METHODS FOR LOWERING URIC ACID LEVELS

Disclosed are methods of reducing serum uric acid levels, the methods comprising administration of substituted indolealkanoic acids to patients in need of such treatment. Also disclosed are such compounds useful in the treatment of gout and related diseases. Also disclosed are pharmaceutical compositions containing the compounds.
Methods for lowering Uric Acid Levels

Background of Invention

This application claims benefit of U.S. Provisional Application S.N. 60/176,273, filed January 14, 2000, which is incorporated herein by reference in its entirety.

Field of the Invention

This invention relates to indole acetic acids and their use in pharmaceutical compositions. More specifically, it relates to substituted indole acetic acids and their use as hypouricemic agents, agents useful for lowering blood uric acid levels.

Detailed Description of the Invention

Uric acid containing deposits (also known as trophi) resulting from unphysiologically elevated plasma uric acid levels tend to occur in various tissues throughout the body, leading to the disease condition known as gout and gouty arthritis. Uric acid containing deposits in such conditions may occur in cartilage, bone, bursae, tendons, connective tissue overlying bony prominences, as well as, subcutaneously and in the area of kidney. Elevated blood uric acid levels also occur in number of other disease conditions including myeloid leukemia, myeloid dysplasia, pernicious anemia, psoriasis, diabetes mellitus and renal disease.
Acute gout responds to colchicine. Nonsteroidal anti-inflammatory agents are also useful in acute attacks. Long-term therapy is directed to preventing hyperuricemia by giving uricosuric drugs. Patients with gout have a tendency to form uric acid kidney stones.

Treatment for gout consists of the administration of anti-inflammatory agents, dietary modifications, and the use of drugs that diminish uric acid formation, as well as drugs that enhance excretion of uric acid by the kidney. The latter drugs are the uricosuric agents, some of which act as competitive inhibitors of both uric acid transport and the transport of other organic anions.

One of the peculiar characteristics of the uric acid transport system is that, although the net activity of tubular function is reabsorption of uric acid, the molecule is both secreted and reabsorbed during its passage through the nephron. The secretory and reabsorptive mechanisms vary in importance along the proximal tubule, with reabsorption dominating in the S1 and S3 segments and secretion dominating in the S2 segment.

As a consequence of this bidirectional transport, drugs that inhibit uric acid transport may decrease rather than increase the excretion of uric acid. Obviously, such an effect compromises their therapeutic usefulness.
Summary of the Invention

This invention provides methods for lowering blood uric acid levels in mammals, e.g., humans.

As used in the claims and specification hereof, treatment is meant to include both the prevention and alleviation of such conditions.

The methods of the invention comprise administering to a mammal in need of blood uric acid lowering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof:

\[
\begin{align*}
R_1 & \quad R_2 \\
R_3 & \quad R_4 \\
Z & \quad Ar \\
R_5 & \quad N \\
R_6 & \quad ACO
\end{align*}
\]

wherein

A is a C₁-C₄ alkylene group optionally substituted with C₁-C₂ alkyl or mono- or disubstituted with halogen, preferably fluoro or chloro;

Z is a bond, O, S, C(O)NH, or C₁-C₃ alkylene optionally substituted with C₁-C₂ alkyl;

R₁ is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, nitro, amino, or mono- or di(C₁-C₆)alkylamino;
R₁, R₂, R₃, and R₄ are each independently
hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon
atoms (which may be substituted with one or more halogens);

5 \text{OR}_{1}, \text{SR}_{1}, \text{S(O)R}_{1}, \text{S(O)₂R}_{1}, \text{C(O)N(R)₂}, \text{or N(R)₂}, \text{wherein each R}₁ \text{is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionall y substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; or a group of the formula}

\[
\begin{array}{c}
\text{(CH}_2)_n \\
\text{N~(CH}_2)_n \\
\end{array}
\]

\text{where}

\text{J is a bond, CH}₂, \text{oxygen, or nitrogen; and}
each $r$ is independently 2 or 3;

$R_6$ is hydroxy or a prodrug group;

$R_a$ is hydrogen, $C_1$-$C_6$ alkyl, fluoro, or trifluoromethyl; and

$Ar$ represents aryl or heteroaryl, each of which is optionally

substituted with up to five groups.

The compounds of the invention have been discovered to

lower blood uric acid levels. The discovery of this biological

activity for the compounds of the invention is unexpected. As

a result of this biological activity, the compounds of the

invention can be used to treat any of the various diseases

associated with elevated levels of uric acid, e.g., gout. Thus, in a broad aspect, the invention provides methods for

reducing serum uric acid levels. In a related aspect, the

invention provides a method of preventing or treating gout.

Administration of the compound(s) of this invention is/are

not limited to a particular mode, and could be administered

systemically or topically to the eye in an appropriate

ophthalmic solution. The compounds of the invention may be

administered in combination therapy with other known hypouremic

agents. Also, the compounds of the invention may be

administered with compounds useful in the treatment of myeloid

leukemia, myeloid dysplasia, pernicious anemia, psoriasis,

diabetes mellitus and renal disease.

In still another aspect, the invention provides

pharmaceutical compositions containing a compound of Formula I,
and more specifically, an effective amount of at least one compound of Formula I. Thus, in the methods of the invention, the compounds of Formula I may be administered in a pharmaceutical composition together with a pharmaceutically acceptable carrier.
Detailed Description of the Invention

As used herein, the term "treatment" includes both prevention and alleviation. Prevention can be achieved readily according to the invention by administering an amount of a compound of Formula I to a mammalian subject, preferably a human. The subject need not necessarily be presenting symptoms of gout; it is sufficient for the subject to only be suspected of being in need of preventative therapy according to the invention.

The numbering system for the compounds of Formula I is as follows:

As noted above, the invention provides novel substituted indole alkanoic acids useful in treating and/or preventing complications or disease states associated with elevated levels of uric acid. These compounds are represented by Formula I above.

In compounds of Formula I, the aryl and heteroaryl groups represented by Ar include:

a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more
halogens), nitro, OR, SR, S(O)R, S(O)₂R, or N(R)₂ wherein R, is hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino, or the phenyl group may be condensed with benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl, perfluoroethyl, trifluoroacetyl, or (C₁-C₆)alkanoyl, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alklythio, trifluoromethoxy, trifluoromethylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfonyl;
a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, (C₁-C₆)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thiényl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or (C₁-C₆)alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alklythio, trifluoromethoxy, trifluoromethylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfonyl or trifluoromethyl,
or two fluoro or two trifluoromethyl with one hydroxy or one (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thiienyl optionally substituted in the 3-position by fluoro, chloro, bromo, (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by one or two (C<sub>1</sub>-C<sub>6</sub>)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thiienyl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bromo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thiienyl optionally substituted in the 3-position by fluoro, chloro, (C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bromo, methoxy, or trifluoromethyl;

oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methythio or methylsulfinyl;
imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or (C₁₋₅)alkoxy, or two of fluoro or chloro; thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl; thienotriazole optionally substituted by one of chloro or trifluoromethyl; naphthothiazole; naphthoxazole; or thienoisothiazole.

More specific compounds of the invention are those of Formula I wherein Ar is optionally substituted benzothiazolyl, benzoxazolyl, isoquinolyl, benzothiophen-yl, benzofuran-yl or benzimidazolyl, or substituted oxadiazolyl or indolyl. Other more specific compounds are of Formula I those wherein R₄ is trifluoromethyl, Z is a covalent bond or CH₂, R₅ is hydroxy, and each of R₂-R₅ are independently hydrogen, halogen, more preferably bromo or chloro, C₁₋₅ alkyl, phenoxy, benzyloxy, or C₁₋₅ alkoxy, and R₁ is hydrogen or methyl. Particularly preferred Ar groups include optionally substituted benzothiazolyl. Preferred Ar substituents include C₁₋₅ alkyl, C₁₋₅ alkoxy, hydroxy, halogen, nitro, amino, mono- and di(C₁₋₅)alkyl amino, and trifluoromethyl.

