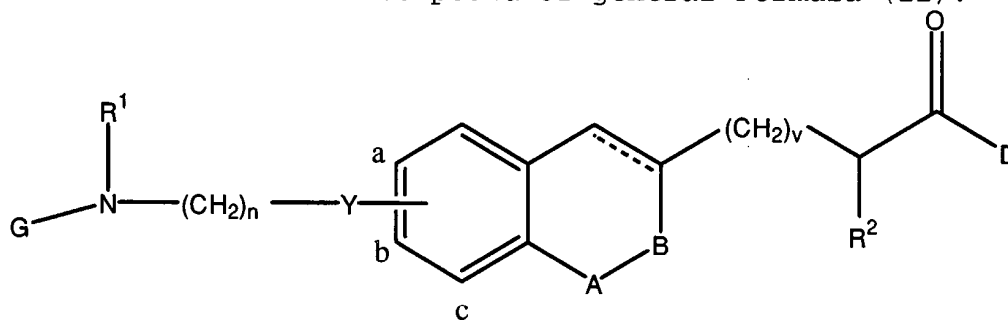
- 5 [7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- 10 [1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]-acetic acid Trifluoroacetate
- [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
15 quinolin-3-yl]-acetic acid
- [1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetra-
hydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- 20 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid,
- [7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
acetic acid Hydrochloride,
- 25 [7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
acetic acid,
- [7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-
30 acetic acid Trifluoroacetate,
- [7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Hydrochloride,
- 35 [7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-acetic acid Hydrochloride,
- {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-
naphthalen-2-yl}-acetic acid methyl ester,
- 40

- 5 {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- 10
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester bis(hydrochloride),
- 15
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid ethyl ester, acetic acid salt,
- 20 4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-benzenesulfonamide, trifluoroacetic acid salt,
- [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
- 25 3-yl]-acetic acid,
- [6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid trifluoroacetate,
- 30 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid,
- 3-[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-propionic acid,
- 35
- [8-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,
- [8-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
- 40 3-yl]-acetic acid,

- 5 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]propionic acid nitric acid salt,
 10 4-Methyl-N-{{7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-acetyl}-benzenesulfonamide, and
 15 [8-(5-Guanidino-pentoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

- 20 17. A method of blocking or inhibiting bone resorption by antagonizing the $\alpha_v\beta_3$ integrin receptor mediated binding of an osteoclast to a bone matrix which comprises administering to a mammal in need thereof an effective amount of a compound of general Formula (II):

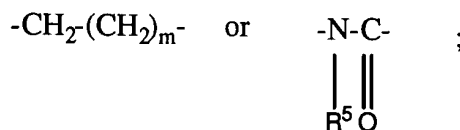


25

Formula II

wherein:

- represents the presence of an optional double bond;
 30 n is an integer of 2 to 5;
 v is an integer of 0 or 1;
 A-B is a diradical of the formulae:

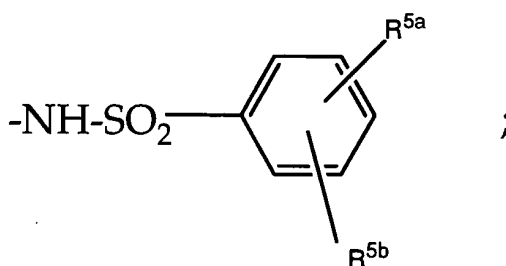


m is an integer of 1 or 2;

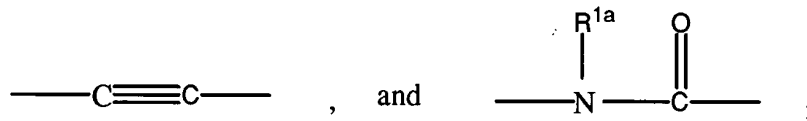
D is a moiety selected from the group consisting of:



and



Y is selected from the group consisting of -O-,
-CH₂-CH₂-, -CH=CH-,



R¹ is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms; heterocyclalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocycl moiety is selected from a 5- or 6-membered heterocyclic ring which contains 1 to 3 heteroatoms which may be the same or different, selected from nitrogen, oxygen and sulfur optionally substituted with one or more substituents which may be the same or different, and are selected from

5 hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro;

