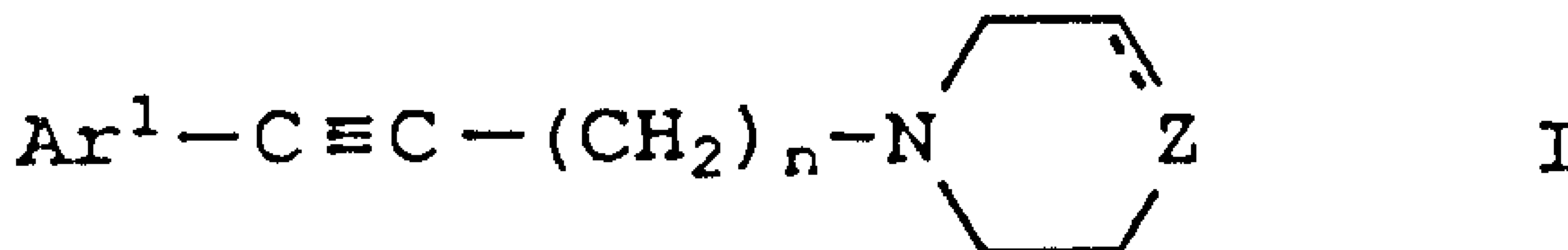




(86) Date de dépôt PCT/PCT Filing Date: 1991/10/29
(87) Date publication PCT/PCT Publication Date: 1992/05/14
(45) Date de délivrance/Issue Date: 2002/02/12
(85) Entrée phase nationale/National Entry: 1993/04/22
(86) N° demande PCT/PCT Application No.: US 1991/008017
(87) N° publication PCT/PCT Publication No.: 1992/007831
(30) Priorités/Priorities: 1990/11/05 (609,274) US;
1991/10/24 (778,248) US

(51) Cl.Int.⁵/Int.Cl.⁵ C07D 401/06, A61K 31/495,
A61K 31/435, C07D 211/82, C07D 211/70,
C07D 417/14, C07D 409/14, C07D 405/14, C07D 471/04
(72) Inventeurs/Inventors:
Wise, Lawrence David, US;
Smith, Sarah Jane, US;
Jaen, Juan Carlos, US;
Glase, Shelly, US
(73) Propriétaire/Owner:
WARNER-LAMBERT COMPANY, US
(74) Agent: MACRAE & CO.

(54) Titre : DERIVES DE SUBSTITUTION DE TETRAHYDROPYRIDINES ET D'HYDROXYPIPERIDINES, AGENTS
THERAPEUTIQUES POUR LE SYSTEME NERVEUX CENTRAL
(54) Title: SUBSTITUTED TETRAHYDROPYRIDINES AND HYDROXYPIPERIDINES AS CENTRAL NERVOUS
SYSTEM AGENTS



(57) **Abrégé/Abstract:**

Substituted tetrahydropyridines and hydroxypiperidines of formula (I) and derivatives thereof are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as central nervous system agents and are particularly useful as dopaminergic, antipsychotic, and antihypertensive agents as well as for treating hyperprolactinaemia-related conditions and central nervous system disorders.





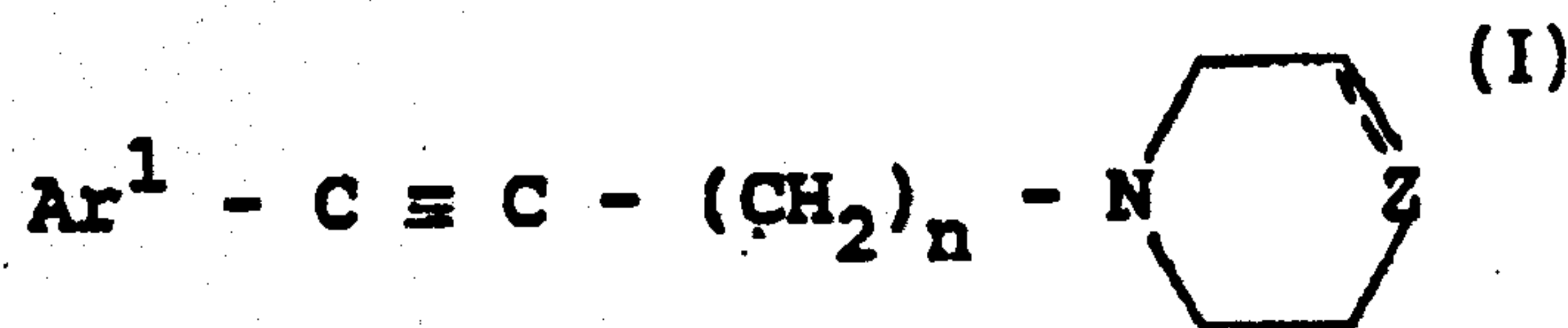
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 211/70, 211/52, 401/06 C07D 409/14, A61K 31/445	A1	(11) International Publication Number: WO 92/07831 (43) International Publication Date: 14 May 1992 (14.05.92)
(21) International Application Number: PCT/US91/08017 (22) International Filing Date: 29 October 1991 (29.10.91) (30) Priority data: 609,274 5 November 1990 (05.11.90) US 778,248 24 October 1991 (24.10.91) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US). (72) Inventors: GLASE, Shelly ; 1533 Natalie Lane, Apt. 203, Ann Arbor, MI 48105 (US). JAEN, Juan Carlos ; 10680 Red Maple, Plymouth, MI 48170 (US). SMITH, Sarah, Jane ; 1468 Bemidji Drive, Ann Arbor, MI 48103 (US). WISE, Lawrence, David ; 1241 Barrister, Ann Arbor, MI 48105 (US).		(74) Agents: TINNEY, Francis, J. et al.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (Euro- pean patent), NL (European patent), SE (European pa- tent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: SUBSTITUTED TETRAHYDROPYRIDINES AND HYDROXYPIPERIDINES AS CENTRAL NERVOUS SYSTEM AGENTS



(57) Abstract

Substituted tetrahydropyridines and hydroxypiperidines of formula (I) and derivatives thereof are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as central nervous system agents and are particularly useful as dopaminergic, antipsychotic, and antihypertensive agents as well as for treating hyperprolactinaemia-related conditions and central nervous system disorders.

-1-

SUBSTITUTED TETRAHYDROPYRIDINES AND
HYDROXYPIPERIDINES AS
CENTRAL NERVOUS SYSTEM AGENTS

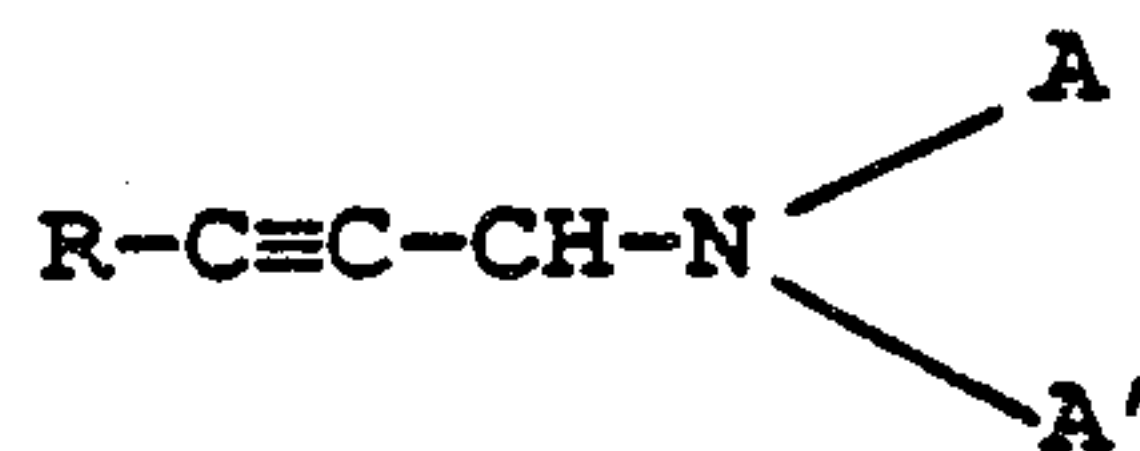
5

BACKGROUND OF THE INVENTION

The present invention relates to novel substituted tetrahydropyridines and hydroxypiperidines and derivatives thereof useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel compounds of the present invention are central nervous system agents. More particularly, the novel compounds of the present invention are dopaminergic agents.

GB 1055548 discloses compounds of formula

20



25

wherein R represents unsubstituted phenyl or phenyl substituted by methyl, halogen, nitro, amino, (lower alkanoyl)amino, or lower alkoxyl; and either A is alkyl of 1 to 4 carbon atoms and A' is alkyl of 1 to 4 carbon atoms, benzyl, chlorobenzyl, or dimethoxybenzyl; or A and A', together with the adjacent nitrogen atom, form one of the following heterocyclic rings: pyrrolidino, morpholino, thiomorpholino, 4-phenylpiperidino, 4-phenyl-4-hydroxypiperidino, N'-methylpiperazino, N'-benzylpiperazino, N'-phenylpiperazino, N'-chlorophenylpiperazino, N'-tolylpiperazino,

30

35

-2-

N'-methoxyphenylpiperazino, N'-(β -hydroxyethyl)-
 piperazino, N'-(β -acetoxyethyl)piperazino,
 N'-(β -propionyloxyethyl)piperazino,
 N'-carbethoxypiperazino, hexamethyleneimino, and
 heptamethyleneimino; provided that when R is phenyl,
 p-methoxyphenyl, o- or p-nitrophenyl, or

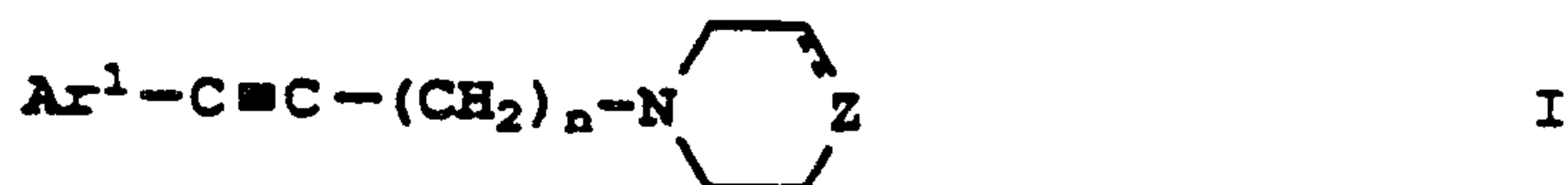
o-aminophenyl, $\text{-N} \begin{array}{l} \text{A} \\ \text{A'} \end{array}$ does not represent

dimethylamino or diethylamino; and their acid addition
 salts, especially those containing physiologically
 innocuous anions having antiulcer activity.

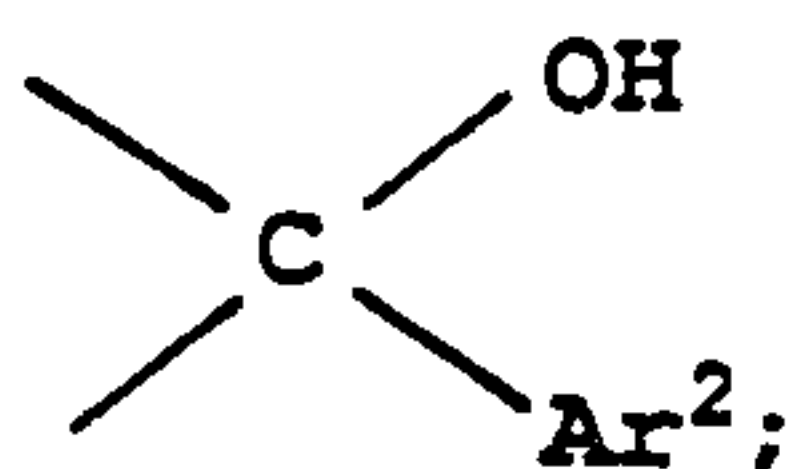
The aforementioned reference does not teach nor
 suggest the combination of structural variations of
 the compounds of the present invention nor their use
 as dopaminergic agents described hereinafter.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a
 compound of Formula I



wherein n is an integer of 2, 3, or 4; Z is $\text{C} - \text{Ar}^2$ or



Ar¹ and Ar² are each independently
 aryl,

aryl substituted by one to four substituents

selected from the group consisting of

-3-

lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
5 lower acyloxy,
amino,
lower alkyl amino,
nitro,

10 $\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R, wherein R is} \end{array}$
aryl,
lower alkyl,
trifluoromethyl or a 5- or 6-membered
15 heteroaromatic ring comprising one
or more heteroatoms selected from
N, S, and O,

-NH-SO₂R, wherein R is as defined above or

-N-(SO₂R)₂, wherein R is as defined above,

20 a 5- or 6-membered heteroaromatic ring comprising
one or more heteroatoms selected from N, S,
and O,

a 5- or 6-membered heteroaromatic ring comprising
one or more heteroatoms selected from N, S,
25 and O, substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

30 lower acyloxy,

amino,

lower alkyl amino,

nitro,

35 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R, wherein R is as defined above,} \end{array}$

-4-

-NH-SO₂R, wherein R is as defined above, or
-N-(SO₂R)₂, wherein R is as defined above,

a 8-, 9-, or 10-membered heteroaromatic bicyclic
ring comprising one or more heteroatoms
selected from N, S, and O, or

a 8-, 9-, or 10-membered heteroaromatic bicyclic
ring comprising one or more heteroatoms
selected from N, S, and O, substituted by
halogen,

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino

lower alkyl amino,
nitro,

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,
-NH-SO₂R, wherein R is as defined above, or
-N-(SO₂R)₂, wherein R is as defined above;

or a pharmaceutically acceptable acid addition salt thereof.

As dopaminergic agents, the compounds of
Formula I are useful as antipsychotic agents for
treating psychoses such as schizophrenia. They are
also useful as antihypertensives and for the treatment
of disorders which respond to dopaminergic activation.
Thus, other embodiments of the present invention
include the treatment, by a compound of Formula I, of
hyperprolactinaemia-related conditions, such as
galactorrhea, amenorrhea, menstrual disorders and
sexual dysfunction, and several central nervous system
disorders such as Parkinson's disease, Huntington's
chorea, and depression.

-5-

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "lower alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

The term "aryl" means an aromatic radical which is a phenyl group or phenyl group substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy,

amino, lower alkyl amino, nitro, -NH-C(=O)-R , wherein R is aryl, lower alkyl, trifluoromethyl or a 5- or 6-membered heteroaromatic ring as defined hereinafter, $\text{-NH-SO}_2\text{R}$, wherein R is lower alkyl, trifluoromethyl, or a 5- or 6-membered heteroaromatic ring as defined hereinafter, or $\text{-N-(SO}_2\text{R)}_2$, wherein R is lower alkyl, trifluoromethyl, or a 5- or 6-membered heteroaromatic ring as defined hereinafter.