Preferred compounds of the invention are those wherein Z is a covalent bond, R₅ is hydroxy, Ar is optionally substituted benzothiazol-2-yl, benzothiazol-5-yl, benzoisothiazol-3-yl, benzoxazol-2-yl, 2-quinolyl, 2-quinoxalyl, oxazolo[4,5-
b) pyridine-2-yl, benzothiophen-2-yl, benzofuran-2-yl, or thiazolo[4,5-pyridine-2-yl, thieno[2,3-b]pyridine2-yl, imidazo[1,5-a]pyridine-2-yl, or indol-2-yl, or substituted 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, isothiazol-5-yl, isothiazol-4-yl, 1,3,4-oxadiazol-5-yl, 1,2,5-thiadiazol-3-yl, oxazol-2-yl, thiazol-2-yl, or thiazol-4-yl, \( R_2 - R_5 \) are independently hydrogen, halogen, more preferably bromo or chloro, \( C_1 - C_2 \) alkyl, phenoxy, benzyloxy or phenyl where each phenyl portion is optionally substituted with \( C_1 - C_6 \) alkyl, halogen, \( C_1 - C_6 \) alkoxy, hydroxy, amino or mono- or di (\( C_1 - C_5 \)) alkylamino \( R_a \) is hydrogen, fluoro or \( C_1 - C_2 \) alkyl, and \( R_i \) is hydrogen or methyl.

Other preferred compounds are those wherein the methylene bridge connecting the indolyl group with \( Ar \) is located alpha with respect to a nitrogen atom in \( Ar \), e.g., wherein \( Ar \) is benzoaxazol-2-yl or 1,2,4-oxadiazol-3-yl mentioned above.

Other more specific compounds of the invention are those wherein \( Z \) is a covalent bond, \( R_6 \) is hydroxy, \( R_a \) is hydrogen, \( Ar \) is optionally 4,5,6 or 7-substituted benzothiazolyl, benzoaxazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, or indolyl, or \( Ar \) is 2-benzothiazolyl substituted on benzo by one trifluoroacetetyl or trifluoromethylthio, or one or two of fluoro chloro, bromo, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or one or, preferably, two fluoro and one trifluoromethyl, or two fluoro or two trifluoromethyl with one methoxy, or three fluoro, or by 6,7-
benzo, and those wherein one of R₃ and R₄ is hydrogen, fluoro, chloro, bromo or methyl, and one of R₃ and R₅ is hydrogen, or chloro, bromo, methyl, isopropyl, methoxy, nitro or trifluoromethyl; or R₃ and R₄ is 5, 6-difluoro, R₅ is hydrogen; and those wherein Ar is optionally substituted benzothiazol-2-yl or quinoxalyl and R₃ and R₄ are each chloro, and R₅ is hydrogen or methyl.

Further more specific compounds are those wherein Z is a covalent bond, R₆ is hydroxy, Ar is optionally substituted benzothiazol-2-yl, R₃ and R₄ are hydrogen, and R₅ is methyl; those wherein Z is a covalent bond, R₆ is hydroxy, R₃, R₄ and R₅ are hydrogen, chloro, fluoro, bromo or C₁-C₂ alkyl, R₅ is hydrogen, and Ar is optionally 4,5,6 or 7 benzosubstituted benzothiazolyl-2-trifluoromethyl, benzoazoxazolyl-2-trifluoromethyl, benzimidazolyl-2-trifluoromethyl, benzofuran-2-trifluoromethyl, benzofuran-3-trifluoromethyl, benzothiophen-2-trifluoromethyl, benzothiophen-3-trifluoromethyl, indolyl-2-trifluoromethyl, or indolyl-3-trifluoromethyl; and those wherein Z is CH₂, R₆ is hydroxy, Ar is optionally substituted benzothiazol-2-yl, benzothiazol-5-yl, benzoisothiazol-3-yl, benzoazol-2-yl, 2-quinolyl, 2-quinoxalyl, oxazolo[4,5-b]pyridine-2-yl, or thiazolo[4,5-b]pyridine-2-yl, or substituted 1,2,4-oxadiazol3-yl, 1,2,4-oxadiazol-5-yl, isothiazol-5-yl, isothiazol-4-yl, 1,3,4-oxadiazol-5-yl, 1,2,5-thiadiazol-3-yl, oxazol-2-yl, thiazol-2-yl, or thiazol-4-yl,
and \( R_3, R_4 \) and \( R_5 \) are independently hydrogen, chloro, fluoro, bromo, \( C_1-C_2 \) alkyl, or trifluoromethyl, and \( R_6 \) is hydrogen.

Generally, \( R_1 \) in the specific compounds described above is hydrogen, halogen, preferably chloro or fluoro, \( C_1-C_6 \) alkyl, or phenyl optionally substituted with up to three groups independently selected from halogen, \( C_1-C_6 \) alkyl, \( C_1-C_6 \) alkoxy, amino, and mono- or di(\( C_1-C_6 \))alkylamino. Preferred \( R_1 \) groups are hydrogen and methyl.

Preferred compounds of the invention include those where \( Ar \) in Formula I is substituted phenyl, i.e., compounds of Formula II:

\[
\begin{align*}
\text{II} \\
\end{align*}
\]

wherein

\( A \) is a \( C_1-C_4 \) alkylene group optionally substituted with \( C_1-C_2 \) alkyl;

\( Z \) is a bond, or \( C_1-C_3 \) alkylene optionally substituted with \( C_1-C_2 \) alkyl;

\( R_8 \) is hydrogen, \( C_1-C_6 \) alkyl, chloro, bromo, fluoro, or trifluoromethyl;

\( R_1 \) is hydrogen, \( C_1-C_6 \) alkyl, fluoro, or phenyl optionally substituted with up to three groups independently selected.
from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

R₂, R₃, R₄ and R₅ are each independently hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR₇, SR₇, S(O)R₇, S(O)₂(NR₇)₂, C(O)N(R₇)₂, or N(R₇)₂, wherein each R₇ is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; or

a group of the formula

\[
\text{(CH}_2_\text{)}_r \quad \text{J} \\
\text{N}^-\text{(CH}_2_\text{)}_r
\]
where

J is a bond, CH₂, oxygen, or nitrogen; and

each r is independently 2, or 3;

Rₖ is hydrogen, an alkoxy group of 1-6 carbon atoms, or -O'M'

where M' is a cation forming a pharmaceutically acceptable

salt; and

R₆, R₇, and R₁₀ are independently hydrogen, fluorine, chlorine,

bromine, trifluoromethyl or nitro.

Other preferred compounds of the invention are those where

Ar is a substituted benzothiazole, i.e., compounds of Formula

III:

III

wherein

A is a C₁-C₄ alkylene group optionally substituted with C₁-C₂

alkyl;

Z is a bond, or C₁-C₅ alkylene optionally substituted with C₁-C₂

alkyl;

R₆ is hydrogen, C₁-C₆ alkyl, chloro, bromo, fluoro, or

trifluoromethyl;

R₁ is hydrogen, C₁-C₆ alkyl, halogen, preferably chloro or

fluoro, or phenyl optionally substituted with with up to

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three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

R₂, R₃, R₄ and R₅ are each independently hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR₇, SR₇, S(O)R₇, S(O)₂N(R₇)₂, C(O)N(R₇)₂, or N(R₇)₂, wherein each R₇ is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; or

a group of the formula

\[
\begin{align*}
&\text{(CH}_2)_r \\
&\text{N-(CH}_2)_r
\end{align*}
\]

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where

J is a bond, CH₂, oxygen, or nitrogen; and

each r is independently 2 or 3;

R₆ is hydroxy, C₁-C₆ alkoxy, or -OM⁺ where M⁺ is a cation
forming a pharmaceutically acceptable salt; and

R₁₁, R₁₂, R₁₃ and R₁₄ are independently hydrogen, halogen, nitro,
hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio,
trifluoromethyl, trifluoromethoxy, C₁-C₆ alkylsulfanyl, or
C₁-C₆ alkylsulfonyl.