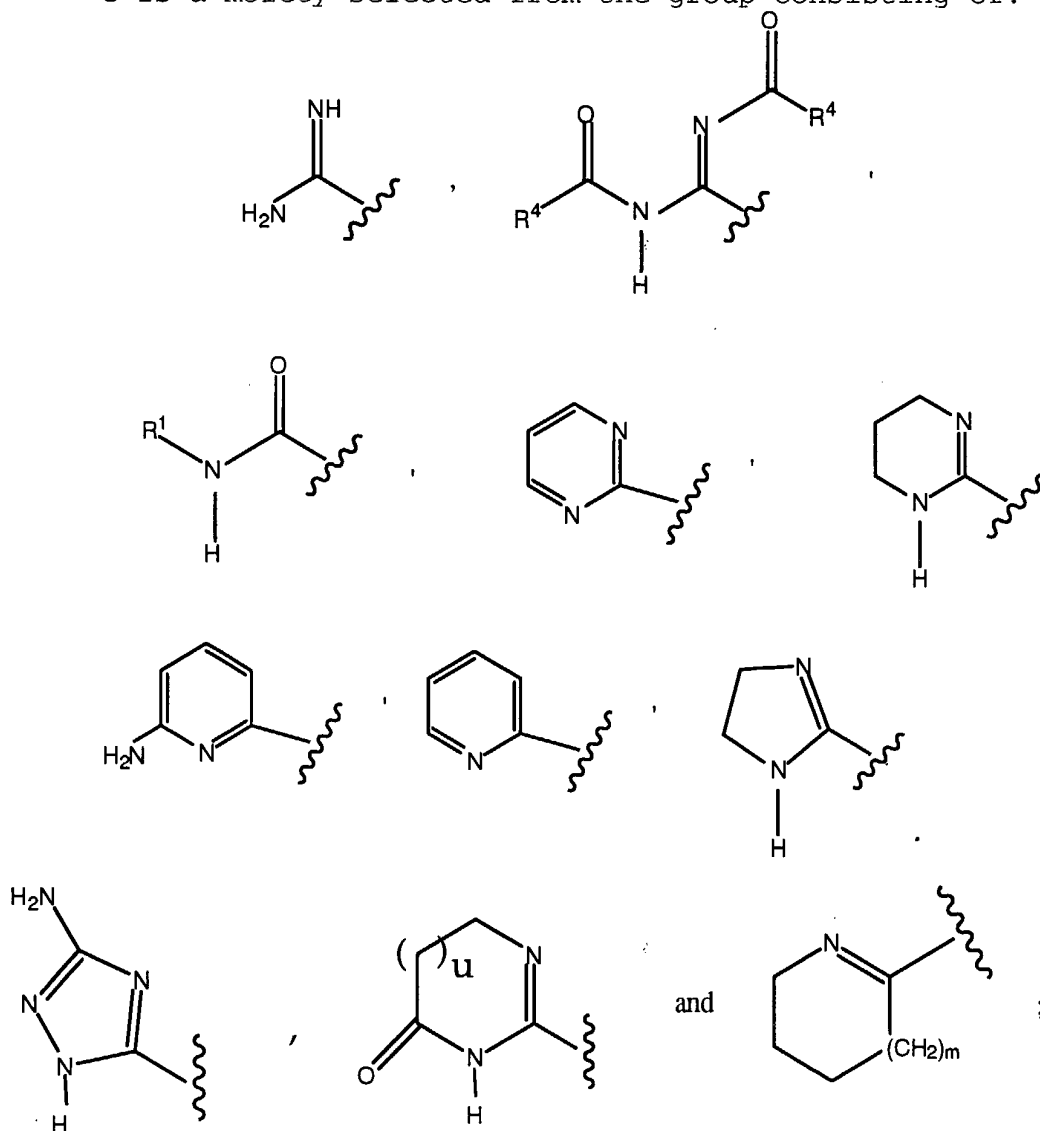
10 R^{1a} is hydrogen or straight chain alkyl of 1 to 6 carbon atoms; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;