The term "5- or 6-membered heteroaromatic ring" comprises but is not limited to: 2-, 3-, or 4-pyridinyl, 2-, 4-, or 5-pyrimidinyl, 2-pyrazinyl, 2- or 3-furanyl, 2- or 3-thienyl, 2-, 4-, or 5-imidazolyl, 2-, 4-, or 5-thiazolyl, unsubstituted or

-6-

substituted by halogen, lower alkyl, hydroxy, lower
acyloxy, lower alkoxy, amino, lower alkyl amino,

5 O
 ||
nitro, -NH-C-R, wherein R is aryl, lower alkyl,
trifluoromethyl or a 5- or 6-membered heteroaromatic
ring as defined herein for "5- or 6-membered
heteroaromatic ring", -NH-SO₂R, wherein R is lower
alkyl, trifluoromethyl, or a 5- or 6-membered
10 heteroaromatic ring as defined herein for "5- or
6-membered heteroaromatic ring", or -N-(SO₂R)₂,
wherein R is lower alkyl, trifluoromethyl, or a 5- or
6-membered heteroaromatic ring as defined herein for
"5- or 6-membered heteroaromatic ring".

15 The term "8-, 9-, or 10-membered heteroaromatic
bicyclic ring" comprises but is not limited to: 2-,
3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or
7-benzo[b]thienyl, 2-, 3-, 4-, 5-, 6-, 7-, or
8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or
20 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or
7-(1,8)naphthyridinyl, unsubstituted or substituted by
halogen, lower alkyl, hydroxy, lower acyloxy, lower
alkoxy, amino, lower alkyl amino, nitro,

25 O
 ||
-NH-C-R, wherein R is aryl, lower alkyl,
trifluoromethyl or a 5- or 6-membered heteroaromatic
ring as defined herein for "5- or 6-membered
heteroaromatic ring", -NH-SO₂R, wherein R is lower
alkyl, trifluoromethyl, or a 5- or 6-membered
30 heteroaromatic ring as defined herein for "5- or
6-membered heteroaromatic ring", or -N-(SO₂R)₂,
wherein R is lower alkyl, trifluoromethyl, or a 5- or
6-membered heteroaromatic ring as defined herein for
35 "5- or 6-membered heteroaromatic ring".

-7-

"Lower alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl of from one to six carbon atoms as defined above for "lower alkyl."

5

O
||

"Lower acyloxy" is -O-C-alkyl of from one to six carbon atoms as defined above for "lower alkyl".

"Halogen" is fluorine, chlorine, bromine, or iodine.

10

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

"Alkaline-earth metal" is a metal in Group IIA of the periodic table and includes, for example, calcium, barium, strontium, magnesium, and the like.

15

"Noble metal" is platinum, palladium, rhodium, ruthenium, and the like.

The dotted line in compounds of Formulas I, VI, and X means a single or double bond.

20

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted

25

alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate,

30

35

dinitrobenzoate, phenylacetate, citrate, lactate,

-8-

maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

A preferred compound of Formula I above is one in which Z is $\text{C}=\text{Ar}^2$.

Another preferred compound of Formula I above is

one in which Z is $\text{C}(\text{OH})(\text{Ar}^2)$.

A more preferred compound of Formula I is one in which Z is $\text{C}=\text{Ar}^2$ and

Ar^1 and Ar^2 are each independently

aryl,

aryl substituted by one to four substituents

selected from the group consisting of

-9-

- lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
5 lower acyloxy,
amino,
lower alkyl amino
nitro, or
- 10 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is
aryl,
lower alkyl,
trifluoromethyl,
15 2-, 3-, or 4-pyridinyl,
2-, 4-, or 5-pyrimidinyl,
2-pyrazinyl,
2- or 3-furanyl,
2- or 3-thienyl,
20 2-, 4-, or 5-imidazolyl, or
2-, 4-, or 5-thiazolyl,
2-, 3-, or 4-pyridinyl,
2-, 3-, or 4-pyridinyl substituted by
halogen,
25 lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
30 lower alkyl amino,
nitro,
- $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
35 above,
 $\text{-NH-SO}_2\text{R,}$ wherein R is as defined

-10-

above, or

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-pyrimidinyl,

5 2-, 4-, or 5-pyrimidinyl substituted by
halogen,

lower alkyl,

lower alkoxy,

hydroxy,

10 lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

20

-N-(SO₂R)₂, wherein R is as
defined above,

2-pyrazinyl,

2-pyrazinyl substituted by

halogen,

25

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

30

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined

-11-

above, or

-N-(SO₂R)₂, wherein R is as
defined above,

2- or 3-furanyl,

2- or 3-furanyl substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂ wherein R is as defined
above,

2- or 3-thienyl,

2- or 3-thienyl substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R wherein R is as defined

-12-

above, or

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-imidazolyl,

5 2-, 4-, or 5-imidazolyl substituted by
halogen,

lower alkyl,

lower alkoxy,

hydroxy,

10 lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

20

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-thiazolyl,

2-, 4-, or 5-thiazolyl substituted by

halogen,

25

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

30

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R wherein R is as defined

-13-

above, or

-N-(SO₂R)₂ wherein R is as defined
above,

2-, 3-, 4-, 5-, 6-, or 7-indolyl,

5 2-, 3-, 4-, 5-, 6-, or 7-indolyl substituted
by

halogen,

lower alkyl,

lower alkoxy,

10 hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

20

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl,

2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl

25

substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

30

lower acyloxy,

amino,

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined

-14-

above,

-NH-SO₂R, wherein R is as defined

above, or

-N-(SO₂R)₂, wherein R is as

5

defined above,

2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl,

2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl

substituted by

halogen,

10

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

15

lower alkyl amino,

nitro,

O

|

-NH-C-R, wherein R is as defined

20

above,

-NH-SO₂R, wherein R is as defined

above, or

-N-(SO₂R)₂, wherein R is as

defined above,

25

1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl,

1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl

substituted by

halogen,

lower alkyl,

30

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

35

nitro,

-15-

O
||
-NH-C-R, wherein R is as defined
above,

5 -NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

10 2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1, or

2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1 substituted by

15 halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
20 nitro,

O
||
-NH-C-R, wherein R is as defined
above,

25 -NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂ wherein R is as defined
above.

Another more preferred compound of Formula I is

30

one in which Z is $\begin{array}{c} \diagup \quad \text{OH} \\ \text{C} \\ \diagdown \quad \text{Ar}^2 \end{array}$ and

Ar¹ and Ar² are each independently
aryl,

35

aryl substituted by one to four substituents
selected from the group consisting of

-16-

- lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
5 lower acyloxy,
amino,
lower alkyl amino,
nitro, or
- 10 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ wherein R is
aryl,
lower alkyl,
trifluoromethyl,
15 2-, 3-, or 4-pyridinyl,
2-, 4-, or 5-pyrimidinyl,
2-pyrazinyl,
2- or 3-furanyl,
2- or 3-thienyl,
20 2-, 4-, or 5-imidazolyl, or
2-, 4-, or 5-thiazolyl,
2-, 3-, or 4-pyridinyl,
2-, 3-, or 4-pyridinyl substituted by
halogen,
25 lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
30 lower alkyl amino,
nitro,
- 35 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,

-17-

-NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5 2-, 4-, or 5-pyrimidinyl,

2-, 4-, or 5-pyrimidinyl substituted by

halogen,

lower alkyl,

lower alkoxy,

10 hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

20

-N-(SO₂R)₂, wherein R is as
defined above,

2-pyrazinyl,

2-pyrazinyl substituted by

25

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

30

amino,

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-18-

-NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5

2- or 3-furanyl,

2- or 3-furanyl substituted by

halogen,

lower alkyl,

lower alkoxy,

10

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

20

-N-(SO₂R)₂ wherein R is as defined
above,

2- or 3-thienyl,

2- or 3-thienyl substituted by

25

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

30

amino,

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R} \end{array}$$
 wherein R is as defined
above,

-19-

-NH-SO₂R wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5

2-, 4-, or 5-imidazolyl,
2-, 4-, or 5-imidazolyl substituted by
halogen,

10

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

15

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

20

-NH-SO₂R, wherein R is as defined
above, or
-N-(SO₂R)₂, wherein R is as
defined above,

25

2-, 4-, or 5-thiazolyl,
2-, 4-, or 5-thiazolyl substituted by
halogen,

30

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

35

$$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-20-

-NH-SO₂R wherein R is as defined
above, or

-N-(SO₂R)₂ wherein R is as defined
above,

5 2-, 3-, 4-, 5-, 6-, or 7-indolyl,
2-, 3-, 4-, 5-, 6-, or 7-indolyl substituted
by

halogen,

lower alkyl,

10 lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

15 nitro,

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

20 -NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

25 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl,
2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl
substituted by

halogen,

lower alkyl,

lower alkoxy,

30 hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

-21-

O
||
-NH-C-R, wherein R is as defined
above,

5 -NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl,

10 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl
substituted by

halogen,

lower alkyl,

lower alkoxy,

15 hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

20 O
 ||
 -NH-C-R, wherein R is as defined
above,

25 -NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl,

30 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl
substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

35 lower acyloxy,

amino,

-22-

lower alkyl amino,
nitro,

5 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

10 -N-(SO₂R)₂, wherein R is as
defined above,

2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1, or

2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1 substituted by

15 halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

20 amino,

lower alkyl amino,

nitro,

25 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,

-NH-SO₂R, wherein R is as defined
above, or

30 -N-(SO₂R)₂ wherein R is as defined
above.

A most preferred compound of Formula I is one in
which Z is $\begin{array}{c} \diagup \\ \text{C-Ar}^2 \end{array}$; n is 2 or 3; and
Ar¹ and Ar² are each independently

aryl,

35 aryl substituted by one to four substituents
selected from the group consisting of

-23-

- lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
5 lower acyloxy,
amino,
lower alkyl amino,
nitro, or
- 10 $\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$ wherein R is
aryl,
lower alkyl,
trifluoromethyl,
15 2-, 3-, or 4-pyridinyl,
2-, 4-, or 5-pyrimidinyl,
2-pyrazinyl,
2- or 3-furanyl,
2- or 3-thienyl,
20 2-, 4-, or 5-imidazolyl, or
2-, 4-, or 5-thiazolyl,
2-, 3-, or 4-pyridinyl,
2-, 3-, or 4-pyridinyl substituted by
halogen,
25 lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
30 lower alkyl amino,
nitro,
- $\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
35 above,

-24-

-NH-SO₂-R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5 2-, 4-, or 5-pyrimidinyl,
2-, 4-, or 5-pyrimidinyl substituted by
halogen,

lower alkyl,
lower alkoxy,
10 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

15 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
-NH-C-R, wherein R is as defined
above,

-NH-SO₂-R, wherein R is as defined
20 above, or

-N-(SO₂R)₂, wherein R is as
defined above,

2- or 3-thienyl,

2- or 3-thienyl substituted by

25 halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
30 amino,
lower alkyl amino,
nitro,

$\begin{array}{c} \text{O} \\ \parallel \end{array}$
35 -NH-C-R, where R is as defined
above,

-25-

-NH-SO₂-R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5

4- or 5-thiazolyl,

4- or 5-thiazolyl substituted by

halogen,

lower alkyl,

lower alkoxy,

10

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

15

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-NH-SO₂-R, wherein R is as defined
above, or

20

-N-(SO₂R)₂, wherein R is as
defined above,

2- or 3-indolyl,

2- or 3-indolyl substituted by

25

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

30

amino,

lower alkyl amino,

nitro,

35

$$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

-26-

-NH-SO₂-R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

5 2-, 3-, or 4-quinolinyl,
2-, 3-, or 4-quinolinyl substituted by
halogen,

lower alkyl,
lower alkoxy,
10 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

15 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,

-NH-SO₂-R, wherein R is as defined
20 above, or

-N-(SO₂R)₂, wherein R is as
defined above

1-, 3-, or 4-isoquinolinyl, or

25 1-, 3-, or 4-isoquinolinyl substituted by
halogen,

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,

30 amino,
lower alkyl amino,
nitro,

35 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,

-27-

-NH-SO₂-R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above.

5 Another most preferred compound of Formula I is

one in which Z is $\begin{array}{c} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{Ar}^2 \end{array}$; n is 2 or 3; and

Ar¹ and Ar² are each independently

10

aryl,

aryl substituted by one to four substituents

selected from the group consisting of

lower alkyl,

lower alkoxy,

15

lower thioalkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

20

nitro, or



-NH-C-R, wherein R is

aryl,

25

lower alkyl,

trifluoromethyl,

2-, 3-, or 4-pyridinyl,

2-, 4-, or 5-pyrimidinyl,

2-pyrazinyl,

30

2- or 3-furanyl,

2- or 3-thienyl,

2-, 4-, or 5-imidazolyl, or

2-, 4-, or 5-thiazolyl,

2-, 3-, or 4-pyridinyl,

35

2-, 3-, or 4-pyridinyl substituted by

halogen,

-28-

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
5 amino,
lower alkyl amino,
nitro,

10 $\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined
above,
-NH-SO₂-R, wherein R is as defined
above, or
15 -N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-pyrimidinyl,
2-, 4-, or 5-pyrimidinyl substituted by
halogen,

20 lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
25 nitro,

$\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined
above,
30 -NH-SO₂-R, wherein R is as defined
above, or
-N-(SO₂R)₂, wherein R is as
defined above,

2- or 3-thienyl,
35 2- or 3-thienyl substituted by
halogen,

-29-

- lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
5 amino,
lower alkyl amino,
nitro,
- 10 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R, where R is as defined} \\ \text{above,} \end{array}$
 $\text{-NH-SO}_2\text{-R, wherein R is as defined}$
above, or
 $\text{-N-(SO}_2\text{R)}_2\text{, wherein R is as}$
15 defined above,
- 4- or 5-thiazolyl,
4- or 5-thiazolyl substituted by
halogen,
lower alkyl,
20 lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
25 nitro,
- $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R, wherein R is as defined} \\ \text{above,} \end{array}$
30 $\text{-NH-SO}_2\text{-R, wherein R is as defined}$
above, or
 $\text{-N-(SO}_2\text{R)}_2\text{, wherein R is as}$
defined above,
- 2- or 3-indolyl,
35 2- or 3-indolyl substituted by
halogen,

-30-

- lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
5 amino,
lower alkyl amino,
nitro,
10 $\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,
 $\text{-NH-SO}_2\text{-R,}$ wherein R is as defined
above, or
15 $\text{-N-(SO}_2\text{R)}_2\text{,}$ wherein R is as
defined above,
2-, 3-, or 4-quinolinyl,
2-, 3-, or 4-quinolinyl substituted by
halogen,
lower alkyl,
20 lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
25 nitro,
 $\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,
30 $\text{-NH-SO}_2\text{-R,}$ wherein R is as defined
above, or
 $\text{-N-(SO}_2\text{R)}_2\text{,}$ wherein R is as
defined above
1-, 3-, or 4-isoquinolinyl, or
35 1-, 3-, or 4-isoquinolinyl substituted by
halogen,

-31-

lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
5 amino,
lower alkyl amino,
nitro,

10 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
-NH-C-R, wherein R is as defined
above,
-NH-SO₂-R, wherein R is as defined
above, or
15 -N-(SO₂R)₂, wherein R is as
defined above.