In preferred compounds of Formula III, the R₂, R₃, R₄ and
R₅ substituents, in combination, represent one of bromo, cyano
or nitro, one or two of fluoro, chloro, hydroxy, (C₁-C₆)alkyl,
(C₁-C₆)alkoxy, or trifluoromethyl, or two fluoro or two methyl
with one hydroxy or one (C₁-C₆)alkoxy, or one or, preferably,
two fluoro and one methyl, or three fluoro groups.
Particularly preferred R₂, R₃, R₄ and R₅ substituents are,
independently, fluorine, chlorine, nitro, and trifluoromethyl.

In preferred compounds of Formulas II and III, A is
preferably methylene, methylene substituted with a methyl
group, or ethylene.

Preferred compounds according to Formula II above include
those wherein R₄ is fluorine, R₆ is hydrogen and R₁₀ is bromine
or those wherein R₆ and R₁₀ are hydrogens and R₉ is nitro.

Preferred compounds of Formula III above are those wherein
the benzothiazole moiety is substituted with nitro, one, two,
or three of fluoro, one or two of chloro, or at least one
trifluoromethyl group. More preferred compounds of Formula II are those where A is methylene, R₁ is hydrogen or methyl, Z is a bond, and R₆ is hydroxy or C₁₋C₆ alkoxy.

Still more preferred compounds of Formula II are those wherein R₁₁, R₁₂, and R₁₄ are fluorines and R₁₃ is hydrogen. Other more preferred compounds of Formula II are those where R₃ is methyl or hydrogen, Z is methylene or, more preferably, a bond, A is CHF or C₁ or C₂ alkylene, preferably methylene, R₁ is methyl or hydrogen, and R₁₁, R₁₂, and R₁₄ are halogens or C₁₋C₃ alkyl. Still other more preferred compounds of Formula III are those where R₃ is methyl or hydrogen, Z is methylene or, more preferably, a bond, A is CHF or C₁ or C₂ alkylene, R₁ is methyl or hydrogen, and R₁₁, R₁₂, and R₁₄ are fluorines or chlorines.

Particularly preferred compounds of Formula I are those where R₃ and R₄ are independently hydrogen, C₁₋C₆ alkyl, C₁₋C₆ alkoxy, or halogen, and R₅ is methyl or hydrogen, Z is a bond, A is methylene, methyl substituted methylene, or ethylene, R₁ is methyl or hydrogen, and R₁₁, R₁₂, and R₁₄ are fluorines or chlorines.

The term "prodrug group" denotes a moiety that is converted in vivo into the active compound of formula I wherein R₆ is hydroxy. Such groups are generally known in the art and include ester forming groups, to form an ester prodrug, such as benzyloxy, di(C₁₋C₆)alkylaminoethoxy, acetoxymethyl, pivaloyloxymethyl, phthalidoyl, ethoxycarbonyloxyethyl, 5-
methyl-2-oxo-1,3-dioxol-4-yl methyl, and \((C_1-C_6)\)alkoxy optionally substituted by N-morpholino and amide-forming groups such as di\((C_1-C_6)\)alkylamino. Preferred prodrug groups include hydroxy, and \(C_1-C_6\) alk oxy. Preferred compounds include the pharmaceutically acceptable salts of the compounds of Formula I e.g., those where \(R_s\) is O'M where M' represents a cation. Preferred cations include sodium, potassium, and ammonium. Other cations include magnesium and calcium. Further preferred prodrug groups include O'M' where M' is a divalent cation such as magnesium or calcium.

In certain situations, compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention include the pharmaceutically acceptable acid addition salts of compounds where \(R_s\) represents O'M and M' includes a basic nitrogen atom, i.e., an alkylamino or morpholino group. In addition, if the compound or prodrug of the invention is obtained as an acid addition salt, the free base can be
obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanolic such as acetic, HOOC-(CH₃)n-ACOOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

As used herein, the terms 2-benzothiazoyl and benzothiazol-2-yl are synonymous.

Representative groups of the formula

\[
\text{J} \quad \text{(CH₂)₇}
\]

include those where J is oxygen and each r is 2 (morpholiny1), J is nitrogen and each r is 2 (piperazinyl) or one r is 2 and the other 3 (homopiperazinyl), or J is CH₂ and each r is 2 (piperidiny1) or one r is 2 and the other 3 (homopiperidiny1).
Preferred groups of this formula are morpholinyl and piperazinyl.

The heterocyclic 5-membered ring having one to three nitrogen atoms, one of which may be replaced by oxygen or sulfur includes imidazolyl, oxazolyl, thiazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, and triazolyl.

The heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur includes triazinyl, pyrimidyl, pyridazinyl, oxazinyl and triazinyl.

The heterocyclic ring may be condensed with benzo so that said ring is attached at two neighboring carbon atoms to form a phenyl group. Such benzoheterocyclic ring may be attached to Z either through the heterocyclic group or through the benzo group of the benzoheterocyclic ring. Specific wherein said heterocyclic ring is condensed with a benzo include benzoazoxazolyl, quinazolin-2-yl, 2-benzimidazolyl, quinazolin-4-yl and benzothiazolyl. The oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms include positional isomers such as oxazolo[4,5-b]pyridine-2-yl, thiazolo[4,5-b]pyridine-2-yl, oxazolo[4,5-c]pyridine-2-yl, thiazolo[4,5-c]pyridine-2-yl, oxazolo[5,4-b]pyridine-2-yl, thiazolo[5,4-b]pyridine-2-yl, oxazolo[5,4-c]pyridine-2-yl, and thiazolo[5,4-c]pyridine-2-yl.
The following compounds of the invention are provided to give the reader an understanding of the compounds encompassed by the invention:

5-ethyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
3-methyl(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid
3-methyl(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-3 propionic acid

3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid

5 5-methyl-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid

3-(3-nitrophenyl)methyl-indole-N-acetic Acid

The above compounds, further described in the Examples and other description of the invention below, are illustrative but are not meant to limit in any way the scope of the contemplated compounds according to the present invention.

The compounds of the invention are administered to a patient or subject in need of treatment either alone or in combination with other compounds having similar or different biological activities. For example, the compounds of the invention may be administered in a combination therapy, i.e., either simultaneously in single or separate dosage forms or in separate dosage forms within hours or days of each other. Examples of such combination therapies include administering the compounds of Formula I with other agents used to treat hyperglycemia, hyperlipidemia, and diabetic complications.

Suitable compounds for use in combination therapy include

For Hyperglycemia:

Insulin
Metformin
Troglitazone
Pioglitazone
Rosiglitazone
Darglitazone
Sulfonylureas such as glipizide and glimepiride
Repaglinide
alpha-glucosidase inhibitors such as acarbose, miglitol

10 For Diabetic complications:

ACE inhibitors: Captopril, lisinopril
Angiotensin II receptor antagonists (AT1-receptor) such as
candesartan, losartan, irbesartan, and valsartan
MMP inhibitors

15 Protein kinase C inhibitors

For Antihyperlipidemia:

Statins such as Atorvastatin, simvastatin, pravastatin,
fluvastatin, lovastatin, cerivastatin

20 Fibrates such as Fenofibrate, bezafibrate, ciprofibrate,
gemfibrozil

The compounds of general Formula I may be administered
orally, topically, parenterally, by inhalation or spray or
rectally in dosage unit formulations containing conventional
non-toxic pharmaceutically acceptable carriers, adjuvants and
vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating
agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or
condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.
Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.
In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels on the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit
forms will generally contain between from about 1 mg to about 1000 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. General methods for synthesizing the compounds are presented below. It is understood that the nature of the substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below. More detailed procedures for particular examples are presented below in the experimental section.