15 R^2 is hydrogen, $-NHR^1$, or $-OR^1$, aryl of 6 to 12 carbon atoms optionally substituted with one or more substituents selected from straight chain alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, $-S$ -alkyl of 1 to 6 carbon atoms, cyano, nitro, halogen and phenyl; the heterocyclyl moiety is selected from a 5- or 6-membered heterocyclic ring which contains 1 to 3 heteroatoms which may be the same or different, selected from nitrogen, oxygen and sulfur optionally substituted with one or more substituents which may be the same or different, and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, cyano and nitro; phenylalkyl wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms; heterocyclylalkyl, wherein the alkyl moiety is a straight chain alkyl of 1 to 6 carbon atoms and the heterocyclyl moiety is selected from a 5- or 6-membered heterocyclic ring which contains 1 to 3 heteroatoms which may be the same or different, selected from nitrogen, oxygen and sulfur optionally substituted with one or more substituents which may be the same or different, and are

5 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, cyano and nitro;

R³ is H, straight chain alkyl of 1 to 6 carbon atoms
optionally substituted with a group selected from amino,
hydroxyl and carboxyl or branched chain alkyl of 3 to 7
10 carbon atoms optionally substituted with a group selected
from amino, hydroxyl and carboxyl;

G is a moiety selected from the group consisting of:



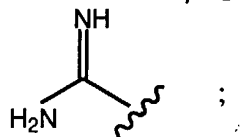
15

u is an integer of 0 or 1;

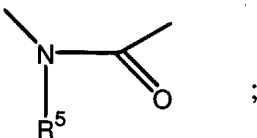
- 5 R⁴ is straight chain alkyl of 1 to 6 carbon atoms,
alkoxy or phenylalkyloxy wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
10 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
- 15 R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
20 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms and dialkylamino of 1 to 6 carbon atoms;
- 25 R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
30 selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
- 35 R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
40 selected from hydroxy, amino, halogen, straight chain alkyl

5 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to 6 carbon atoms;

with the proviso that Y is not -O-; n is not 3 or 4; R¹, R²,
 10 R³ and R⁵ are not H; D is not -OR³; G is not



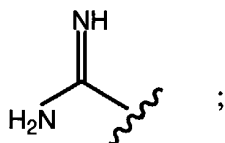
A-B is not



---- is not a single bond;

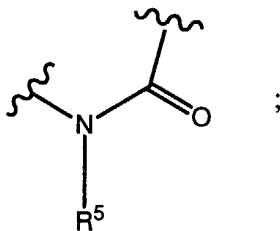
15 a) when v is 0 and substitution is at position a;

with the additional proviso that n is not 2,3 or 4; G is not



20

---- is not a single bond; v is not 1; A-B is not



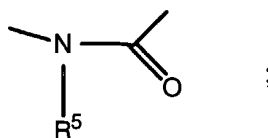
D is not -OR³;

25 a) when Y is O; R¹, R², R³ and R⁵ are H; and substitution is at position a;

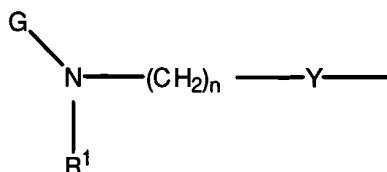
with the still further proviso that when A-B is the moiety

239

5



the moiety



10 is located at the a,b or c positions of the bicyclic nucleus;

and with the additional proviso that the optional double bond ----- is a single bond when A-B is the diradical $-\text{CH}_2-(\text{CH}_2)_m-$;

15 or a pharmaceutically acceptable salt thereof.

18. The method of claim 17 wherein the bone resorption disease in a mammal is selected from the group consisting of osteoporosis, hypercalcemia of malignancy, 20 osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and the result of glucocorticoid treatment.

19. The method of claim 18 wherein the bone 25 resorption disease is osteoporosis.

20. The method of claim 17 in which a compound selected from the group consisting of:

30 [6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid ethyl ester,

[6-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid trifluoroacetate,

35 [7-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-napthalen-2-yl]-acetic acid trifluoroacetate,

- 5 [2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid hydrochloride,
- [2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- 10 [2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- 15 [7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid trifluoroacetate,
- [7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- 20 [7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- [6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid trifluoroacetate,
- 25 [7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- 30 [7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- 35 [7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- 40

- 5 [7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- [1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate
- 10 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid
- [1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetra-
- 15 hydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,
- 20 [7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Hydrochloride,
- [7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid,
- 25 [7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-
- 30 quinolin-3-yl]-acetic acid Hydrochloride,
- [7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- 35 {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester,
- {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-
- 40 naphthalen-2-yl}-acetic acid,