Particularly preferred compounds are:

3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-
butynyl]quinoline;

20 4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-
butynyl]isoquinoline;

3-[4-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-
1-butynyl]pyridine;

3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-
butynyl]pyridine;

25 3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-
pentynyl]quinoline;

3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-
pentynyl]pyridine;

30 3-[5-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-
1-pentynyl]pyridine;

1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-
butynyl]-4-phenylpyridine;

1,2,3,6-Tetrahydro-1-[4-(4-nitrophenyl)-3-
butynyl]-4-phenylpyridine;

35 1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-
butynyl]-4-phenylpyridine;

-32-

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]pyridine;

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine;

5 4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]benzenamine;

5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinamine;

10 N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]acetamide;

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]-2-thiophenecarboxamide;

N-[4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]phenyl]acetamide;

15 N-[5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinyl]acetamide;

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-3-pyridinamine;

20 4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methylbenzenamine;

5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-2-pyridinamine;

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-propyl-3-pyridinamine;

25 N-(Methylsulfonyl)-N-[6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide;

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide;

30 3-[5-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-pentynyl]quinoline;

5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-thiazolamine;

35 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-1H-indole; and

-33-

4-[4-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-
1-butynyl]pyridine;

or a pharmaceutically acceptable acid addition
salt thereof.

5 The compounds of Formula I are valuable
dopaminergic agents. The tests employed indicate that
compounds of Formula I possess dopaminergic activity.
Thus, the compounds of Formula I were tested for their
ability to inhibit locomotor activity in mice
10 according to the assay described by J. R. McLean, et
al, Pharmacology, Biochemistry and Behavior, Volume 8,
pages 97-99 (1978); for their ability to inhibit
[³H]-spiroperidol binding in a receptor assay
described by D. Grigoriadis and P. Seeman, Journal of
15 Neurochemistry, Volume 44, pages 1925-1935 (1985); and
for their ability to inhibit dopamine synthesis in
rats according to the protocol described by
J. R. Walters and R. H. Roth, Naunyn-Schmiedeberg's
Archives of Pharmacology, Volume 296, pages 5-14
20 (1976). The data in the table show the dopaminergic
activity of representative compounds of Formula I.
dopaminergic activity of representative compounds of
Formula I.

25

Biological Activity of Compounds of Formula I
(Page 1 of 5)

Example Number	Compound	% Reversal of			Inhibition of [³ H]Spiroperidol Binding IC ₅₀ , nM
		Inhibition of Locomotor Activity in Mice	Brain Dopamine Synthesis in Rats at 10 mg/kg, IP	ED ₅₀ , mg/kg, IP	
5	1 3-[4-(3, 6-Dihydro-4-phenyl-1-(2H)pyridinyl)-1-butynyl]quinoline	1.1	28	41	
	2 4-[4-(3, 6-Dihydro-4-phenyl-1-(2H)pyridinyl)-1-butynyl]isoquinoline	2.1	32	101	
	3 3-[4-[3, 6-Dihydro-4-(2-thienyl)-1-(2H)-pyridinyl]-1-butynyl]pyridine	0.54	53	354	
	4 3-[4-(3, 6-Dihydro-4-phenyl-1-(2H)pyridinyl)-1-butynyl]pyridine	0.07	79	50	
	6 3-[5-[3, 6-Dihydro-4-phenyl-1-(2H)-pyridinyl)-1-pentynyl]quinoline	3.6		54.5	
	7 3-[5-[3, 6-Dihydro-4-phenyl-1-(2H)-pyridinyl)-1-pentynyl]pyridine	0.72	48	77.2	
10					

Biological Activity of Compounds of Formula I
(Page 2 of 5)

5	Example Number	Compound	Inhibition of Locomotor Activity in Mice		% Reversal of Brain Dopamine Synthesis in Rats at 10 mg/kg, IP	Inhibition of [³ H]Spiroperidol Binding IC ₅₀ , nM
			ED ₅₀ , mg/kg, IP	2.7		
	8	3-[5-[3, 6-Dihydro-4-(2-thienyl)-1 (2H)-pyridinyl]-1-pentynyl]pyridine		2.7		209
	9	1, 2, 3, 6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine		6.9		229
	10	1, 2, 3, 6-Tetrahydro-1-[4-(4-nitrophenyl)-3-butynyl]-4-phenylpyridine		2.6	42	394
	12	4-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]pyridine		0.10	79	43.4
	13	6-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl-3-pyridinamine		0.15	59	85
10	14	4-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]benzenamine		0.36	51	431

Biological Activity of Compounds of Formula I
(Page 3 of 5)

Example Number	Compound	Inhibition of Locomotor Activity in Mice	% Reversal of Brain Dopamine Synthesis in Rats at 10 mg/kg, IP	Inhibition of [³ H]Spiroperidol Binding IC ₅₀ , nM
		ED ₅₀ , mg/kg, IP		
5	15 5-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-2-pyridinamine	0.07	65	25
	16 N-[6-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-3-pyridinyl]-acetamide	0.07	5	70
	17 N-[6-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-3-pyridinyl]-2-thiophenecarboxamide	1.50	0	1090
	18 N-[4-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]phenyl]acetamide	0.23		50
	19 N-[5-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-2-pyridinyl]-acetamide	0.16		
10				

Biological Activity of Compounds of Formula I
(Page 4 of 5)

Example Number	Compound	Inhibition & Reversal of		Inhibition of [³ H]Spiroperidol Binding IC ₅₀ , nM
		Inhibition of Locomotor Activity in Mice ED ₅₀ , mg/kg, IP	Brain Dopamine Synthesis in Rats at 10 mg/kg, IP	
20	6-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-N-methyl-3-pyridinamine	0.22	0	138
21	4-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-N-methylbenzen-amine	0.56	45	129
22	5-[4-(3, 6-dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-N-methyl-2-pyridinamine	6.1	42	77
23	6-[4-(3, 6-Dihydro-4-phenyl-1 (2H)-pyridinyl)-1-butynyl]-N-propyl-3-pyridinamine	0.31		248

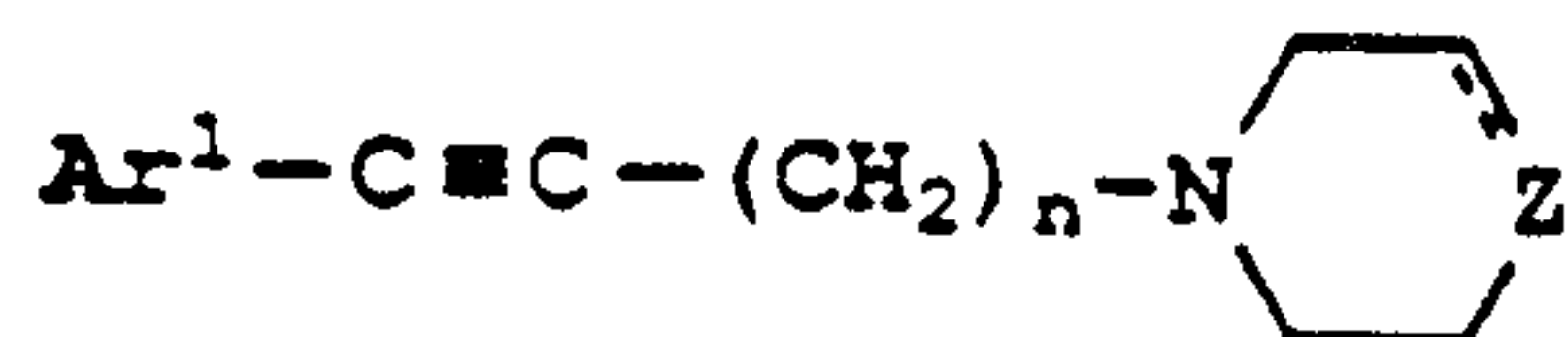
Biological Activity of Compounds of Formula I
(Page 5 of 5)

Example Number	Compound	Inhibition of Locomotor Activity in Mice		% Reversal of Brain Dopamine Synthesis in Rats at		Inhibition of [³ H]Spiroperidol Binding IC ₅₀ , nM
		ED ₅₀ , mg/kg,	IP	10 mg/kg,	IP	
24	N-(Methylsulfonyl)-N-[6- [4-(3,6-dihydro-4-phenyl- 1(2H)-pyridinyl)-1- butynyl]-3-pyridinyl]- methanesulfonamide	0.53		0		94
25	N-[6-[4-(3,6-Dihydro-4- phenyl-1(2H)-pyridinyl)-1- butynyl]-3-pyridinyl]- methanesulfonamide	1.1				64

-39-

Also, the present invention provides a process for the preparation of a compound of Formula I:

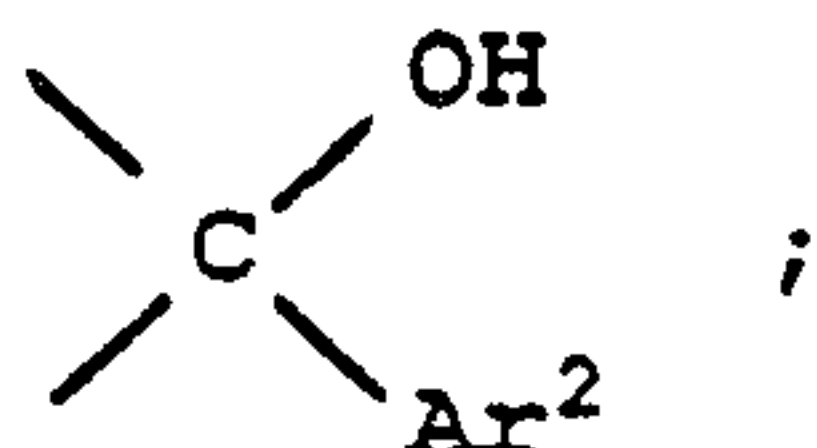
5



I

wherein n is an integer of 2, 3, or 4; Z is $\begin{array}{c} \diagup \\ \diagdown \end{array} \text{C}-\text{Ar}^2$ or

10



Ar^1 and Ar^2 are each independently

aryl,

aryl substituted by one to four substituents

15

selected from the group consisting of

lower alkyl,

lower alkoxy,

lower thioalkoxy,

hydroxy,

20

lower acyloxy,

amino,

lower alkyl amino,

nitro,

25

$\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R} \end{array}$, wherein R is

aryl,

lower alkyl,

trifluoromethyl or a 5- or 6-membered

30

heteroaromatic ring comprising one

or more heteroatoms selected from N,

S, and O,

$-\text{NH}-\text{SO}_2\text{R}$, wherein R is as defined above or

$-\text{N}-(\text{SO}_2\text{R})_2$, wherein R is as defined above,

-40-

- a 5- or 6-membered heteroaromatic ring comprising one or more heteroatoms selected from N, S, and O,
- 5 a 5- or 6-membered heteroaromatic ring comprising one or more heteroatoms selected from N, S, and O, substituted by
- halogen,
- lower alkyl,
- lower alkoxy,
- 10 hydroxy,
- lower acyloxy,
- amino,
- lower alkyl amino,
- nitro,
- 15 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
- NH-C-R, wherein R is as defined above,
- NH-SO₂R, wherein R is as defined above, or
- N-(SO₂R)₂, wherein R is as defined above,
- 20 a 8-, 9-, or 10-membered heteroaromatic bicyclic ring comprising one or more heteroatoms selected from N, S, and O, or
- a 8-, 9-, or 10-membered heteroaromatic bicyclic ring comprising one or more heteroatoms
- 25 selected from N, S, and O, substituted by
- halogen,
- lower alkyl,
- lower alkoxy,
- hydroxy,
- 30 lower acyloxy,
- amino
- lower alkyl amino,
- nitro,
- 35 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
- NH-C-R, wherein R is as defined above,

-41-

-NH-SO₂R, wherein R is as defined above, or
-N-(SO₂R)₂, wherein R is as defined above;
or a pharmaceutically acceptable acid addition salt
thereof, which comprises

5 a) reacting a compound of Formula II

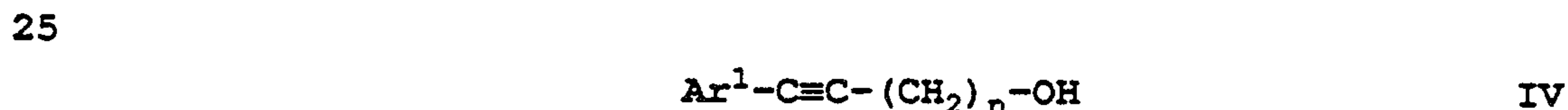


10 wherein X is Cl, Br, or I, and Ar¹ is as defined above
with a compound of Formula III



15 wherein n is an integer of 2, 3, or 4 in a solvent, such
as, for example, dichloromethane and the like, in the
presence of an acid scavenger, such as, for example,
triethylamine and the like, and in the presence of a
catalytically effective amount of

20 bis(triarylphosphine)palladium(II)chloride
([(Ar³)₃P]₂PdCl₂), bis(triarylphosphine)palladium(II)
acetate ([(Ar³)₃P]₂ Pd(O₂CCH₃)₂), or triarylphosphine-
palladium(II)acetate ((Ar³)₃P/Pd(O₂CCH₃)₂), wherein Ar³ is
phenyl or phenyl substituted by lower alkyl, and cuprous
iodide (CuI) to afford a compound of Formula IV



30 wherein Ar¹ and n are as defined above. Preferably, the
reaction is carried out with dichloromethane in the
presence of triethylamine and bis(triphenylphosphine)-
palladium(II)chloride and cuprous iodide;

b) reacting an alcohol of Formula IV with an
alkyl- or aryl-sulfonyl halide such as, for example,
methanesulfonyl chloride and the like in a solvent such
35 as, for example, dichloromethane and the like, in the

-42-

presence of an acid scavenger such as, for example, triethylamine, diisopropylethylamine and the like to afford a compound of Formula Va:



wherein L_a is alkyl- or aryl-sulfonyloxy and Ar^1 and n are as defined above. Preferably, the reaction is carried out with methanesulfonyl chloride in
 10 dichloromethane in the presence of triethylamine; or alternatively reacting an alcohol of Formula IV with a triarylphosphine such as, for example, triphenylphosphine and the like, combined with a tetrahalomethane such as, for example, tetrabromomethane
 15 and the like to afford a compound of Formula Vb



wherein L_b is a halogen atom and Ar^1 and n are as
 20 defined above. Preferably, the reaction is carried out with triphenylphosphine and tetrabromomethane;
 c) reacting a compound of Formula Va or Vb with a compound of Formula VI



wherein Z is as defined above, in a solvent such as, for
 30 example, dimethylformamide and the like, in the presence of a base such as, for example, sodium bicarbonate and the like, to afford a compound of Formula I above. Preferably, the reaction is carried out in dimethylformamide in the presence of sodium bicarbonate.
 35 The present invention provides another process for