Methods of Preparation

The compounds of the invention where Ar is benzothoniazoly1 can be conveniently prepared from a substituted indole moiety using general Scheme A set forth below.
Scheme A

Treatment of a nitrile indole IV with a strong base such as, for example, sodium hydride, butyl lithium or sodium tert-butoxide, in a polar aprotic solvent such as acetonitrile, tetrahydrofuran or N,N-dimethylformamide followed by an treatment with an alkylating agent, e.g., ethyl or tert-butyl bromoacetate, provides the desired N-alkylated product V. Alternatively, phase transfer catalysis can be used in a biphasic solvent system. A general review of such alkylations can be found in Sundberg, R. J. Indoles; Chapter 11, Academic Press Inc., San Diego, CA, 1996. Condensation with a suitable
2-amino thiophenol hydrochloride salt VI provides benzothiazole intermediate VII. These reactions are most often carried out in an alcohol solvents at elevated temperatures; however, other solvents like \( N,N \)-dimethylformamide and \( N \)-methylpyrrolidone can be used or the reactions can be carried out in the absence of solvents altogether. The scope of the reaction conditions useful for this transformation have been described previously (U.S. Pat. No. 5,700,819). General methods for the preparation of various substituted 2-amino thiophenols are also well known (J. Med. Chem. 1991, 34, 108 and Chem. Pharm. Bull. 1994, 42, 1264). In general, the best method of synthesis is determined by such factors as availability of starting materials and ease of synthesis. Deprotection of the alkanoic acid moiety VII can be carried out by methods common to those skilled in the art to result in compounds of Formula III. The method used in the deprotection depends on the type of protecting group. A description of such protecting groups and methods for deprotecting them may be found in: Protective Groups in Organic Synthesis, Second Edition, T. W. Green and P. G. M. Wuts, John Wiley and Sons, New York, 1991. When a methyl or ethyl ester is used, an aqueous sodium hydroxide solution in ethanol or dimethoxyethane is conveniently employed for its removal.

If not commercially available, nitrile IV can be prepared substantially as described below in Scheme B depicting the formation of 3-acetonitrile substituted indoles of Formula IV.
where Z is a bond. Thus, an indole moiety in a weak acid solution, for example, acetic acid in ethanol, is treated with aqueous formaldehyde and dimethyl amine in an alcohol solvent. The 3-(dimethylamino)methyl indole product can then be treated with sodium or potassium cyanide in N,N-dimethylformamide at elevated temperatures to provide the 3-acetonitrile substituted indole intermediate. Alternatively, an iminium salt like N,N-dimethylmethyleneammonium chloride can be used to prepare the 3-(dimethylamino)methyl indole intermediate.

![Diagram](image)

Scheme B

The 3-(dimethylamino)methyl indole intermediate can also be converted to the the 3-acetonitrile substituted indole intermediate via the trimethyl ammonium salt. The salt can be prepared by treating the gramine intermediate with an alkalating agent like methyl iodide. The trimethyl ammonium
salt intermediate can then be converted to the nitrile by treatment with sodium or potassium cyanide in a solvent like N,N-dimethylformamide. In general, the conversion to the acetonitrile occurs under more mild conditions when the trimethyl ammonium salt is used.


It is understood that, depending on the specific chemistry used, a protecting group, P, may be required. In general, P represents groups such as acyloxy, alkyl, sulfonyl or A-COOR.

Scheme C

In general, the intermediate compounds wherein $R_{2-6}$ is aryl or heteroaryl can be synthesized by the chemistry illustrated in reaction Scheme D below. For example, treatment of the potassium salt of an optionally substituted bromoindole with tert-butyllithium at low temperature in an ethereal solvent such as ether or tetrahydrofuran followed by the addition of an electrophile represents a general method for obtaining substituted indoles, as described by Rapoport, H. (J. Org. Chem. 1986, 51, 5106). For a discussion of a synthesis where R is acyl, see Bior. Med. Chem. Lett. 1999, 9, 333; where R is thiomethyl, see Heterocycles, 1992, 34, 1169; and where R is cycloalkyl, see J. Med. Chem. 1999, 42, 526.

More specifically the addition of a trialkyl borate followed by an acidic work-up provides the desired indole boronic acids (Heterocycles, 1992, 34, 1169). Indole boronic acids can be used in well established transition metal
catalyzed coupling reactions like the Suzuki reaction to provide aryl and heteroaryl indoles. These reactions are most often carried out in a mixture of ethereal or alcohol solvents with aqueous base in the presence of palladium catalyst, such as Pd(OAc)\(_2\), Pd(OAc)\(_2\) w/ PPh\(_3\), or Pd(PPh\(_3\))\(_4\), as described in *Tetrahedron Lett.* 1998, 39, 4467, *J. Org. Chem.* 1999, 64, 1372 and *Heterocycles* 1992, 34, 1395.

Alternatively, an optionally substituted bromoindole can be treated with an arylboronic acid and a palladium catalyst to provide arylindoles in large quantities (*Synlett* 1994, 93). A general review of Suzuki cross-couplings between boronic acids and aryl halides can be found in Miyaura, N; Suzuki, A. *Chem. Rev.* 1995, 95, 2457.

![Scheme D](image)

For example, treatment of the advanced intermediate indole X with an aryl or heteroaryl boronic acid using Pd-mediated coupling conditions provides the desired aryl and heteroaryl
indole product XI as shown in scheme (E). In general the utility of this method is determined by the ease of synthesis of advanced intermediates of type X and the commercial availability of aryl and heteroaryl boronic acids.

\[
\begin{align*}
\text{Br} & \quad \text{CN} \\
\text{X} & \quad \text{OEt} \\
\text{CN} & \quad \text{ArB(OH)_2, DME} \\
\text{Pd(OAc)_2, PPH_3,} & \quad 2 \text{M Na}_2\text{CO}_3 \\
\end{align*}
\]

Scheme E

In addition, certain organometallic reactions eliminate the need for de novo construction of the indole nucleus. For example, the Stille reaction serves as a general method for the synthesis of regiocontrolled substitution of indole intermediates as described by Farina, V.; Krishnamurthy, V; Scott, W., *Organic Reactions*, **1998**, *50*, 1-652. As indicated in the scheme below, the indole may serve as the organotin species or the aryl halide. The stannylindole (XII), where P is a suitable protecting group such as [2-(trimethyl)ethoxy]methyl (SEM) or an alkyl substituent, is treated with a variety of partners (i.e., vinyl/allylic halides, vinyl triflates, aryl/heteroaryl halides and acyl halides) in the presence of a Pd(0)Lₙ catalyst to provide the desired indoles (XII) (*Synnlett* 1993, 771, *Helv. Chim. Acta* 1993, *76*, 2356 and *J. Org. Chem.* 1994, *59*, 4250). Conversely, a haloindole (XIV) is treated with a variety of tin reagents under Stille conditions
to provide the desired substituted indoles (XV) as described in *Heterocycles* 1988, 27, 1585 and *Synth. Comm* 1992, 22, 1627).

A general procedure for the synthesis of intermediate compounds using amines of the formula NR$_x$R$_{x2}$ (NR$_x$R$_x$ in the scheme below) is given in scheme F below. In Scheme F, R$_x$ and R$_{x2}$ are the same or different and represent hydrogen, C$_1$-C$_6$ alkyl, or R$_x$ and R$_{x2}$ together represent a group of the formula:

$$\begin{array}{c}
\text{(CH}_2)_r
\end{array}$$

where J and each r is as defined above for formula I.