- 5 {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl
10 ester bis(hydrochloride),
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid ethyl
15 ester, acetic acid salt,
- 4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-
propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-
benzenesulfonamide, trifluoroacetic acid salt,
- 20 [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid,
- 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-propionic acid,
25
- 3-[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-propionic acid,
- [8-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid,
30
- [8-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid,
- 35 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-
40 yl]propionic acid nitric acid salt,

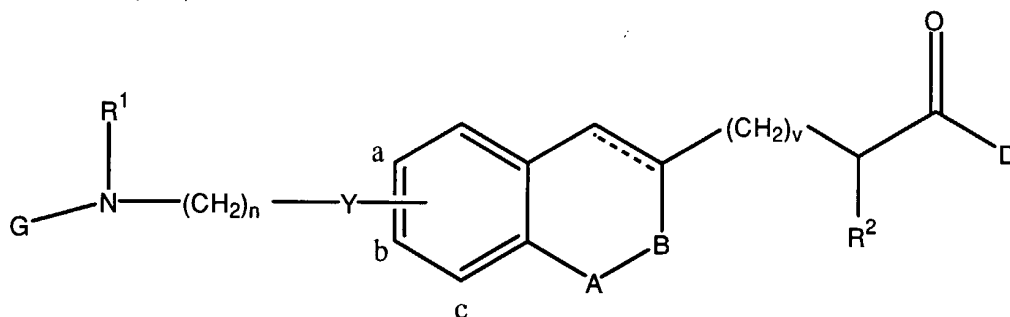
5 4-Methyl-N-{{7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl}-acetyl}-benzenesulfonamide, and
 [8-(5-Guanidino-pentoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid

10

or a pharmaceutically acceptable salt thereof is administered.

21. A method of treating diseases characterized by bone resorption of mineralized tissue and by bone loss, resulting from an imbalance between bone resorption and bone formation which comprises administering to a mammal in need thereof an effective amount of a compound of general Formula (II):

20



Formula II

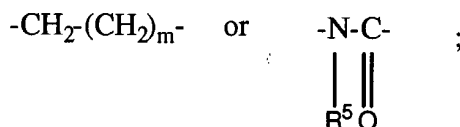
wherein:

----- represents the presence of an optional double bond;

n is an integer of 2 to 5;

25 v is an integer of 0 or 1;

A-B is a diradical of the formulae:

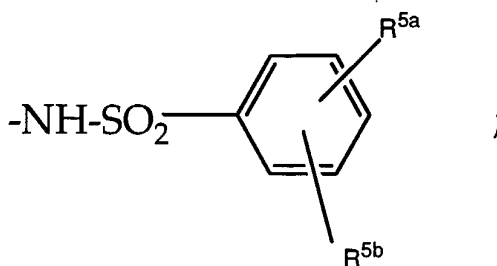


m is an integer of 1 or 2;

D is a moiety selected from the group consisting of:

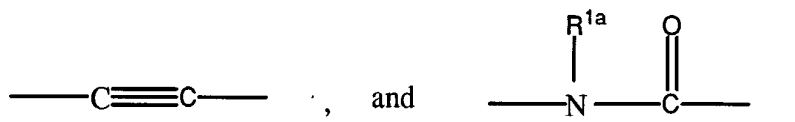
-OR³

and



5

Y is selected from the group consisting of -O-,
-CH₂-CH₂-, -CH=CH-,



R¹ is hydrogen or straight chain alkyl of 1 to 6
10 carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
15 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;
heterocyclalkyl, wherein the alkyl moiety is a straight
chain alkyl of 1 to 6 carbon atoms and the heterocycl
20 moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more substituents
which may be the same or different, and are selected from
25 hydroxy, amino, halogen, straight chain alkyl of 1 to 6
carbon atoms, cyano and nitro;

R^{1a} is hydrogen or straight chain alkyl of 1 to 6
carbon atoms; phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl

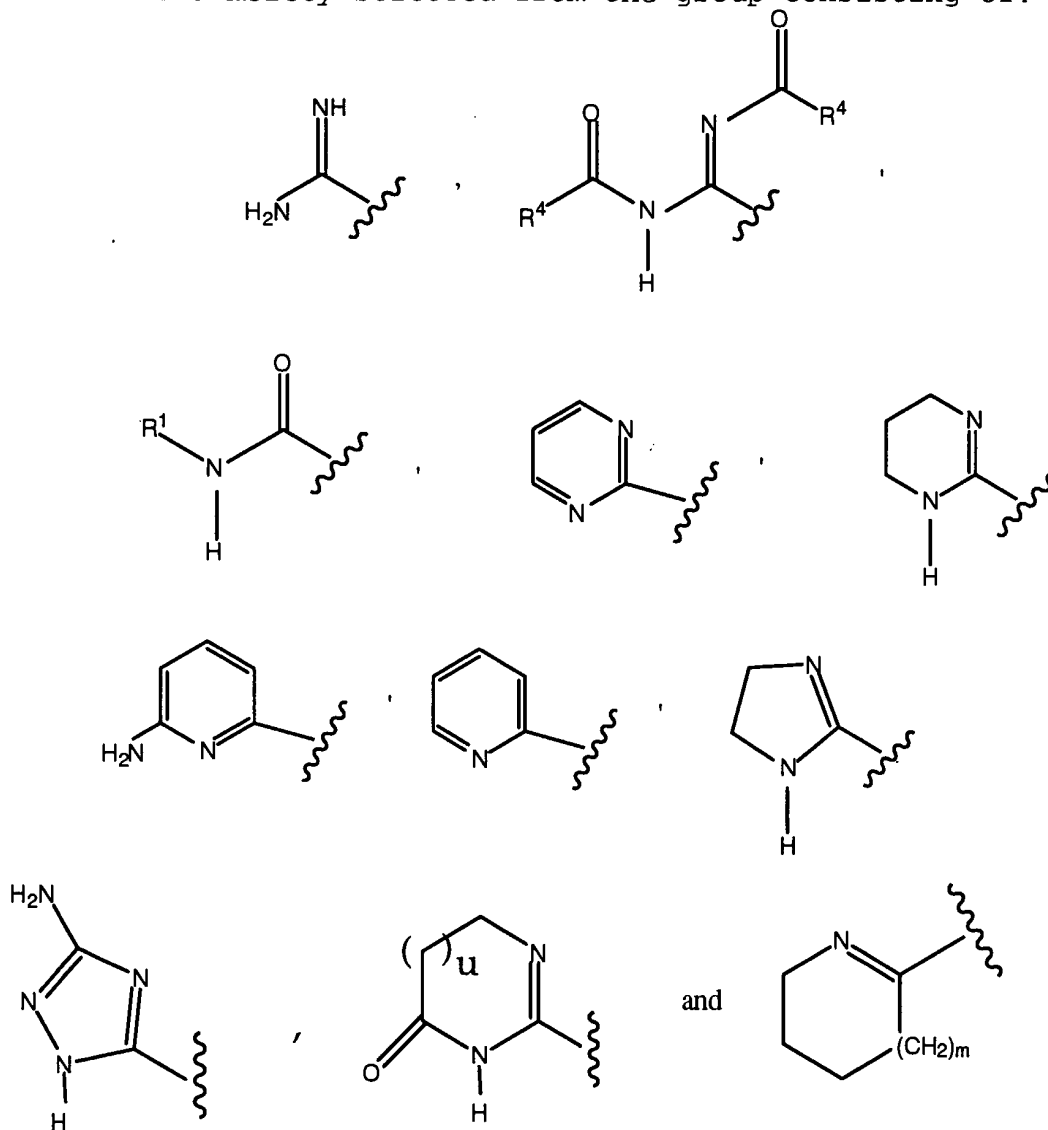
5 moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
10 atoms, and dialkylamino of 1 to 6 carbon atoms;

R^2 is hydrogen, $-NHR^1$, or $-OR^1$, aryl of 6 to 12 carbon
atoms optionally substituted with one or more substituents
selected from straight chain alkyl of 1 to 6 carbon atoms,
alkoxy of 1 to 6 carbon atoms, $-S$ -alkyl of 1 to 6 carbon
15 atoms, cyano, nitro, halogen and phenyl; the heterocyclyl
moiety is selected from a 5- or 6-membered heterocyclic
ring which contains 1 to 3 heteroatoms which may be the
same or different, selected from nitrogen, oxygen and
sulfur optionally substituted with one or more
20 substituents which may be the same or different, and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, cyano and nitro; phenylalkyl
wherein the alkyl moiety is a straight chain alkyl of 1 to
6 carbon atoms and the phenyl moiety is optionally
25 substituted with one or more substituents which may be the
same or different and are selected from hydroxy, amino,
halogen, straight chain alkyl of 1 to 6 carbon atoms,
branched chain alkyl of 3 to 7 carbon atoms, cyano, nitro,
alkylamino of 1 to 6 carbon atoms, and dialkylamino of 1 to
30 6 carbon atoms; heterocyclylalkyl, wherein the alkyl moiety
is a straight chain alkyl of 1 to 6 carbon atoms and the
heterocyclyl moiety is selected from a 5- or 6-membered
heterocyclic ring which contains 1 to 3 heteroatoms which
may be the same or different, selected from nitrogen,
35 oxygen and sulfur optionally substituted with one or more
substituents which may be the same or different, and are
selected from hydroxy, amino, halogen, straight chain alkyl
of 1 to 6 carbon atoms, cyano and nitro;