-43-

the preparation of a compound of Formula I above, which comprises:

a) reacting a compound of Formula II



wherein X is Cl, Br or I and Ar^1 is as defined above with the compound of Formula VII



in a solvent such as, for example, dichloromethane and the like, in the presence of an acid scavenger such as, for example, triethylamine and the like, in the presence of a catalytically effective amount of
15 bis(triarylphosphine)palladium(II)chloride
($[(\text{Ar}^3)_3\text{P}]_2\text{PdCl}_2$), bis(triarylphosphine)palladium(II)acetate($[(\text{Ar}^3)_3\text{P}]_2\text{Pd}(\text{O}_2\text{CCH}_3)_2$), or triarylphosphine-palladium(II)acetate($(\text{Ar}^3)_3\text{P}/\text{Pd}(\text{O}_2\text{CCH}_3)_2$), wherein Ar^3 is
20 phenyl or phenyl substituted by lower alkyl and cuprous iodide (CuI) to afford a compound of Formula VIII



25 wherein Ar^1 is as defined above. Preferably, the reaction is carried out in a solvent such as, for example, dichloromethane and the like in the presence of triethylamine and bis(triphenylphosphine)-palladium(II)chloride and cuprous iodide;

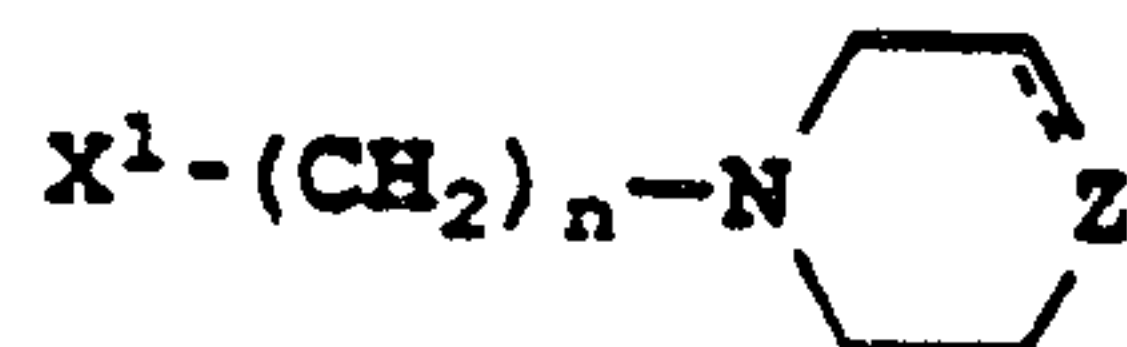
30 b) removing the trimethylsilyl group using a base such as, for example, potassium hydroxide and the like, and an alcohol such as, for example, ethanol and the like, to afford a compound of Formula IX



-44-

wherein Ar^1 is as defined above. Preferably, the reaction is carried out in ethanol in the presence of potassium hydroxide;

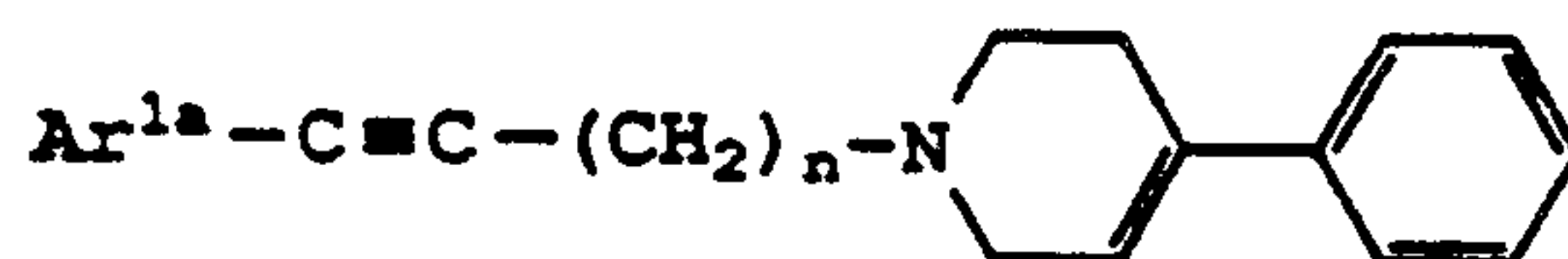
c) reacting a compound of Formula IX with an organolithium compound such as, for example, *n*-butyllithium and the like, at a temperature of about 0°C, and with a compound of Formula X



X

wherein X^1 is Cl, Br, or I and *n* and Z are as defined above in a solvent such as, for example, a mixture of tetrahydrofuran:hexamethylphosphoric triamide and the like to afford a compound of Formula I. Preferably, the reaction is carried out with *n*-butyllithium in a mixture of tetrahydrofuran hexamethylphosphoric triamide.

Preferably, a compound of Formula Ia.



Ia

wherein *n* is an integer of 2, 3, or 4 and Ar^{1a} is aryl substituted by nitro, or

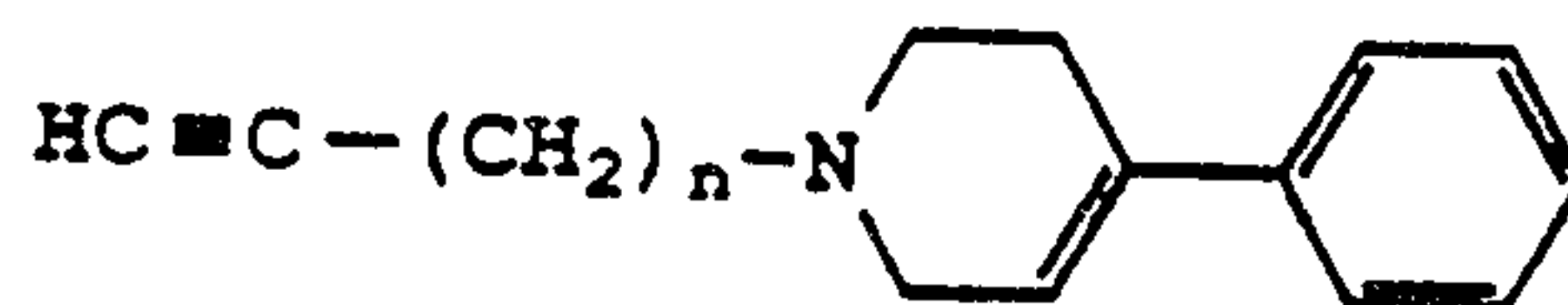
2-, 3-, or 4-pyridinyl substituted by nitro or a pharmaceutically acceptable acid addition salt thereof, comprises reacting a compound of Formula IIa



IIa

-45-

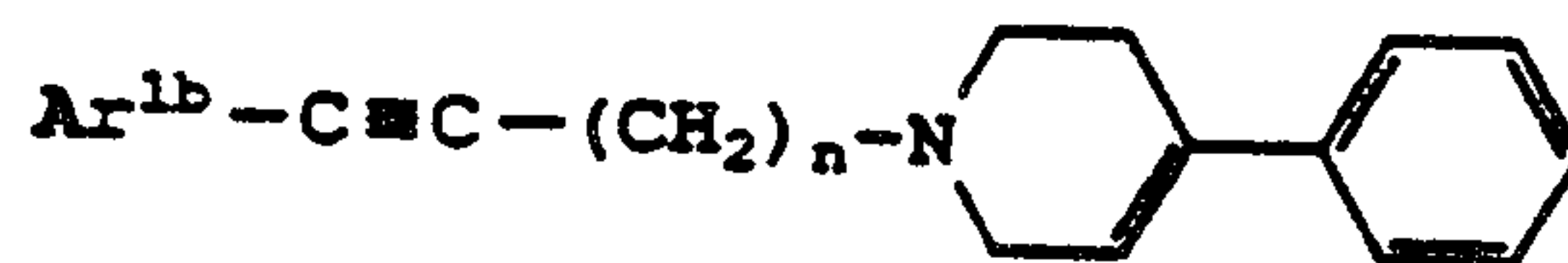
wherein Ar^{1a} and X are as defined above with a compound of Formula XII



XII

10 wherein n is as defined above using the methodology used to prepare a compound of Formula IV from a compound of Formula II and a compound of Formula III to afford a compound of Formula Ia.

15 Preferably, a compound of Formula Ib



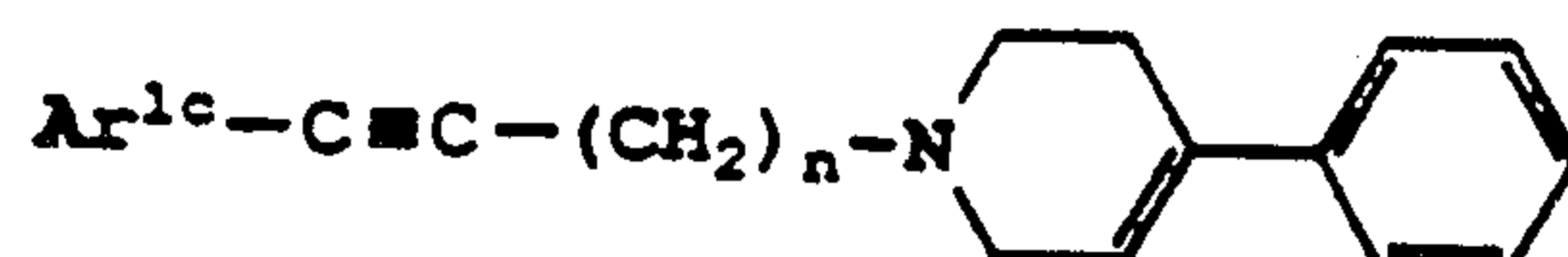
Ib

25 wherein n is an integer of 2, 3, or 4 and Ar^{1b} is aryl substituted by amino, or 2-, 3-, or 4-pyridinyl substituted by amino or a pharmaceutically acceptable acid addition salt thereof, comprises reacting a compound of Formula Ia with hydrogen in the presence of a catalyst such as, for
30 example, platinum, palladium, rhodium, ruthenium, and the like, iron in the presence of an acid such as, for example, hydrochloric acid and the like in a solvent such as, for example, ethanol and the like at about 0°C to about the reflux temperature of the solvent to afford
35 a compound of Formula Ib. Preferably, the reaction is

-46-

carried out with iron and hydrochloric acid in ethanol at about 80°C.

Preferably, a compound of Formula Ic



Ic

wherein n is an integer of 2, 3, or 4 and Ar^{1c} is aryl substituted by



aryl,

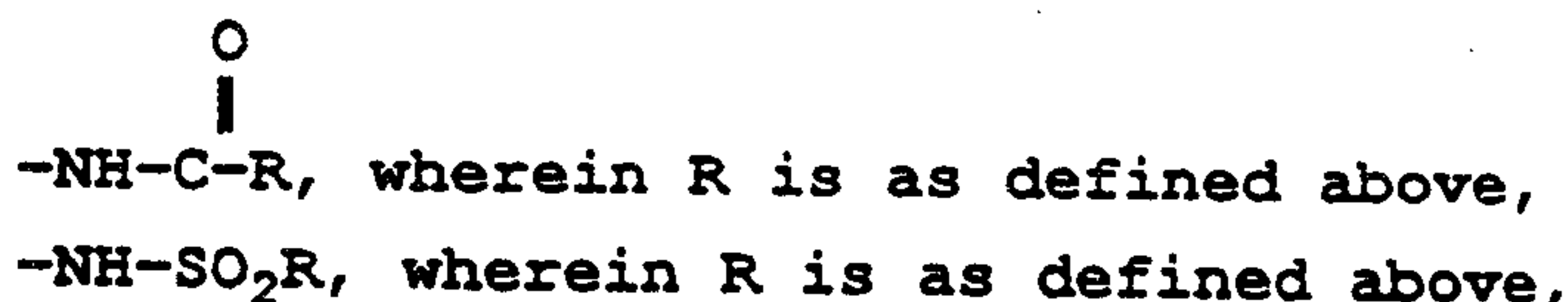
lower alkyl,

trifluoromethyl, or

a 5- or 6-membered heteroaromatic ring comprising one or more heteroatoms selected from N, S, and O,

-NH-SO₂R, wherein R is as defined above, or

-N-(SO₂R)₂, wherein R is as defined above, or
2-, 3-, or 4-pyridinyl substituted by



or

-N-(SO₂R)₂, wherein R is as defined above, or

a pharmaceutically acceptable acid addition salt thereof, comprises reacting a compound of Formula Ib with a compound of Formula XIII

-47-

 R^1-X

XIII

5

wherein R_1 is $R-\overset{\overset{O}{\parallel}}{C}-$ or $(R-SO_2)_2-$ and X is as defined above in the presence of a base such as, for example, triethylamine and the like and optionally a catalytic quantity of N,N-dimethylaminopyridine in a solvent such as, for example, dichloromethane and the like at about 0°C to about the reflux temperature of the solvent to afford a compound of Formula Ic. Preferably, the reaction is carried out in the presence of triethylamine in dichloromethane containing a catalytic amount of N,N-dimethylaminopyridine at about room temperature. In the case wherein the substituent group in Ar^{1c} in a compound of Formula Ic is $R-SO_2NH-$, it is prepared by reacting a compound of Formula Ib with a compound of Formula XIV

20



25

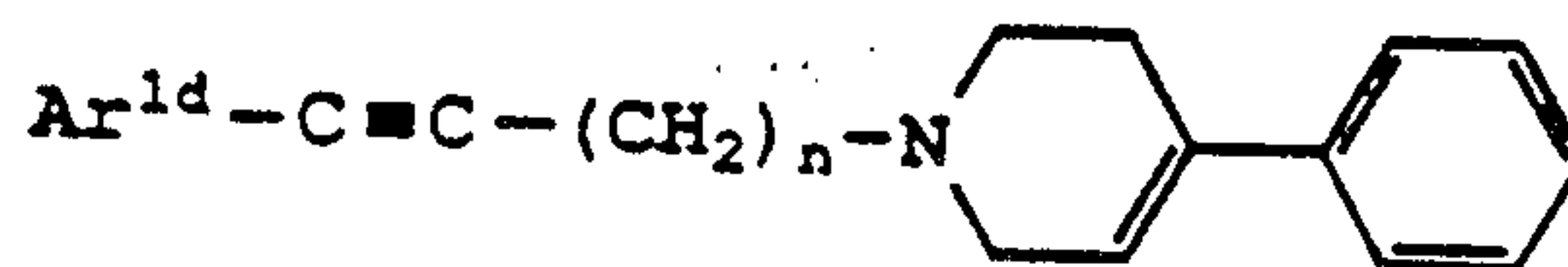
XIV

30

wherein R is as defined above in the presence of a base such as, for example, triethylamine and the like in a solvent such as, for example, dichloromethane and the like at about -78°C to afford a compound of Formula Ic. Preferably, the reaction is carried out in the presence of triethylamine in dichloromethane at about -78°C.