As shown in Scheme F, nucleophilic substitution of X (X is halogen, preferably fluorine) in an aromatic system is a method often used to substitute aromatic rings with amine and ether functionalities. Both 4- and 5-fluoro-2-nitrotoluene are sufficiently activated to undergo substitution with amines in the presence of K$_2$CO$_3$ in a polar aprotic solvent such as, for example, DMSO as described in *J. Med. Chem.* 1993, 36, 2716.
The Leimgruber-Batcho two-step method is a general process for the construction of the indole ring system from the appropriate o-nitrotoluene. This reaction involves the condensation of an o-nitrotoluene with \( N,N \)-dimethylformamide dimethyl acetal followed by a reductive cyclization under suitable conditions such as hydrogen over a palladium catalyst or Zn/HOAc as described in Sundberg, R.J. Indoles; Chapter 2, Academic Press Inc., San Diego, CA, 1996. A representative description of the process can also be found in Organic Synthesis, 1984, 63, 214.

\[
\begin{align*}
\text{R}_1^\text{H} & \xrightarrow{\text{K}_2\text{CO}_3} \text{R}_1^\text{H} \\
\text{DMSO, } & \Delta \\
\text{H}_2, \text{Pd/C} & \xrightarrow{55 \text{ psi}} \text{R}_1^\text{H} \\
\text{EtOAc/HOAc} & \xrightarrow{\text{or Zn/HOAc}} \\
\Delta & \xrightarrow{} \\
\end{align*}
\]

Scheme F

A general procedure for the synthesis of intermediate compounds wherein \( R \) is an aromatic, heteroaromatic or alkyl group is indicated in Scheme G below. As previously described, nucleophilic substitution of halogen, preferably fluorine, in an aromatic system is a method often used to substitute aromatic rings with amine and ether functionalities. Both 4- and 5-fluoro-2-nitrotoluene are sufficiently activated enough
to undergo substitution with alcohols or phenols in the presence of K₂CO₃ in a polar aprotic solvent such as DMSO. A similar system using KOH and phenol is described in J. Med. Chem. 1994, 37, 1955. Alternatively, solid-liquid phase transfer catalysis (PTC) methods have been used to prepare intermediate ethers of this type as described in Synth. Comm. 1990, 20, 2855. The appropriately substituted o-nitrotoluene can then be converted to the appropriate indole by the Leimgruber-Batcho method previously described.

\[
\begin{align*}
\text{F} & \text{NO}_2 \\
\text{ROH, K₂CO₃} & \text{DMSO, 80°C} \\
\text{R}^{\text{O}} & \text{MeO, DMF} \\
\Delta & \\
\text{Reduction} & \\
\text{R}^{\text{O}} & \text{H} \\
\end{align*}
\]

Scheme G

The preparation of intermediate alkoxy indole compounds wherein R is C₁-C₆ alkyl is outlined in Scheme H below. Commercially available nitrophenols can be alkylated under mild conditions with a base such as, for example, K₂CO₃ or Cs₂CO₃, in a polar aprotic solvent, e.g. CH₃CN, with a variety of suitable alkyl halides. See Synth. Comm. 1995, 25, 1367. The
alkoxy o-nitrotoluene can then be converted to the desired indole as described above.

![Chemical structure diagram]

Scheme H

Alternatively, some examples of the invention where Z is a bond and Ar is a substituted heterocycle such as a thiazole; or Z is amide and Ar is a substituted phenyl can be conveniently prepared from an indole 3-acetic acid derivative as illustrated in Scheme I. Using this method, the carboxylic acid moiety is activated and coupled with an aryl amine. Some examples of activating methods well-known to those skilled in the art include formation of acid chloride, mixed anhydrides and coupling reagents such as 1,3-dicyclohexylcarbodiimide (DCC). A review of such method can be found in Bodanszky, M. Principles of Peptide Synthesis; Springer-Verlag: New York, 1984. For the examples where Z is a bond and Ar is a substituted benzothiazole or benzoxazole, the intermediate amide or thioamide can be cyclized into the aromatic ring. Examples of these types of heterocycle forming reactions are described in Mylar, B. L. et al. J. Med. Chem. 1991, 34, 108.
In addition, the carboxylic acid can be converted to a chloro- or bromomethyl ketone and condensed with nucleophiles like thioamides or 2-aminothiophenols to produce thiazole or benzothiazine derivatives. Examples of methods to prepare the chloro- and bromomethyl ketones are illustrated in Rotella, D.P.; Tetrahedron Lett. 1995, 36, 5453 and Albeck, A.; Persky, R.; Tetrahedron 1994, 50, 6333. Depending on the reaction conditions in a given synthetic sequence a protecting group may be required. It is also understood that the specific order of steps used in the synthesis depends on the particular example being prepared. P may represent H, A-COOH, A-COO-lower alkyl or a simple protecting group that can be removed at a late stage of the synthesis. When such a protecting group is used, the A-CO2R6 group can be introduced near the end of the synthesis after the Z-Ar group has been assembled. Method of introducing the Z-Ar group are similar to those already described.
Another strategy involves the synthesis of substituted indoles via an intramolecular cyclization of an aniline nitrogen onto a substituted alkyne as shown in Scheme I.
Typical approaches utilize commercially available o-iodoaniline derivatives. When these intermediates are unavailable, the regioselective ortho iodination of aromatic amines is used to generate the required intermediate (*J. Org. Chem.* 1996, 61, 5804). For example, Iodophenyl intermediates are treated with trimethylsilylacetylene in the presence of a Pd catalyst and a Cu(I) source, such as cupric iodide, to produce o-alkynylanilines. See *Heterocycles*, 1996, 43, 2471 and *J. Org. Chem.* 1997, 62, 6507. Further elaboration of the o-alkynylaniline to the desired indole can be done by a copper-mediated cyclization or a base-induced amine ring closure onto the alkyne functionality (*J. Med. Chem.* 1996, 39, 892). Alternative modifications have been made in the acetylenic derivatives to generate more elaborate indole structures as described in *J. Am. Chem. Soc.* 1991, 113, 6689, *Tetrahedron Lett.* 1993, 24, 2823 and *Tetrahedron Lett.* 1993, 34, 6471.

\[
\text{Reduction} \quad \xrightarrow{\text{RO}} \quad \text{Scheme J}
\]

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary.
to achieve some of the above transformations. In general, the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The preparation of the compounds of the present invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example 1:

Preparation of 2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

2-Methyl-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 2-methylindole was used instead of 5-chloroindole in part 1: 178-180°C; 1H NMR (DMSO-d6, 300 MHz) δ 7.75-7.62 (m, 1 H), 7.45 (d, J = 9.0 Hz, 1 H), 7.39 (d, J = 9.0 Hz, 1 H), 7.08 (t, J = 9 Hz, 1 H), 6.99 (t, J = 9.0 Hz, 6.99 (t, J = 9.0 Hz,
1 H), 5.00 (s, 2 H), 4.60 (s, 2 H), 2.38 (s, 3 H); LRMS calc'd for C_{19}H_{13}F_{3}N_{2}O_{2}S: 390.0; found 391.0 (M + 1)'. Anal. Calcd for C_{19}H_{13}F_{3}N_{2}O_{2}S: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.47; H, 3.29; N, 7.12; S, 8.18.