R^3 is H, straight chain alkyl of 1 to 6 carbon atoms
40 optionally substituted with a group selected from amino,
hydroxyl and carboxyl or branched chain alkyl of 3 to 7

5 carbon atoms optionally substituted with a group selected from amino, hydroxyl and carboxyl;

G is a moiety selected from the group consisting of:



10

u is an integer of 0 or 1;

R⁴ is straight chain alkyl of 1 to 6 carbon atoms, alkoxy or phenylalkoxy wherein the alkyl moiety is a
 15 straight chain alkyl of 1 to 6 carbon atoms and the phenyl moiety is optionally substituted with one or more substituents which may be the same or different and are selected from hydroxy, amino, halogen, straight chain alkyl

5 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

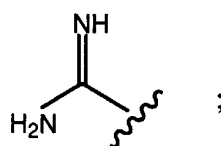
R⁵ is hydrogen, straight chain alkyl of 1 to 6 carbon
10 atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
15 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms and dialkylamino of 1 to 6 carbon atoms;

R^{5a} is hydrogen, straight chain alkyl of 1 to 6 carbon
20 atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
25 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

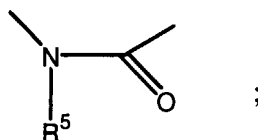
R^{5b} is hydrogen, straight chain alkyl of 1 to 6 carbon
30 atoms, or phenylalkyl wherein the alkyl moiety is a
straight chain alkyl of 1 to 6 carbon atoms and the phenyl
moiety is optionally substituted with one or more
substituents which may be the same or different and are
selected from hydroxy, amino, halogen, straight chain alkyl
35 of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7
carbon atoms, cyano, nitro, alkylamino of 1 to 6 carbon
atoms, and dialkylamino of 1 to 6 carbon atoms;

with the proviso that Y is not -O-; n is not 3 or 4; R¹, R²,
40 R³ and R⁵ are not H; D is not -OR³; G is not

5



A-B is not

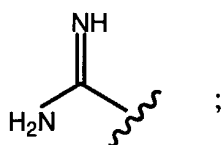


---- is not a single bond;

a) when v is 0 and substitution is at position a;

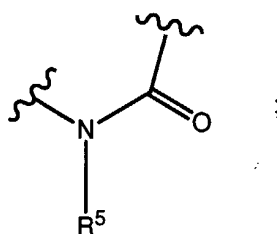
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with the additional proviso that n is not 2,3 or 4; G is not



15

---- is not a single bond; v is not 1; A-B is not

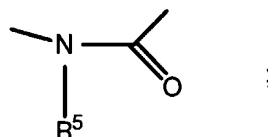


D is not -OR³;

a) when Y is O; R¹, R², R³ and R⁵ are H; and substitution is at position a;

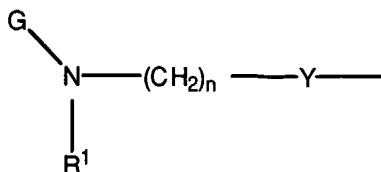
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with the still further proviso that when A-B is the moiety



25

the moiety



5

is located at the a,b or c positions of the bicyclic nucleus;

and with the additional proviso that the optional double
 10 bond ----- is a single bond when A-B is the diradical
 $-\text{CH}_2-(\text{CH}_2)_m-$;
 or a pharmaceutically acceptable salt thereof.

22. The method of claim 21 wherein the bone
 15 resorption of mineralized tissue and by bone loss resulting
 from an imbalance between bone resorption and bone
 formation in a mammal is selected from the group consisting
 of osteoporosis, hypercalcemia of malignancy, osteopenia
 due to bone metastases, periodontal disease,
 20 hyperparathyroidism, periarticular erosions in rheumatoid
 arthritis, Paget's disease, immobilization-induced
 osteopenia and the result of glucocorticoid treatment.