-48-

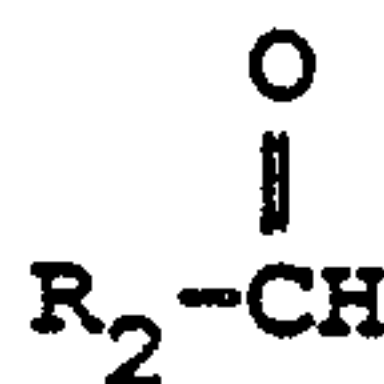
Preferably, a compound of Formula Id



Id

10 wherein n is an integer of 2, 3, or 4 and Ar^{1d} is
aryl substituted by lower alkyl amino or
2-, 3-, or 4-pyridinyl substituted by lower alkyl
amino or

15 a pharmaceutically acceptable acid addition salt
thereof, comprises reacting a compound of Formula Ib
with a compound of Formula XV



XV

25 wherein R² is lower alkyl in the presence of a metal
hydride such as, for example, sodium cyanoborohydride,
sodium triacetoxyborohydride, lithium aluminum hydride
and the like optionally in the presence of an acid such
as, for example, acetic acid and the like in a solvent
such as, for example, dichloroethane, dichloromethane
and the like at about 0°C to about room temperature.

30 Preferably, the reaction is carried out with sodium
triacetoxyborohydride in the presence of acetic acid in
dichloroethane at about room temperature.

35 Alternatively, in the case wherein the substituent group
in Ar^{1d} in a compound of Formula Id is methylamino, it
is prepared by reacting a compound of Formula Ib with a
mixture of acetic anhydride and formic acid in a solvent

-49-

such as, for example, tetrahydrofuran and the like and subsequent reaction with a metal hydride reagent such as, for example, lithium aluminum hydride and the like to afford a compound of Formula Id.

5 A compound of Formula X is prepared from a compound of Formula VI and a compound of Formula XI



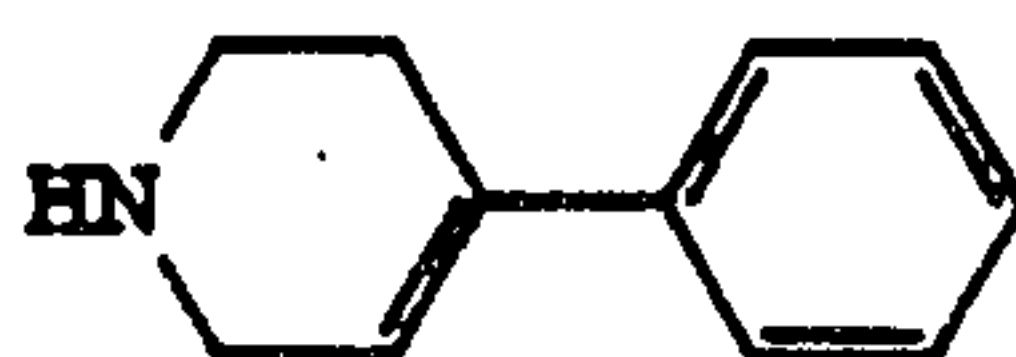
10 wherein X^1 and n are as defined above in the presence of a solvent such as, for example, dichloromethane, and the like, in the presence of an acid scavenger, such as, for example, triethylamine and the like, to afford a compound of Formula X. Preferably, the reaction is
15 carried out in dichloromethane in the presence of triethylamine.

A compound of Formula XII is prepared from a compound of Formula XVI



XVI

wherein L is a halogen atom or an alkyl or
25 arylsulfonyloxy and n is as defined above with the compound of Formula XVII



30

XVII

using the methodology used to prepare a compound of
35 Formula I from a compound of Formula Va or Vb and VI.

-50-

A compound of Formula XVI is prepared from a compound of Formula III using the methodology used to prepare a compound of Formula Va and Vb from a compound of Formula IV.

5 Compounds of Formula II, IIa, III, VI, VII, XI, XIII, XIV, XV, and XVII are either known or capable of being prepared by methods known in the art.

10 The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

15 For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

20 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

25 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

30 The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin,

35

-51-

dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid

-52-

form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferable in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as antipsychotic agents, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 1 mg to about 50 mg per kilogram daily. A daily dose range of about 5 mg to about 25 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small

-53-

increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

5 The following nonlimiting examples illustrate the inventors' preferred compounds of the invention and methods for their preparation.

EXAMPLE 1

10 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-quinoline

Step (a): Preparation of 4-(3-Quinoliny)-3-butyn-1-ol

 A solution of 3-bromoquinoline (13.57 mL, 0.10 mol) and 3-butyn-1-ol (9.0 mL, 0.12 mol) in 40 mL of
15 triethylamine and 75 mL of dichloromethane is degassed by bubbling in dry nitrogen for 15 minutes, and 0.7 g (0.001 mol) of bis(triphenylphosphine)palladium chloride and 0.013 g of cuprous iodide are added. The flask is
20 flushed with nitrogen and the mixture is heated to reflux for 5 hours. The cooled mixture is diluted with dichloromethane and washed with water, dried (sodium sulfate), and concentrated to give 27 g of an oil. The oil is triturated with diethyl ether to give 18.2 g of the title compound as a tan solid; mp 95.7-96.7°C.

25

Step (b): Preparation of 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline

 A solution of the alcohol prepared in Step (a) (1.98 g, 0.01 mol), N,N-diisopropylethylamine (3.5 mL, 0.02 mol) and a catalytic amount of 4-dimethylamino-
30 pyridine is cooled to 0°C, and methanesulfonyl chloride (0.8 mL, 0.0105 mol) is added dropwise. The solution is stirred at 0°C for 18 hours, and then concentrated under reduced pressure. The residue is taken up in
35 dimethylformamide (20 mL), and to this solution is added

-54-

4-phenyl-1,2,3,6-tetrahydropyridine (2.41 g, 0.015 mol) and sodium bicarbonate (3.4 g, 0.04 mol). The mixture is heated at 40°C for 5 hours, and the solvent is removed under reduced pressure. The residue is partitioned between 50 mL of ethyl acetate and 50 mL of water. The aqueous layer is extracted with 50 mL of ethyl acetate and the combined organic layers are dried (sodium sulfate), and the solvent is removed in vacuo. The residue is chromatographed (silica gel, 2% methanol/98% dichloromethane) to give the title compound, containing 0.4 mol of water; mp 94.3-95.8°C.

Following the procedure of Example 1, the following compounds are prepared:

EXAMPLE 2

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butyryl]-isoquinoline, containing 0.4 mol of water; mp 58-59°C.

EXAMPLE 3

3-[4-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl)-1-butyryl]pyridine, containing 0.4 mol of water; mp 77-78°C.

EXAMPLE 4

3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butyryl]pyridine, containing 0.6 mol of water; mp 72-73°C.

EXAMPLE 5

3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butyryl]pyridine, monohydrochloride, containing 0.35 mol of water; mp 167-168°C.

The monohydrochloride salt of the compound of Example 4 described in Example 5 is prepared by

-55-

conventional means starting from the compound of Example 4.

EXAMPLE 6

5 3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-pentynyl]-
 quinoline, 1.6 mol hydrochloride, containing 0.5 mol of
 water; mp 191-192°C.

EXAMPLE 7

10 3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-pentynyl]-
 pyridine, containing 0.25 mol of water; mp 63.0-63.5°C.

EXAMPLE 8

15 3-[5-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-
 pentynyl]pyridine, monohydrochloride, mp 190.0-190.5°C.

EXAMPLE 9

1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-
 butynyl]-4-phenylpyridine

20 Step (a): Preparation of 4-(3,6-Dihydro-4-phenyl-1(2H)-
 piperidinyl)-1-butyne

 A solution of 3-butyne tosylate (25.0 g,
 0.11 mol), 4-phenyl-1,2,3,6-tetrahydropyridine (21.8 g,
 0.11 mol) and sodium bicarbonate (10.3 g, 0.12 mol) in
25 300 mL of dimethylformamide is heated at 80°C for
 18 hours. The solvent is removed under reduced
 pressure, and the residue is partitioned between 200 mL
 of dichloromethane and 200 mL of water. The aqueous
 layer is extracted with 100 mL of dichloromethane and
30 the combined organic layers are dried (sodium sulfate),
 and the solvent is removed in vacuo. The residue is
 chromatographed (silica gel, 25% ethyl acetate/75%
 hexane) to give the title compound as a yellow solid;
 mp 36.5-37.5°C.

35

-56-

Step (b): Preparation of 1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine

5 A solution of 2-bromo-5-nitropyridine (4.23 g, 0.02 mol) and the alkyne prepared in Step (a) (4.0 g, 0.019 mol) in 7.9 mL of triethylamine and 100 mL of acetonitrile is degassed by bubbling in dry nitrogen for 15 minutes, and 0.27 g (0.0004 mol) of bis(triphenylphosphine)palladium chloride and 0.07 g (0.0004 mol) of cuprous iodide are added. The flask is flushed with
10 nitrogen and the mixture is stirred at room temperature for 6 hours. The solvent is removed under reduced pressure and the residue is partitioned between 100 mL of dichloromethane and 100 mL of saturated aqueous sodium bicarbonate. The aqueous layer is extracted with
15 50 mL of dichloromethane and the combined organic layers are washed with 50 mL of water and dried (sodium sulfate), and the solvent is removed in vacuo. The residue is chromatographed (silica gel, 1% methanol/99% dichloromethane) to give the title compound,
20 containing 0.3 mol of water; mp 133-134°C.

Following the procedure of Example 9, the following compounds are prepared:

25

EXAMPLE 10

1,2,3,6-Tetrahydro-1-[4-(4-nitrophenyl)-3-butynyl]-4-phenylpyridine; mp 148-149°C.

EXAMPLE 11

30

1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine.

-57-

EXAMPLE 12

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]pyridine, containing 0.7 mol of water; mp 112-113°C.

5

EXAMPLE 13

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine

10 A solution of 1,2,3,6-tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine (Example 9) (2.0 g, 0.006 mol), reduced iron (3.1 g), and 0.10 mL of concentrated hydrochloric acid in 30 mL of 95% ethanol and 10 mL of water is heated at 80°C with vigorous stirring for 30 minutes. The hot solution is filtered
15 through diatomaceous earth (Celite*), and the filter cake is washed with 300 mL of hot ethanol. The solvent is removed under reduced pressure, and the residue is partitioned between 50 mL of dichloromethane and 50 mL of saturated aqueous sodium bicarbonate. The aqueous
20 layer is extracted with dichloromethane and the combined organic layers are washed with water and dried (sodium sulfate), and the solvent is removed in vacuo. The residue is chromatographed (silica gel, 2% methanol/98% dichloromethane) to give the title compound,
25 containing 0.3 mol of water; mp 135.5-137°C.

Following the procedure of Example 13, the following compounds are prepared:

30

EXAMPLE 14

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-benzenamine, containing 0.2 mol of water; mp 88-89°C.

* Trade-mark

-58-

EXAMPLE 15

5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinamine; mp 180-181°C.

5

EXAMPLE 16

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]acetamide

A solution of 6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) (1.5 g, 0.005 mol), triethylamine (0.76 mL, 0.0054 mol) and N,N-dimethylaminopyridine (catalytic amount) in 50 mL of dichloromethane is cooled to 0°C and acetyl chloride (0.42 mL, 0.006 mol) is added dropwise. The cold bath is removed and the solution is stirred at room temperature for 1 hour. The reaction is quenched with saturated aqueous sodium bicarbonate, the organic layer is washed with water and dried (sodium sulfate), and the solvent is removed under reduced pressure. The residue is chromatographed (silica gel, 2% methanol/98% dichloromethane) to give the title compound, containing 0.35 mol of water; mp 158.5-159.5°C.

Following the procedure of Example 16, the following compounds are prepared:

25

EXAMPLE 17

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]-2-thiophenecarboxamide

The title compound is prepared from 6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) and 2-thiophenecarbonyl chloride, containing 0.3 mol of water; mp 187-188°C.

-59-

EXAMPLE 18

N-[4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]phenyl]acetamide

5 The title compound is prepared from 4-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl-1-butynyl]benzenamine (Example 14) and acetyl chloride, containing 0.1 mol of water; mp 172-173.4°C.

EXAMPLE 19

10 N-[5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinyl]acetamide

15 The title compound is prepared from 5-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl-2-pyridinamine (Example 15) and acetyl chloride; mp 169-170°C.

EXAMPLE 20

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-3-pyridinamine

20 To 0.50 mL (6.8 mmol) of acetic anhydride is added 0.32 mL (8.4 mmol) of 88% formic acid dropwise under nitrogen. Anhydrous tetrahydrofuran (10 mL) is added, and the solution is heated at 50°C for 2 hours. To the cooled solution is added a suspension of 6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) (0.8 g, 2.6 mmol) in 10 mL of tetrahydrofuran, and the solution is stirred at room temperature for 18 hours. The mixture is concentrated in vacuo, and the residue is partitioned between
25 dichloromethane and 5% ammonium hydroxide. The organic layer is dried and concentrated in vacuo. The residue, in 10 mL of tetrahydrofuran, is added dropwise under nitrogen to a suspension of 0.14 g (3.9 mmol) of lithium aluminum hydride in 20 mL of dry tetrahydrofuran at 0°C.
30 The reaction mixture is stirred at 0°C for 5 hours. The

-60-

reaction is quenched by sequential addition of 0.52 mL of 10% hydrochloric acid solution, 0.52 mL of 30% sodium hydroxide solution, and 0.52 mL of water. The resulting mixture is filtered through diatomaceous earth (Celite*), evaporated in vacuo, and chromatographed (silica gel, 1% methanol/99% dichloromethane) to give the title compound, containing 0.5 mol of water; mp 164.5-165.5°C.

Following the procedure of Example 20, the following compounds are prepared:

EXAMPLE 21

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methylbenzenamine, containing 0.3 mol of water; mp 106-107°C.

EXAMPLE 22

5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-2-pyridinamine, containing 0.36 mol of water; mp 169-170°C.

EXAMPLE 23

6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-propyl-3-pyridinamine

A solution of propionaldehyde (0.18 mL, 2.5 mmol), 6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) (0.83 g, 2.7 mmol) and glacial acetic acid (0.14 mL, 2.5 mmol) in 20 mL of dichloroethane is treated with sodium triacetoxymethylborohydride (0.79 g, 3.7 mmol) under nitrogen and is stirred at room temperature for 18 hours. The reaction is quenched with saturated aqueous sodium bicarbonate, diluted with dichloromethane, and the organic layer is dried (sodium sulfate) and concentrated under reduced pressure. The residue is chromatographed

* Trade-mark

-61-

(silica gel, 1% methanol/99% dichloromethane) to give the title compound, containing 0.20 mol of water; mp 138-139°C.

5

EXAMPLE 24

N-(Methylsulfonyl)-N-[6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide

A solution of 6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) (0.89 g, 2.9 mmol), triethylamine (0.61 mL, 4.4 mmol) and N,N-dimethylaminopyridine (catalytic amount) in 20 mL of dichloromethane is cooled to 0°C and methanesulfonyl chloride (0.30 mL, 3.5 mmol) is added dropwise under nitrogen. The cold bath is removed and the solution is stirred at room temperature for 18 hours. The solution is diluted with dichloromethane and washed with 30 mL of saturated aqueous sodium bicarbonate solution and 30 mL of water, and the organic layer is dried (sodium sulfate). The solvent is removed under reduced pressure and the residue is chromatographed (silica gel, 1% methanol/99% dichloromethane) to give the title compound as a white solid; mp 168-169.5°C.