Example 2:

Preparation of 5-chloro-3-((4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid

\[
\text{\begin{tikzpicture}
\node[draw,shape=circle,fill=black,minimum size=5pt,inner sep=0pt] at (0,0) (a) {};
\end{tikzpicture}}
\]

5-chloroindole-3-acetonitrile:

A solution of aqueous formaldehyde (37%, 2.95 mL, 66.0 mmol) and dimethylamine (40%, 5.30 mL, 66.0 mmol) in 20 mL EtOH was cooled to 0°C. 5-Chloroindole (4.0 g, 26.4 mmol) was dissolved in a HOAc:EtOH mixture (1:1, 40 mL) and added dropwise to the reaction mixture. After stirring at this temperature for 2 h, the mixture was allowed to warm to room temperature and stir overnight. The mixture was added to a sat’d solution of NaHCO₃. 1 N NaOH was added until the pH was between 9-10. The resulting mixture was extracted with CH₂Cl₂ (3X). The organics were combined and washed with a sat’d aq. NaCl, dried over MgSO₄, filtered and concentrated in vacuo to give 4.65 g (85%) of 5-chloro-3-[(dimethylamino)methyl] indole
as a yellow powder. Without further purification, 5-chloro-3-
[(dimethylamino)methyl] indole (4.65 g, 22.4 mmol) was
dissolved in dimethylformamide (80 mL) at room temperature with
stirring. To this was added KCN (2.18 g, 33.5 mmol) in H₂O (10
mL). The mixture was warmed to 140 °C and stirred for 14 h. H₂O
was added and the mixture was extracted with EtOAc (2X). The
organics were combined and washed with sat’d brine, dried over
MgSO₄, filtered and concentrated in vacuo. The residue was
purified by SiO₂ flash chromatography (3:2, Heptane: EtOAc) to
give 2.65 g (63%) of 5-chloroindole-3-acetonitrile. ¹H NMR
(DMSO-d₆, 300 MHz) δ 11.30 (br s, 1 H), 7.63 (s, 1 H), 7.42-
7.38 (m, 2 H), 7.05 (d, J = 6.0 Hz, 1 H), 5.70 (s, 2 H),

5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-
acetic acid:

5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-
indole-N-acetic acid was prepared in a manner analogous to that
set forth in Example 3 (parts 1-7), except 5-chloroindole-3-
acetonitrile was used instead of 3-indolyl acetonitrile in part
5: mp 188-189 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.73-7.68 (m, 1
H), 7.63 (d, J = 1.8 Hz, 1 H), 7.51 (s, 1 H), 7.45 (d, J = 9.0
Hz, 1 H), 7.14 (dd, J₁ = 9.0, J₂ = 2.4 Hz, 1 H), 5.04 (s, 2 H),
4.65 (s, 2 H); LRMS calcd for C₁₈H₁₅F₃N₂O₂SCl: 410.0; found 411.0
(M + 1)⁺. Anal. Calcd for C₁₈H₁₅F₃N₂O₂SCl: C, 52.63; H, 2.45; N,
6.82; S, 7.81. Found: C, 52.56; H, 2.40, N, 6.71, S, 7.72.
Example 3:

**Preparation of 3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid**

2,3,5,6-Tetrafluoroacetanilide:

A solution of 2,3,5,6-tetrafluoroaniline (200 g, 1.21 mol) in anhydrous pyridine (103 mL, 1.27 mol) was treated with acetic anhydride (120 mL, 1.27 mol) and heated to 120 °C for 2 h. After cooling to room temperature, the solution was poured into ice-cold water (500 mL). The resulting precipitate was filtered, dissolved in ethyl acetate, dried over MgSO₄, filtered and concentrated. The solid material was washed with heptane (200 mL) and dried to give 2,3,5,6-tetrafluoroacetanilide as a white crystalline solid (206 g, 82%): mp 136-137 °C; Rf 0.48 (50% ethyl acetate in heptane); ¹H NMR (DMSO-d₆, 300 MHz) δ 10.10 (s, 1 H), 7.87-7.74 (m, 1 H), 2.09 (s, 3 H). Anal. Calcd for C₈H₅F₂NO: C, 46.39; H, 2.43; N, 6.67. Found C, 46.35; H, 2.39; N, 6.68.

2,3,5,6-Tetrafluorothioacetanilide:

A flame-dried, 4-necked 5,000 mL round-bottomed flask was charged with phosphorous pentasulfide (198 g, 0.45 mol) and
diluted with anhydrous benzene (3,000 mL, 0.34 M). 2,3,5,6-
tetrafluoroacetanilide (185 g, 0.89 mol) was added in one
portion and the bright yellow suspension was heated to a gentle
reflux for 3 h. The solution was cooled to 0 ºC and filtered.
The insoluble material was washed with ether (2 x 250 mL) and
the combined filtrate was extracted with 10%aq. NaOH (750 mL,
500 mL). After cooling the aqueous layer to 0 ºC, it was
carefully acidified with conc. HCl (pH 2-3). The precipitated
product was collected by filtration and washed with water (500
mL). The yellow-orange material was dissolved in ethyl acetate
(1,000 mL), dried over MgSO₄ and activated charcoal (3 g),
filtered through a short pad of silica (50 g), and
concentrated. The resulting solid was triturated with heptane
(500 mL) and filtered to give 2,3,5,6-
tetrafluorothioacetanilide (174.9 g, 88%): mp: 103-104ºC; Rf
0.67 (50% ethyl acetate in heptane); ¹H NMR (DMSO-d₆, 300 MHz)
δ 11.20 (s, 1 H), 8.00-7.88 (m, 1 H), 2.66 (s, 3 H). Anal.
Calcd for C₇H₆F₃NS: C, 43.05; H, 2.26; N, 6.28. Found C,
43.10; H, 2.23; N, 6.19.

4,5,7-Trifluoro-2-methylbenzothiazole:

A flame-dried 5,000 mL round-bottomed flask equipped with
over-head stirrer was charged with sodium hydride (15.9 g, 0.66
mol) and diluted with anhydrous toluene (3,000 mL, 0.2 M). The
suspension was cooled to 0 ºC, and treated with 2,3,5,6-
tetrafluorothioacetanilide (134 g, 0.60 mol) in one portion.
The solution was warmed to room temperature over 1 h, then heated to a gentle reflux. After 30 min, dimethylformamide (400 mL) was carefully added and the mixture was stirred for an additional 2 h. The solution was cooled to 0 °C and added to ice-water (2,000 mL). The solution was extracted with ethyl acetate (1,500 mL) and washed with sat’d. aq. NaCl (1,000 mL). The organic layer was concentrated to dryness, diluted with heptane and successively washed with water (300 mL) and sat’d. aq. NaCl (1,000 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give 4,5,7-trifluoro-2-methylbenzothiazole (116.8 g, 96%) as a light brown solid: mp: 91-92 °C; Rₚ 0.56 (30% ethyl acetate in heptane); ¹H NMR (DMSO-d₆, 300 MHz) δ 7.76-7.67 (m, 1 H), 2.87 (s, 3 H); . Anal. Calcd for C₅H₄F,NS: C, 47.29; H, 1.98; N, 6.82; S, 15.78. Found C, 47.56; H, 2.07; N, 6.82; S, 15.59.

2-Amino-3,4,6-trifluorothiophenol Hydrochloride:

A solution of 4,5,7-trifluoro-2-methylbenzothiazole (25.0 g, 123 mmol) in ethylene glycol (310 mL, 0.4 M) and 30% aq. NaOH (310 mL, 0.4 M) was degassed using a nitrogen stream then heated to a gentle reflux (125 °C) for 3 h. The solution was cooled to 0 °C and acidified to pH 3-4 using conc. HCl (approx. 200 mL). The solution was extracted with ether (750 mL) and washed with water (200 mL). The organic layer was dried over Na₂SO₄, filtered and treated with 2,2-di-tert-butyl-4-methylphenol (0.135 g, 0.5 mol%). After concentrating to
dryness, the crude product was dissolved in anhydrous methanol (200 mL) and treated with an HCl solution in 1,4-dioxane (37 mL, 4 N, 148 mmol). The resulting mixture was concentrated to dryness, triturated with isopropylether (100 mL) and filtered to give 2-amino-3,4,6-trifluorothiophenol hydrochloride (19.3 g, 73%) as a light brown solid that was used without further purification. mp. 121-124 C; Rf 0.43 (30% ethyl acetate in heptane); Anal. Calcd for C9H6ClF3NS: C, 33.42; H, 2.34; N, 6.50; S, 14.87. Found C, 33.45; H, 2.27; N, 6.48; S, 14.96.