23. The method of claim 22 wherein the disease
 characterized by bone loss, resulting from an imbalance
 25 between bone resorption and bone formation disease is
 osteoporosis.

24. The method of claim 21 in which a compound
 selected from the group consisting of:

30 [6-(3-Guanidinopropoxy)-1,2,3,4-tetrahydro-naphthalen-
 2-yl]-acetic acid ethyl ester,

[6-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-
 2-yl]-acetic acid trifluoroacetate,

35

[7-(3-Guanidino-propoxy)-1,2,3,4-tetrahydro-naphthalen-2-
 yl]-acetic acid trifluoroacetate,

- 5 [2-(2-Guanidino-ethoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid hydrochloride,
- [2-(3-Guanidino-propoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- 10 [2-(4-Guanidino-butoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl]-acetic acid trifluoroacetate,
- [7-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-
- 15 quinolin-3-yl]-acetic acid trifluoroacetate,
- [7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
- quinolin-3-yl]-acetic acid Hydrochloride,
- 20 [7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
- quinolin-3-yl]-acetic acid Hydrochloride,
- [6-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
- 3-yl]-acetic acid trifluoroacetate,
- 25 [7-(4-Guanidino-but-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
- quinolin-3-yl]-acetic acid Hydrochloride,
- [7-(5-Guanidino-pent-1-ynyl)-2-oxo-1,2,3,4-tetrahydro-
- 30 quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(4-Guanidino-but-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
- quinolin-3-yl]-acetic acid Trifluoroacetate,
- 35 [7-(5-Guanidino-pent-1-enyl)-2-oxo-1,2,3,4-tetrahydro-
- quinolin-3-yl]-acetic acid Trifluoroacetate,
- [7-(4-Guanidino-butyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-
- 40 yl]-acetic acid Trifluoroacetate,

- 5 [7-(5-Guanidino-pentyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate
- 10 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid
[1-Ethyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
- 15 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid,
- 20 [7-(4-Guanidino-butoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Hydrochloride,
[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid,
- 25 [7-(3-Guanidino-propoxy)-2-oxo-1,2-dihydro-quinolin-3-yl]-acetic acid Trifluoroacetate,
[7-(2-Guanidino-ethylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- 30 [7-(3-Guanidino-propylcarbamoyl)-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-acetic acid Hydrochloride,
- 35 {6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl ester,
{6-[3-(Pyrimidin-2-ylamino)-propoxy]-1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- 40

- 5 {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid,
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid methyl
10 ester bis(hydrochloride),
- {6-[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propoxy]-
1,2,3,4-tetrahydro-naphthalen-2-yl}-acetic acid ethyl
15 ester, acetic acid salt,
- 4-Methyl-N-({6-[3-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-
propoxyl]1,2,3,4-tetrahydro-naphthalen-2-yl}-acetyl)-
benzenesulfonamide, trifluoroacetic acid salt,
- 20 [6-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid,
- 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-propionic acid,
25
- 3-[7-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-
quinolin-3-yl]-propionic acid,
- [8-(3-Guanidino-propoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
30 3-yl]-acetic acid,
- [8-(4-Guanidino-butoxy)-2-oxo-1,2,3,4-tetrahydro-quinolin-
3-yl]-acetic acid,
- 35 [1-Benzyl-7-(3-guanidino-propoxy)-2-oxo-1,2-dihydro-
quinolin-3-yl]-acetic acid Trifluoroacetate,
- 3-[7-(2-Guanidino-ethoxy)-2-oxo-1,2-dihydro-quinolin-3-
yl]propionic acid nitric acid salt,
40

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 00/19885

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/4704 A61P19/10 C07D239/14 C07D215/22

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 820 991 A (HOECHST) 28 January 1998 (1998-01-28) page 3 -page 4; examples ---	1, 13
A	WO 98 31359 A (MERCK) 23 July 1998 (1998-07-23) page 4 -page 9 -----	1, 13

 Further documents are listed in the continuation of box C.

 Patent family members are listed in annex.

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Date of the actual completion of the international search

14 November 2000

Date of mailing of the international search report

24/11/2000

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/19885

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