25

EXAMPLE 25

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide

To a solution of 6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine (Example 13) (0.50 g, 1.6 mmol) and triethylamine (0.25 mL, 1.8 mmol) in 20 mL of dichloromethane at -78°C is added a solution of methanesulfonic anhydride (0.60 g, 2.8 mmol) in 10 mL of dichloromethane dropwise under nitrogen. The solution is stirred at -78°C for 2 hours and then warmed to room temperature over 2 hours. The reaction is

-62-

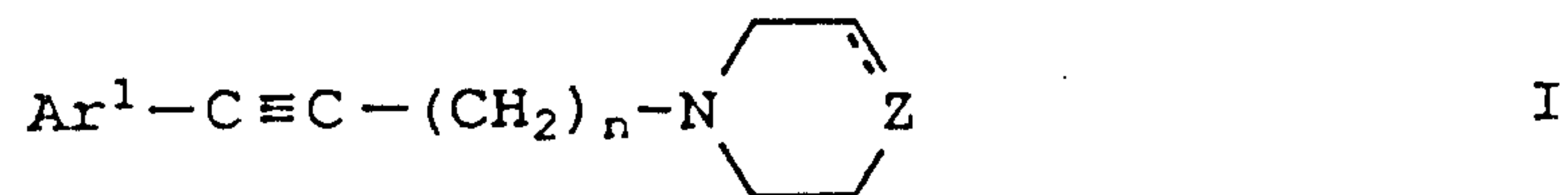
quenched with water, the organic layer is dried (sodium sulfate), and the solvent is removed under reduced pressure. The residue is chromatographed (silica gel 1% methanol/99% dichloromethane) to give the title

5 compound, containing 0.3 mol of water; mp 138-139°C.

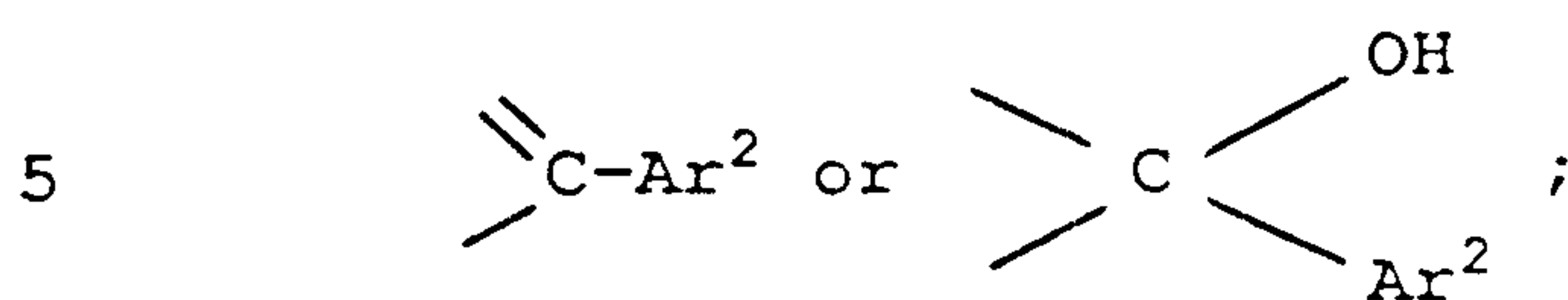
-63-

CLAIMS

1. A compound of Formula I:



wherein n is an integer of 2, 3, or 4; Z is



Ar^1 and Ar^2 are each independently
phenyl,

phenyl substituted by one to four substituents
10 selected from the group consisting of
lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
15 lower acyloxy,
amino,
lower alkyl amino,
nitro,

20 $\text{NH}-\text{C}(=\text{O})-\text{R}$, wherein R is
phenyl,

lower alkyl,
trifluoromethyl or a 5- or
25 6-membered heteroaromatic ring
comprising one or more
heteroatoms selected from N, S,
and O,

$\text{NH}-\text{SO}_2\text{R}$, wherein R is as defined above
30 or

-64-

-N-(SO₂R)₂, wherein R is as defined
above,

- 35 a 5- or 6-membered heteroaromatic ring
comprising one or more heteroatoms
selected from N, S, and O,
- a 5- or 6-membered heteroaromatic ring
comprising one or more heteroatoms
selected from N, S, and O, substituted by
halogen,
40 lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
45 lower alkyl amino,
nitro,
- $$\begin{array}{c} \text{O} \\ || \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,
50 -NH-SO₂R, wherein R is as defined above,
or
-N-(SO₂R)₂, wherein R is as defined
above,
- 55 a 8-, 9-, or 10-membered heteroaromatic
bicyclic ring comprising one or more
heteroatoms selected from N, S, and O, or
- a 8-, 9-, or 10-membered heteroaromatic
bicyclic ring comprising one or more
heteroatoms selected from N, S, and O,
60 substituted by
halogen,
lower alkyl,
lower alkoxy,
hydroxy,
65 lower acyloxy,
amino

-65-

lower alkyl amino,
nitro,

70

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined above,
-NH-SO₂R, wherein R is as defined above,
or

75

-N-(SO₂R)₂, wherein R is as defined
above;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of Claim 1 wherein Z is $\begin{array}{c} \diagup \\ \text{C}-\text{Ar}^2 \\ \diagdown \end{array}$.

3. A compound of Claim 1 wherein Z is $\begin{array}{c} \diagup \\ \text{C} \begin{array}{l} \diagup \text{OH} \\ \diagdown \text{Ar}^2 \end{array} \\ \diagdown \end{array}$.

4. A compound of Claim 2 in which Z is $\begin{array}{c} \diagup \\ \text{C}-\text{Ar}^2 \\ \diagdown \end{array}$ and
Ar¹ and Ar² are each independently
phenyl,

5

phenyl substituted by one to four substituents
selected from the group consisting of

10

lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino
nitro, or

15

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is
phenyl,
lower alkyl,

-66-

20 trifluoromethyl,
 2-, 3-, or 4-pyridinyl,
 2-, 4-, or 5-pyrimidinyl,
 2-pyrazinyl,
 2- or 3-furanyl,
 2- or 3-thienyl,
 25 2-, 4-, or 5-imidazolyl, or
 2-, 4-, or 5-thiazolyl,
 2-, 3-, or 4-pyridinyl,
 2-, 3-, or 4-pyridinyl substituted by
 halogen,
 30 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,
 amino,
 35 lower alkyl amino,
 nitro,

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
 40 above,
 $\text{-N-(SO}_2\text{R)}_2$, wherein R is as defined
 above, or
 $\text{-NH-SO}_2\text{R}$, wherein R is as defined
 above,
 45 2-, 4-, or 5-pyrimidinyl,
 2-, 4-, or 5-pyrimidinyl substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 50 hydroxy,
 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,

-67-

55

O
||
-NH-C-R, wherein R is as defined
above,

60

-NH-SO₂R, wherein R is as defined
above, or
-N-(SO₂R)₂, wherein R is as
defined above,

2-pyrazinyl,

2-pyrazinyl substituted by

65

halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,

70

amino,
lower alkyl amino,
nitro,

75

O
||
-NH-C-R, wherein R is as defined
above,
-NH-SO₂R, wherein R is as defined
above, or
-N-(SO₂R)₂, wherein R is as
defined above,

80

2- or 3-furanyl,

2- or 3-furanyl substituted by

85

halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

90

-68-

- $$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,
- 95 $\text{-NH-SO}_2\text{R}$, wherein R is as defined
above, or
 $\text{-N-(SO}_2\text{R)}_2$ wherein R is as defined
above,
- 100 2- or 3-thienyl,
 2- or 3-thienyl substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
- 105 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,
- 110
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R} \end{array}$$
 wherein R is as defined
above,
 $\text{-NH-SO}_2\text{R}$ wherein R is as defined
above, or
- 115 $\text{-N-(SO}_2\text{R)}_2$, wherein R is as
defined above,
 2-, 4-, or 5-imidazolyl,
 2-, 4-, or 5-imidazolyl substituted by
 halogen,
- 120 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,
 amino,
- 125 lower alkyl amino,
 nitro,

-69-

130
135
140
145
150
155
160

$$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$$
 wherein R is as defined
above,
$$-\text{NH}-\text{SO}_2\text{R},$$
 wherein R is as defined
above, or
$$-\text{N}-(\text{SO}_2\text{R})_2,$$
 wherein R is as
defined above,
2-, 4-, or 5-thiazolyl,
2-, 4-, or 5-thiazolyl substituted by
halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,
$$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$$
 wherein R is as defined
above,
$$-\text{NH}-\text{SO}_2\text{R}$$
 wherein R is as defined
above, or
$$-\text{N}-(\text{SO}_2\text{R})_2$$
 wherein R is as defined
above,
2-, 3-, 4-, 5-, 6-, or 7-indolyl,
2-, 3-, 4-, 5-, 6-, or 7-indolyl substituted
by
halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,

-70-

nitro,

165

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,

$$\text{-NH-SO}_2\text{R,}$$
 wherein R is as defined above, or

170

$$\text{-N-(SO}_2\text{R)}_2,$$
 wherein R is as defined above,

 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl,
 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl
 substituted by

175

 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,

180

 amino,
 lower alkyl amino,
 nitro,

185

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,

$$\text{-NH-SO}_2\text{R,}$$
 wherein R is as defined above, or

190

$$\text{-N-(SO}_2\text{R)}_2,$$
 wherein R is as defined above,

 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl,
 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl
 substituted by

195

 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,

-71-

- 200 amino,
lower alkyl amino,
nitro,
- 205 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,
 $\text{-NH-SO}_2\text{R,}$ wherein R is as defined
above, or
 $\text{-N-(SO}_2\text{R)}_2,$ wherein R is as defined
above,
- 210 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl,
1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl
substituted by
halogen,
lower alkyl,
215 lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
220 nitro,
- $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
above,
- 225 $\text{-NH-SO}_2\text{R,}$ wherein R is as defined
above, or
 $\text{-N-(SO}_2\text{R)}_2,$ wherein R is as defined
above,
- 230 2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1, or
2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyri-
diny1 substituted by
halogen,
lower alkyl,

-72-

235

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

240

nitro,

O

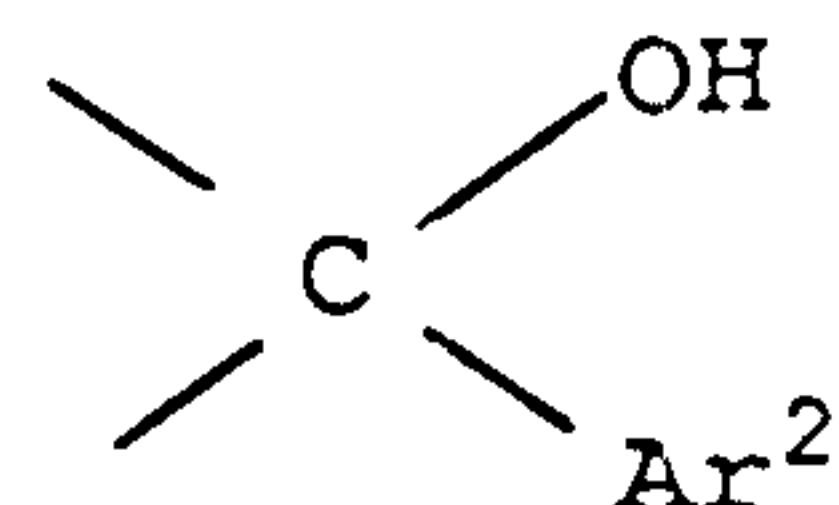
||

-NH-C-R, wherein R is as defined
above,

245

-NH-SO₂R, wherein R is as defined
above, or-N-(SO₂R)₂ wherein R is as defined
above.

5. A compound of Claim 3 in which Z is



and

5

Ar¹ and Ar² are each independently
phenyl,phenyl substituted by one to four substituents
selected from the group consisting of

10

lower alkyl,

lower alkoxy,

lower thioalkoxy,

hydroxy,

lower acyloxy,

amino,

15

lower alkyl amino

nitro, or

O

||

-NH-C-R, wherein R is

20

phenyl,

lower alkyl,

-73-

25 trifluoromethyl,
 2-, 3-, or 4-pyridinyl,
 2-, 4-, or 5-pyrimidinyl,
 2-pyrazinyl,
 2- or 3-furanyl,
 2- or 3-thienyl,
 2-, 4-, or 5-imidazolyl, or
 2-, 4-, or 5-thiazolyl,
 30 2-, 3-, or 4-pyridinyl,
 2-, 3-, or 4-pyridinyl substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 35 hydroxy,
 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,
 40 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined
 above,
 -NH-SO₂R, wherein R is as defined
 45 above, or
 -N-(SO₂R)₂, wherein R is as defined
 above,
 2-, 4-, or 5-pyrimidinyl,
 2-, 4-, or 5-pyrimidinyl substituted by
 50 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,
 55 amino,
 lower alkyl amino,
 nitro,

-74-

- 60 $\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined
above,
- NH-SO₂R, wherein R is as defined
above, or
- 65 -N-(SO₂R)₂, wherein R is as
defined above,
- 2-pyrazinyl,
- 2-pyrazinyl substituted by
- halogen,
- lower alkyl,
- 70 lower alkoxy,
- hydroxy,
- lower acyloxy,
- amino,
- lower alkyl amino,
- 75 nitro,
- $\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined
above,
- 80 -NH-SO₂R, wherein R is as defined
above, or
- N-(SO₂R)₂, wherein R is as
defined above,
- 2- or 3-furanyl,
- 85 2- or 3-furanyl substituted by
- halogen,
- lower alkyl,
- lower alkoxy,
- hydroxy,
- 90 lower acyloxy,
- amino,
- lower alkyl amino,
- nitro,

-75-

95

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined
above,

$$\text{-NH-SO}_2\text{R,}$$
 wherein R is as defined
above, or

100

$$\text{-N-(SO}_2\text{R)}_2$$
 wherein R is as defined
above,

2- or 3-thienyl,

2- or 3-thienyl substituted by
halogen,

105

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

110

lower alkyl amino,

nitro,

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R} \end{array}$$
 wherein R is as defined
above,

115

$$\text{-NH-SO}_2\text{R}$$
 wherein R is as defined
above, or

$$\text{-N-(SO}_2\text{R)}_2,$$
 wherein R is as
defined above,

120

2-, 4-, or 5-imidazolyl,

2-, 4-, or 5-imidazolyl substituted by
halogen,

lower alkyl,

lower alkoxy,

125

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

-76-

130

O
||
-NH-C-R, wherein R is as defined
above,

135

-NH-SO₂R, wherein R is as defined
above, or
-N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-thiazolyl,

2-, 4-, or 5-thiazolyl substituted by

140

halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

145

150

O
||
-NH-C-R, wherein R is as defined
above,
-NH-SO₂R wherein R is as defined
above, or
-N-(SO₂R)₂ wherein R is as defined
above,

155

2-, 3-, 4-, 5-, 6-, or 7-indolyl,

2-, 3-, 4-, 5-, 6-, or 7-indolyl substituted
by

160

halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
amino,

165

lower alkyl amino,

-77-

nitro,

O
||
-NH-C-R, wherein R is as defined
above,

170

-NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

175

2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl,
2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl
substituted by

halogen,

lower alkyl,

180

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

185

nitro,

O
||
-NH-C-R, wherein R is as defined
above,

190

-NH-SO₂R, wherein R is as defined
above, or

-N-(SO₂R)₂, wherein R is as
defined above,

195

2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl,
2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl
substituted by

halogen,

lower alkyl,

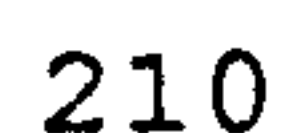
lower alkoxy,

200

hydroxy,

lower acyloxy,

205



1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl,
1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl
substituted by

215

220



230

2-, 3-, 4-, 5-, 6-, or 7-(1,8)naphthyridinyl substituted by

235

halogen,
lower alkyl,

-79-

- 240 lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,
- 245 $\begin{array}{c} \text{O} \\ | \\ -\text{NH}-\text{C}-\text{R} \end{array}$, wherein R is as defined
above,
-NH-SO₂R, wherein R is as defined
above, or
- 250 -N-(SO₂R)₂ wherein R is as defined
above.