3-cyanomethyl-indole-N-acetic acid, Ethyl Ester:

Under an atmosphere of nitrogen, a solution of 3-indolyl acetonitrile (25.0 g, 160 mmol) in dry acetonitrile (530 mL, 0.3 M) was treated with sodium hydride (95%, 4.2 g, 168 mmol) and stirred for 30 min. Ethyl bromoacetate (21.3 mL, 192 mmol) was added in a dropwise manner over 10 min and the solution was stirred at room temperature for 16 h. After concentrating under reduced pressure, the resulting residue was dissolved in ethyl acetate and washed with sat’d. aq. NaCl. The organic extracts were dried over MgSO4, filtered and concentrated. The crude product was recrystallized from heptane and ethyl acetate to give the target compound as a white crystalline solid (19 g, 49%): mp 98-99 °C; Rf 0.29 (30% ethyl acetate in heptane); 1H NMR (DMSO-d6, 300 MHz) δ 7.59 (dd, J1 = 7.8 Hz, J2 = 0.6 Hz, 1 H), 7.40 (dd, J1 = 8.1 Hz, J2 = 0.6 Hz, 1 H), 7.36 (s, 1 H), 7.18 (b t, J = 7.2 Hz, 1 H), 7.10 (b t, J = 7.2 Hz, 1 H), 5.12
(s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.06, (s, 2 H), 1.20 (t, J = 7.2 Hz, 3 H); LRMS calcd for C_{14}H_{18}N_{2}O_{2}: 242.3; found 243.0 (M + 1)^{+}. Anal. Calcd for C_{14}H_{18}N_{2}O_{2}: C, 69.49; H, 5.82; N, 11.56. Found C, 69.39; H, 5.89; N, 11.59.

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, Ethyl Ester: Under a nitrogen atmosphere, a solution of 3-acetonitrile-indole-N-acetic acid, ethyl ester (11.0 g, 45.4 mmol) in anhydrous ethanol (90 mL, 0.5 M) was treated with 2-amino-3,4,6-trifluorothiophenol hydrochloride (12.7 g, 59.0 mmol) and heated to a gentle reflux for 16 h. After cooling to room temperature, the solution was concentrated under reduced pressure, diluted with ethyl acetate and washed with 2N HCl and sat’d. aq. NaCl. The organic layer was dried over MgSO_{4}, filtered and concentrated. Purification by MPLC (10-50% ethyl acetate in heptane, 23 mL/min, 150 min) to give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester (6.0 g, 36%) as a white crystalline solid: mp 110-111 °C; R_{f} 0.41 (30% ethyl acetate in heptane);

^{1}H NMR (DMSO-d_{6}, 300 MHz) δ 7.74-7.66 (m, 1 H), 7.54 (d, J = 7.8 Hz, 1 H), 7.46 (s, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.15 (br t, J = 6.9 Hz, 1 H), 7.04 (br t, J = 7.8 Hz, 1 H), 5.14, s, 2 H), 4.66 (s, 2 H), 4.14 (q, J = 7.2 Hz, 3 H); LRMS calcd for C_{20}H_{13}F_{3}N_{2}O_{2}S: 404.4; found 405.0 (M + 1)^{+}. Anal. Calcd for C_{20}H_{13}F_{3}N_{2}O_{2}S: C, 59.40; H,3.74; N, 6.93; S, 7.93. Found C, 59.52; H, 3.721 N, 6.92; S, 8.04.

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3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid:

A solution of give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester (5.91 g, 14.6 mmol) in 1,2-dimethoxyethane (73 mL, 0.2 M) was cooled to 0 °C and treated with aq. NaOH (1.25 N, 58 mL, 73.1 mmol) in a dropwise manner over 15 min. After the addition was complete, the solution was stirred for an additional 30 min, acidified to pH 3 with 2N HCl, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with sat’d. aq. NaCl (30 mL). The organic extract was dried over Na₂SO₄, filtered and concentrated. The resulting material was stirred as a suspension in heptane, filtered and dried to give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid (5.38 g, 98%) as a pale yellow solid: mp 177-178 °C; Rₖ 0.44 (20% methanol in dichloromethane); 'H NMR (DMSO-d₆, 300 MHz) δ 7.74-7.65 (m, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.46 (s, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.15 (b t, J = 6.9 Hz, 1 H), 7.03 (b t, J = 7.2 Hz, 1 H), 5.03 (s, 2 H), 4.65 (s, 2 H); LRMS calcd for C₁₅H₁₁F₃N₂O₂S: 376.4; found 375.0 (M - 1)⁻. Anal. Calcd for C₁₅H₁₁F₃N₂O₂S: C, 57.44; H, 2.95; N, 7.44; S, 8.52. Found C, 57.58; H, 2.99; N, 7.38; S, 8.51.

Example 4:
Preparation of 5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

5-Methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-methylindole was used instead of 5-chloroindole in part 1: mp 131-133 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.73-7.62 (m, 1 H), 7.39 (s, 1 H), 7.30 (s, 1 H), 7.27 (d, J = 9.0 Hz, 1 H), 6.96 (dd, J₁ = 9.0 Hz, J₂ = 2.4 Hz, 1 H), 4.98 (s, 2 H), 4.60 (s, 2 H), 2.32 (s, 3 H); LRMS calcd for C₁₃H₁₂F₂N₂O₂S: 390.0; found 391.0 (M + 1)⁺. Anal. Calcd for C₁₉H₁₄F₂N₂O₂S: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.36; H, 3.30, N, 7.10, S, 8.20.

Example 5:

Preparation of 7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-Methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 7-methylindole was used instead of 5-chloroindole in part 1: mp 216-218 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.73-7.63 (m, 1H), 7.36-7.32 (m, 2 H), 6.92-6.88 (m,
2 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 2.55 (s, 3 H); LRMS calcd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S: 390.0; found 391.0 (M + 1)<sup>+</sup>. Anal. Calcd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.37; H, 3.37; N, 7.11; S, 8.13.

Example 6:

Preparation of 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

6-Chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except 6-chloroindole was used instead of 5-chloroindole in part 1: mp 194-195°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.73-7.63 (m, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.46-7.42 (m, 2 H), 7.00 (dd, J<sub>1</sub> = 8.4 Hz, J<sub>2</sub> = 2.1 Hz, 1 H), 4.76 (s, 2 H), 4.62 (s, 2 H); LRMS calcd for C<sub>18</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S: 410.0; found 411.0 (M + 1)<sup>+</sup>. Analysis calculated for C<sub>18</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S: C, 52.63; H, 2.45; N, 6.82; S, 7.81. Found: C, 52.50; H, 2.44, N, 6.74, S, 7.69.

Example 7:

Preparation of 5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid
5-Benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methylindole-\textit{N}-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-benzyloxyindole was used instead of 5-chloroindole in part 1: mp 165-168°C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.73-7.65 (m, 1 H), 7.40-7.30 (m, 3 H), 7.28-7.10 (m, 4 H), 7.10 (d, $J = 2.4$ Hz, 1 H), 6.87-6.80 (m, 1 H), 5.05 (s, 2 H), 4.95 (s, 2 H), 4.57 (s 2 H); LRMS calcd for C$_{25}$H$_{17}$F$_3$N$_2$O$_2$S: 482.0; found 483.0 (M + 1)*.