6. A compound of Claim 4 in which Z is $\begin{array}{c} \diagup \\ \text{C}-\text{Ar}^2 \\ \diagdown \end{array}$; n is
2 or 3; and
Ar¹ and Ar² are each independently
phenyl,
- 5 phenyl substituted by one to four substituents
selected from the group consisting of
lower alkyl,
lower alkoxy,
lower thioalkoxy,
10 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro, or
- $\begin{array}{c} \text{O} \\ | \\ -\text{NH}-\text{C}-\text{R} \end{array}$, wherein R is
phenyl,
lower alkyl,
trifluoromethyl,
20 2-, 3-, or 4-pyridinyl,

-80-

25 2-, 4-, or 5-pyrimidinyl,
 2-pyrazinyl,
 2- or 3-furanyl,
 2- or 3-thienyl,
 2-, 4-, or 5-imidazolyl, or
 2-, 4-, or 5-thiazolyl,
 2-, 3-, or 4-pyridinyl,
 2-, 3-, or 4-pyridinyl substituted by
 30 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
 lower acyloxy,
 amino,
 35 lower alkyl amino,
 nitro,
 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R, wherein R is as} \end{array}$
 defined above,
 40 $\text{-NH-SO}_2\text{-R, wherein R is as}$
 defined above, or
 $\text{-N-(SO}_2\text{R)}_2\text{, wherein R is as}$
 defined above,
 2-, 4-, or 5-pyrimidinyl,
 45 2-, 4-, or 5-pyrimidinyl substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 hydroxy,
 50 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,

55 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ wherein R is as
defined above,
 $\text{-NH-SO}_2\text{-R,}$ wherein R is as
defined above, or
60 $\text{-N-(SO}_2\text{R)}_2\text{,}$ wherein R is as
defined above,
2- or 3-thienyl,
2- or 3-thienyl substituted by
halogen,
lower alkyl,
65 lower alkoxy,
hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
70 nitro,
 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ where R is as defined
above,
 $\text{-NH-SO}_2\text{-R,}$ wherein R is as
75 defined above, or
 $\text{-N-(SO}_2\text{R)}_2\text{,}$ wherein R is as
defined above,
4- or 5-thiazolyl,
4- or 5-thiazolyl substituted by
80 halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
85 amino,
lower alkyl amino,
nitro,

-82-

- $$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,
- $$\text{-NH-SO}_2\text{-R,}$$
 wherein R is as defined above, or
- $$\text{-N-(SO}_2\text{R)}_2,$$
 wherein R is as defined above,
- 2- or 3-indolyl,
- 2- or 3-indolyl substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,
- $$\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as defined above,
- $$\text{-NH-SO}_2\text{-R,}$$
 wherein R is as defined above, or
- $$\text{-N-(SO}_2\text{R)}_2,$$
 wherein R is as defined above,
- 2-, 3-, or 4-quinolinyl,
- 2-, 3-, or 4-quinolinyl substituted by

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

nitro,

- 83 -

125 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined above,
-NH-SO₂-R, wherein R is as defined above, or
-N-(SO₂R)₂, wherein R is as defined above

130 1-, 3-, or 4-isoquinolinyl, or
1-, 3-, or 4-isoquinolinyl substituted by
halogen,
lower alkyl,
lower alkoxy,
135 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

140 $\begin{array}{c} \text{O} \\ | \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined above,
-NH-SO₂-R, wherein R is as defined above, or
145 -N-(SO₂R)₂, wherein R is as defined above.

7. A compound of Claim 5 in which Z is $\begin{array}{c} \diagup \\ \diagdown \end{array} \text{C} \begin{array}{c} \diagup \text{OH} \\ \diagdown \text{Ar}^2 \end{array}$;

5 n is 2 or 3; and
 Ar¹ and Ar² are each independently
 phenyl,
 phenyl substituted by one to four substituents
 selected from the group consisting of
 lower alkyl,

-84-

10 lower alkoxy,
 lower thioalkoxy,
 hydroxy,
 lower acyloxy,
 amino,
 15 lower alkyl amino,
 nitro, or

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is
 20 phenyl,
 lower alkyl,
 trifluoromethyl,
 2-, 3-, or 4-pyridinyl,
 2-, 4-, or 5-pyrimidinyl,
 25 2-pyrazinyl,
 2- or 3-furanyl,
 2- or 3-thienyl,
 2-, 4-, or 5-imidazolyl, or
 2-, 4-, or 5-thiazolyl,
 30 2-, 3-, or 4-pyridinyl,
 2-, 3-, or 4-pyridinyl substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 35 hydroxy,
 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,
 40
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$$
 wherein R is as
 defined above,

$$\text{-NH-SO}_2\text{-R,}$$
 wherein R is as
 45 defined above, or

-85-

-N-(SO₂R)₂, wherein R is as
defined above,

2-, 4-, or 5-pyrimidinyl,

2-, 4-, or 5-pyrimidinyl substituted by

50

halogen,

lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

55

amino,

lower alkyl amino,

nitro,

O

||

60

-NH-C-R, wherein R is as

defined above,

-NH-SO₂-R, wherein R is as

defined above, or

-N-(SO₂R)₂, wherein R is as

65

defined above,

2- or 3-thienyl,

2- or 3-thienyl substituted by

halogen,

lower alkyl,

70

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

lower alkyl amino,

75

nitro,

O

||

-NH-C-R, where R is as defined

above,

80

-NH-SO₂-R, wherein R is as

defined above, or

-86-

-N-(SO₂R)₂, wherein R is as
defined above,

4- or 5-thiazolyl,

85 4- or 5-thiazolyl substituted by
halogen,

lower alkyl,

lower alkoxy,

hydroxy,

90 lower acyloxy,

amino,

lower alkyl amino,

nitro,

95 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as
defined above,

-NH-SO₂-R, wherein R is as
defined above, or

100 -N-(SO₂R)₂, wherein R is as
defined above,

2- or 3-indolyl,

2- or 3-indolyl substituted by

halogen,

105 lower alkyl,

lower alkoxy,

hydroxy,

lower acyloxy,

amino,

110 lower alkyl amino,

nitro,

115 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as
defined above,

-NH-SO₂-R, wherein R is as
defined above, or

-87-

-N-(SO₂R)₂, wherein R is as
defined above,

- 120 2-, 3-, or 4-quinolinyl,
2-, 3-, or 4-quinolinyl substituted by
halogen,
lower alkyl,
lower alkoxy,
125 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,
- 130 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
-NH-C-R, wherein R is as
defined above,
-NH-SO₂-R, wherein R is as
135 defined above, or
-N-(SO₂R)₂, wherein R is as
defined above
1-, 3-, or 4-isoquinolinyl, or
1-, 3-, or 4-isoquinolinyl substituted by
140 halogen,
lower alkyl,
lower alkoxy,
hydroxy,
lower acyloxy,
145 amino,
lower alkyl amino,
nitro,
- 150 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
-NH-C-R, wherein R is as
defined above,
-NH-SO₂-R, wherein R is as
defined above, or

-88-

-N-(SO₂R)₂, wherein R is as
defined above.

155

8. A compound according to Claim 1 selected from the group consisting of:

3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]quinoline;

5 4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]isoquinoline;

3-[4-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-butynyl]pyridine;

10 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]pyridine;

3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-pentynyl]quinoline;

3-[5-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-pentynyl]pyridine;

15 3-[5-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-pentynyl]pyridine;

1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine;

20 1,2,3,6-Tetrahydro-1-[4-(4-nitrophenyl)-3-butynyl]-4-phenylpyridine;

1,2,3,6-Tetrahydro-1-[4-(5-nitro-2-pyridinyl)-3-butynyl]-4-phenylpyridine;

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]pyridine;

25 6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinamine;

4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]benzenamine;

30 5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinamine;

N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]acetamide;

-89-

- 35 N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]-2-thiophenecarboxamide;
- N-[4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]phenyl]acetamide;
- 40 N-[5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-pyridinyl]acetamide;
- 6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-3-pyridinamine;
- 4-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methylbenzenamine;
- 45 5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-methyl-2-pyridinamine;
- 6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-N-propyl-3-pyridinamine;
- 50 N-(Methylsulfonyl)-N-[6-[4-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide;
- N-[6-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-3-pyridinyl]methanesulfonamide;
- 55 3-[5-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-pentynyl]quinoline;
- 5-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-2-thiazolamine;
- 3-[4-(3,6-Dihydro-4-phenyl-1(2H)-pyridinyl)-1-butynyl]-1H-indole; and
- 60 4-[4-[3,6-Dihydro-4-(2-thienyl)-1(2H)-pyridinyl]-1-butynyl]pyridine.

9. For use in treating psychoses, depression, hypertension, galactorrhea, amenorrhea, menstrual disorders, sexual dysfunction, Parkinson's disease, or Huntington's chorea, a therapeutic effective

-90-

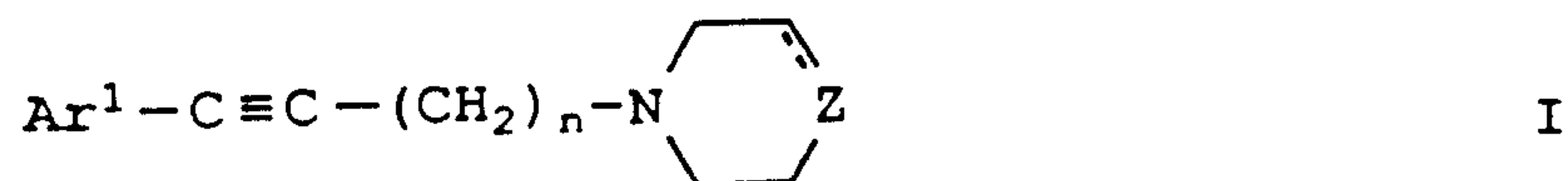
amount of a compound according to Claim 1 in unit dosage form.

10. For use in treating schizophrenia, a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

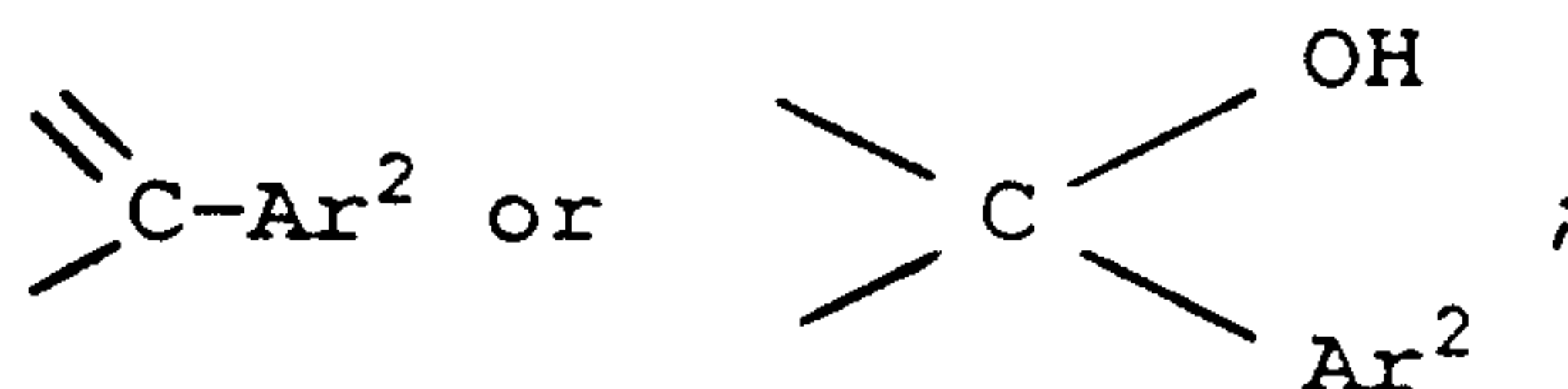
11. For use in treating depression, a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

12. A pharmaceutical composition adapted for administration as a dopaminergic, antipsychotic, antihypertensive, or antidepressant agent comprising a therapeutic effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

13. A method for the preparation of a compound of Formula I:



wherein n is an integer of 2, 3, or 4; Z is



-91-

Ar¹ and Ar² are each independently
phenyl,

- 10 phenyl substituted by one to four substituents
selected from the group consisting of
lower alkyl,
lower alkoxy,
lower thioalkoxy,
15 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,
20 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is
phenyl,
lower alkyl,
25 trifluoromethyl or a 5- or
6-membered heteroaromatic ring
comprising one or more
heteroatoms selected from N, S,
and O,
30 -NH-SO₂R, wherein R is as defined above
or
-N-(SO₂R)₂, wherein R is as defined
above,
a 5- or 6-membered heteroaromatic ring
35 comprising one or more heteroatoms
selected from N, S, and O,
a 5- or 6-membered heteroaromatic ring
comprising one or more heteroatoms
selected from N, S, and O, substituted by
40 halogen,
lower alkyl,
lower alkoxy,
hydroxy,

-92-

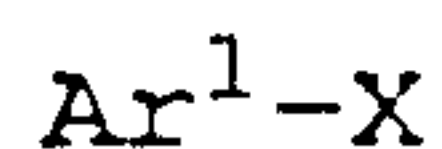
45 lower acyloxy,
 amino,
 lower alkyl amino,
 nitro,
 50 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined above,
 $\text{-NH-SO}_2\text{R,}$ wherein R is as defined above,
 or
 $\text{-N-(SO}_2\text{R)}_2,$ wherein R is as defined
 above,
 55 a 8-, 9-, or 10-membered heteraromatic
 bicyclic ring comprising one or more
 heteroatoms selected from N, S, and O, or
 a 8-, 9-, or 10-membered heteroaromatic
 bicyclic ring comprising one or more
 60 heteroatoms selected from N, S, and O,
 substituted by
 halogen,
 lower alkyl,
 lower alkoxy,
 65 hydroxy,
 lower acyloxy,
 amino
 lower alkyl amino,
 nitro,
 70 $\begin{array}{c} \text{O} \\ \parallel \\ \text{-NH-C-R,} \end{array}$ wherein R is as defined above,
 $\text{-NH-SO}_2\text{R,}$ wherein R is as defined above,
 or
 75 $\text{-N-(SO}_2\text{R)}_2,$ wherein R is as defined
 above;

or a pharmaceutically acceptable acid addition salt thereof, which comprises

a) reacting a compound of Formula II

-93-

80



II

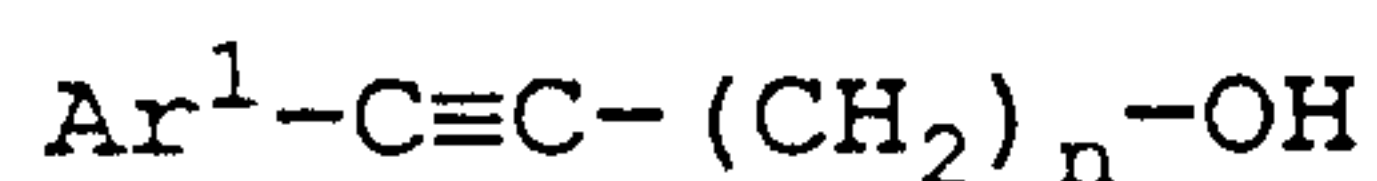
wherein X is Cl, Br, or I and Ar^1 is as defined above with a compound of Formula III



III

85

wherein n is an integer of 2, 3, or 4 in a solvent in the presence of an acid scavenger and a catalyst to afford a compound of Formula IV

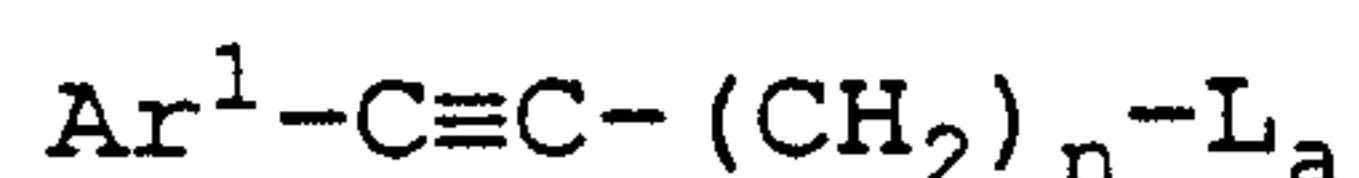


IV

wherein Ar^1 and n are as defined above;

90

b) reacting an alcohol of Formula IV with an alkyl- or aryl-sulfonyl halide in a solvent and in the presence of an acid scavenger to afford a compound of Formula Va

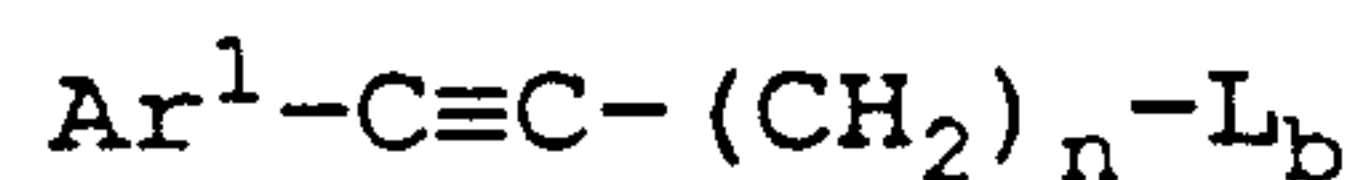


Va

95

wherein L_a is alkyl- or aryl-sulfonyloxy and Ar^1 and n are as defined above;

or alternatively reacting an alcohol of Formula IV with triarylphosphine combined with a tetrahalomethane to afford a compound of Formula Vb



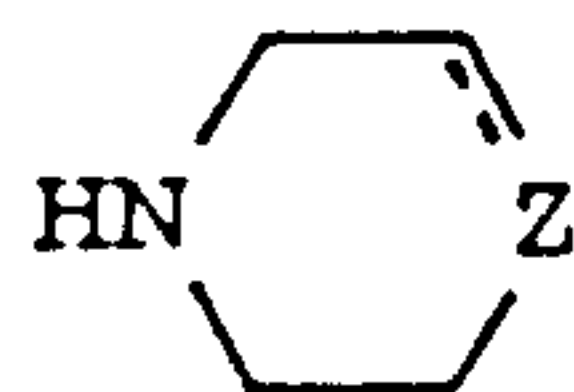
Vb

100

wherein L_b is a halogen atom and Ar^1 and n are as defined above;

c) reacting a compound of Formula Va or Vb with a compound of Formula VI

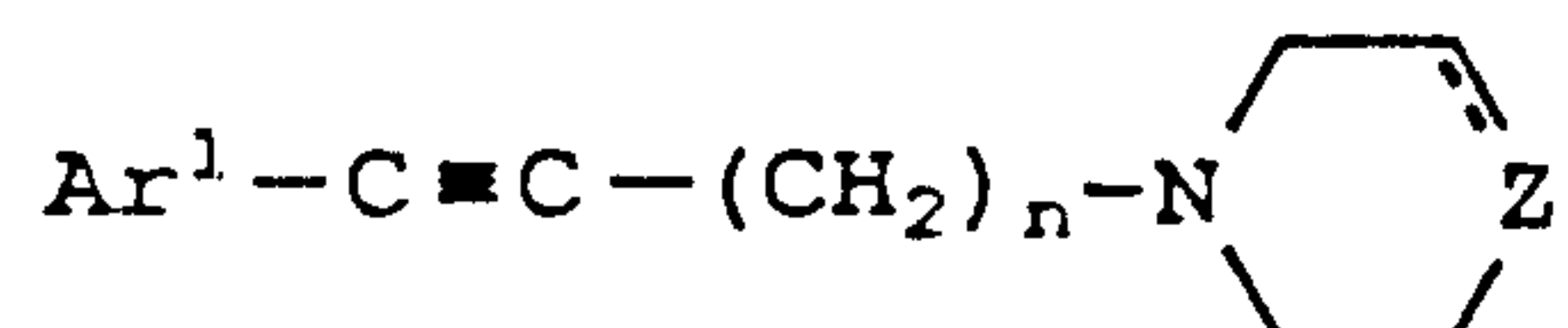
-94-



VI

105 wherein Z is as defined above in a solvent in the
 presence of a base to afford a compound of
 Formula I and, if desired, converting the compound
 of Formula I to a corresponding pharmaceutically
 acceptable acid addition salt and, if so desired,
 110 converting the corresponding pharmaceutically acceptable
 acid addition salt to a compound of Formula I.

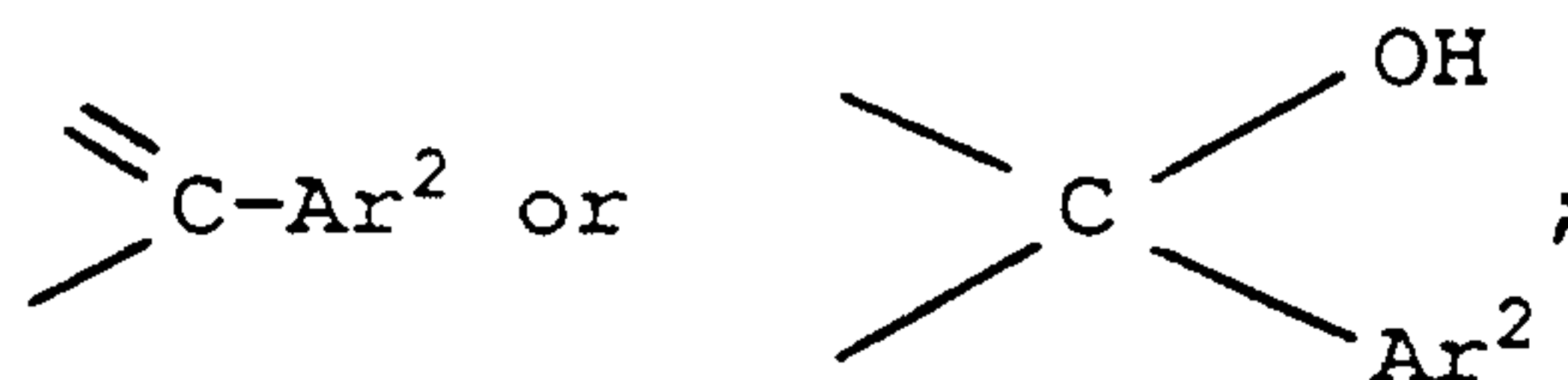
14. A method for the preparation of a compound of
 Formula I



I

wherein n is an integer of 2, 3, or 4; Z is

5



-95-

Ar¹ and Ar² are each independently
phenyl,

10 phenyl substituted by one to four substituents
selected from the group consisting of

lower alkyl,
lower alkoxy,
lower thioalkoxy,
15 hydroxy,
lower acyloxy,
amino,
lower alkyl amino,
nitro,

20
$$\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R}, \end{array}$$
 wherein R is
phenyl,
lower alkyl,

25 trifluoromethyl or a 5- or
6-membered heteroaromatic ring
comprising one or more
heteroatoms selected from N, S,
and O,

30 -NH-SO₂R, wherein R is as defined above
or
-N-(SO₂)-R)₂, wherein R is as defined
above,

35 a 5- or 6-membered heteroaromatic ring
comprising one or more heteroatoms
selected from N, S, and O,

a 5- or 6-membered heteroaromatic ring
comprising one or more heteroatoms
selected from N, S, and O, substituted by
40 halogen,
lower alkyl,
lower alkoxy,
hydroxy,

-96-

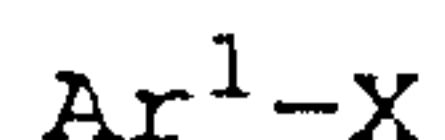
- 45 lower acyloxy,
amino,
lower alkyl amino,
nitro,
- 50 $\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined above,
 $-\text{NH}-\text{SO}_2\text{R}$, wherein R is as defined above,
or
 $-\text{N}-(\text{SO}_2\text{R})_2$, wherein R is as defined
above,
- 55 a 8-, 9-, or 10-membered heteroaromatic
bicyclic ring comprising one or more
heteroatoms selected from N, S, and O, or
a 8-, 9-, or 10-membered heteroaromatic
bicyclic ring comprising one or more
60 heteroatoms selected from N, S, and O,
substituted by
halogen,
lower alkyl,
lower alkoxy,
65 hydroxy,
lower acyloxy,
amino
lower alkyl amino,
nitro,
- 70 $\begin{array}{c} \text{O} \\ || \\ -\text{NH}-\text{C}-\text{R}, \end{array}$ wherein R is as defined above,
 $-\text{NH}-\text{SO}_2\text{R}$, wherein R is as defined above,
or
75 $-\text{N}-(\text{SO}_2\text{R})_2$, wherein R is as defined
above;

or a pharmaceutically acceptable acid addition salt
thereof, which comprises

- a) reacting a compound of Formula II

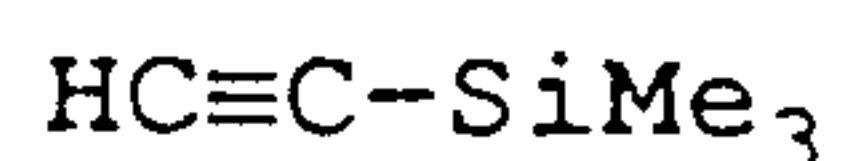
-97-

80



II

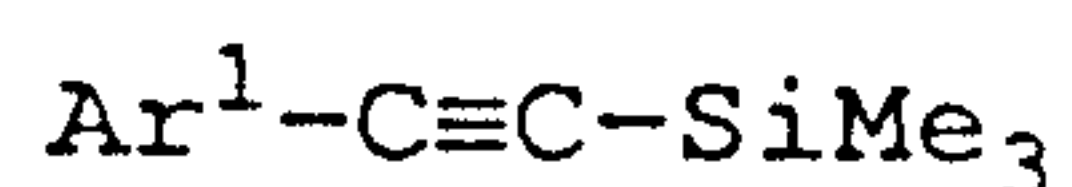
wherein X is Cl, Br, or I and Ar^1 is as defined above with the compound of Formula VII



VII

85

in a solvent in the presence of an acid scavenger and a catalyst to afford a compound of Formula VIII

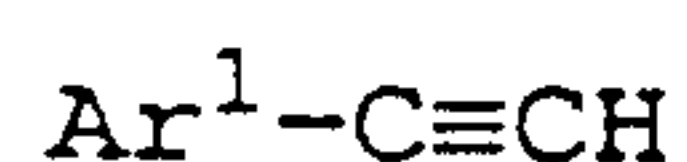


VIII

wherein Ar^1 is as defined above;

b) removing the trimethylsilyl group using a base and an alcohol to afford a compound of Formula IX

90

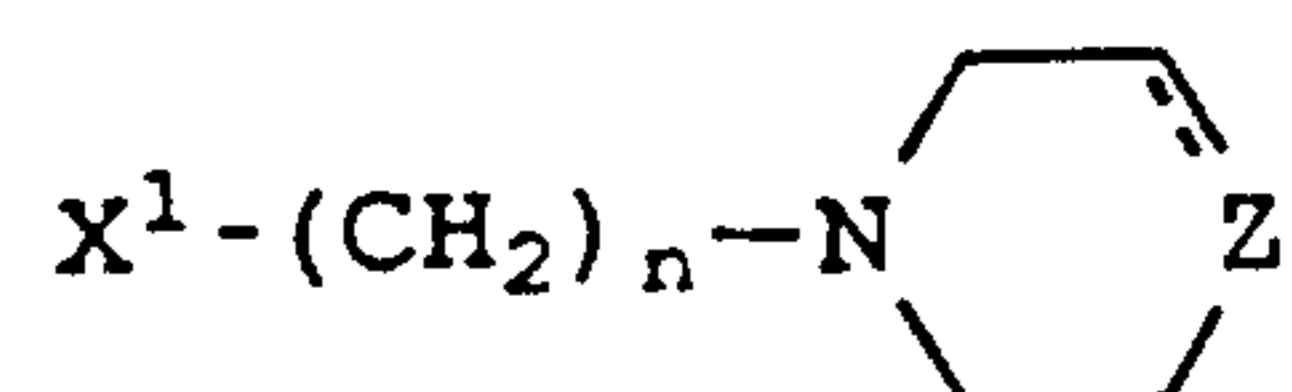


IX

wherein Ar^1 is as defined above;

c) reacting a compound of Formula IX with an organolithium compound and with a compound of Formula X

95



X

100

wherein X^1 is Cl, Br, or I, and n and Z are as defined above, in a solvent to afford a compound of Formula I; and if desired, converting the compound of Formula I to a corresponding pharmaceutically acceptable acid addition salt and, if so desired, converting the corresponding pharmaceutically acceptable acid addition salt to a compound of Formula I.