Example 8:

\textbf{Preparation of 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-\textit{N}-acetic acid}  

6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methylindole-\textit{N}-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 6-fluoroindole was used instead of 5-chloroindole in part 1: mp 200-203 C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.73-7.65 (m, 1 H), 7.53 (dd, $J_1 = 8.4$ Hz, $J_2 = 3.3$ Hz, 1 H), 7.44 (s, 1 H), 7.34 (dd, $J_1 = 10.5$ Hz, $J_2 = 2.4$ Hz, 1 H), 6.93-6.68 (m, 1 H), 5.11 (s, 2 H), 4.64 (s, 2 H); LRMS calcd for C$_{18}$H$_{16}$F$_4$N$_2$O$_2$S: 394.0; found 395 (M + 1).
Example 9:

Preparation of 5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-fluoroindole was used instead of 5-chloroindole in part 1: mp 193-195°C; \(^1\)H NMR (DMSO-d\(_6\), 300 MHz) \(\delta\) 7.65 (m, 1 H), 7.51 (s, 1 H), 7.42 (br dd, \(J_1 = 9.0\) Hz, \(J_2 = 4.8\) Hz, 1 H), 7.34 (br dd, \(J_1 = 9.9\) Hz, \(J_2 = 2.4\) Hz, 1 H), 7.02-6.96 (m, 1 H), 5.03 (s, 2 H), 4.62 (s, 2 H); LRMS calcd for \(C_{16}H_{10}F_4N_2O_2S\): 394.0; found 395 (M + 1).

Example 10:

Preparation of 6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 6-methylindole was used instead of 5-chloroindole in part 1: mp 211-213°C, \(R_f 0.50\) (10% methanol in dichloromethane); \(^1\)H NMR (DMSO-d\(_6\), 300 MHz) \(\delta\) 7.72-7.63 (m, 1 H), 7.37 (d, \(J = 7.1\) Hz, 1 H), 7.35 (s, 1 H), 7.18
(s, 1 H), 6.85 (d, J=8.4 Hz, 1 H), 5.08 (s, 2 H), 4.60 (s, 2 H), 2.37 (s, 3 H).

Example 11:

Preparation of 3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic Acid

3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic Acid was prepared in a manner analogous to that set forth in Example 3 (parts 5-7), except 2-amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2-amino-3,4,6-trifluorothiophenol hydrochloride in part 6: mp 233-234 °C; 'H NMR (DMSO-d₆, 300 MHz) δ 8.29 (s, 1 H), 8.19 (br d, J = 8.1 Hz, 1 H), 7.68 (br d, J = 9.0 Hz, 1 H), 7.49 (br d, J = 6.9 Hz, 1 H), 7.41 (s, 1 H), 7.38 (br d, J = 8.4 Hz, 1 H), 7.12 (br t, J = 6.9 Hz, 1 H), 7.00 (br t, J = 6.9 Hz, 1 H), 5.01 (s, 2 H), 4.60 (s, 2 H).

Example 12:

Preparation of 5-Methyl-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid

5-Methyl-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except 5-methylindole was used instead of 5-chloroindole in part 1 and, 2-amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2-amino-3,4,6-trifluorothiophenol hydrochloride in part 2 (Example 3, part
Example 13:

Preparation of 3-(3-nitrophenyl)methyl-indole-N-acetic acid

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\[ \text{Preparation of indole-N-acetic acid, ethyl ester} \]

Under an atmosphere of nitrogen, a solution of indole (15.0 g, 128 mmol) in dry acetonitrile (300 mL, 0.4 M) was treated with sodium hydride (95%, 3.69 g, 153 mmol) and stirred for 30 min. Ethyl bromoacetate (17.0 mL, 153 mmol) was added in a dropwise manner over 10 min and the solution was stirred at room temperature for 16 h. After concentrating under reduced pressure, the resulting residue was dissolved in ethyl acetate and washed with sat’d. aq. NaCl. The organic extracts were dried over MgSO₄, filtered and concentrated. The crude product was purified by flash column chromatography (50% ethyl acetate in heptane): Rf0.25 (40% ethyl acetate in heptane) \(^1\text{H} \)

NMR (DMSO-d₆, 300 MHz) \( \delta \) 7.53 (d, \( J = 6.3 \text{ Hz}, 1 \text{ H} \)), 7.38-7.31
(m, 2 H), 7.11 (br t, J = 7.2 Hz, 1 H), 7.02 (br t, J = 7.2 Hz, 1 H), 6.45-6.43 (m, 1 H), 5.10 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H).

Preparation of 3-(3-nitrophenyl)methyl-indole-N-acetic acid, ethyl ester

Indole-N-acetic acid, ethyl ester (0.500 g, 2.50 mmol) was dissolved in 1,4-dioxane (5 mL) at room temperature with stirring. To this solution was added Ag₂CO₃/Celite (50% by weight, 0.500 g, 0.9 mmol). The mixture was warmed to 90°C and maintained overnight. H₂O was added to the reaction mixture followed by extracted with EtOAc (2X). The organics were combined and washed with a sat’d brine solution, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by SiO₂ flash chromatography (3:2 Heptane: EtOAc) to give 180 mg (22%) as a pale yellow oil. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.10 (s, 1H), 8.02 (d, J = 8.1 Hz, 1 H), 7.75 (d, J = 7.2 Hz, 1 H), 7.59-7.57 (m, 1 H), 7.46-7.39 (m, 1 H), 7.33 (d, J = 8.1 Hz, 1 H), 7.20 (s, 1 H), 7.13-6.89 (m, 2 H), 5.06 (s, 2 H), 4.19 (s, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 1.18 (t, J = 7.2 Hz, 3 H).

Preparation of 3-(3-nitrophenyl)methyl-indole-N-acetic Acid

3-(3-Nitrophenyl)methyl-indole-N-acetic Acid, ethyl ester (0.175 g, 0.5 mmol) was dissolved in THF: EtOH (1:4, 5 mL) at
room temperature with stirring. The mixture was cooled to 0°C and treated with 1N NaOH (1.55 mL, 1.6 mmol). The mixture was allowed to stir at this temperature for 2 h. 1 N HCl was added and the mixture extracted with EtOAc (2X). The organics were combined and washed with a sat’d brine solution, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with heptane and vacuum-filtered with several heptane washings to give 110 mg (69%) the desired compound as an off-white powder. mp 163-165 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ

8.11 (s, 1 H), 8.03 (d, J = 8.1 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.53 (t, J = 8.1 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.20 (s, 1 H), 7.11 (t, J = 7.2 Hz, 1 H), 6.97 (t, J = 7.2 Hz, 1 H), 4.96 (s, 2 H), 4.18 (s, 2 H);
LRMS calcd for C₁₇H₁₄N₂O₄S: 310.0; found 311 (M + 1)⁺.

Example 14

Preparation of 2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

![Chemical Structure](image)

2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 2-phenylindole was used instead of 5-chloroindole in part 1: mp 238-239°C; Rₙ 0.60 (10%
methanol in chloroform); 'H NMR (DMSO-d$_6$, 300 MHz) $\delta$ 7.60-7.70 (m, 1H), 7.39-7.58 (m, 7H), 7.20 (t, $J = 9$ Hz, 1H), 7.07 (t, $J = 9$ Hz, 1H), 4.80 (s, 2H), 4.45 (s, 2H); LRMS calcd for C$_{24}$H$_{15}$F$_3$N$_2$O$_2$S: 452.0; found 453.0 (M + 1)$^*$. Anal. Calcd for C$_{24}$H$_{15}$F$_3$N$_2$O$_2$S: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.46; H, 3.32; N, 6.11; S, 6.96.

**Example 15**

**Preparation of 5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid**

3-cyanomethyl-5-phenyl-indole-N-acetic acid, ethyl ester

5-Bromo-3-cyanomethyl-indole-N-acetic acid, ethyl ester (1.0 g, 3.1 mmol) and phenylboronic acid (0.418 g, 3.4 mmol) were dissolved in anhydrous DME at room temperature under a nitrogen atmosphere and treated with Pd(OAc)$_2$ (2.1 mg, 0.0093 mmol) and PPh$_3$ (7.4 mg, 0.028 mmol). This mixture was heated to reflux and 2 M Na$_2$CO$_3$ (3.11 mL, 6.2 mmol) was added via syringe. After 12h, the mixture was cooled to room temperature and added to H$_2$O (50mL). The resultant mixture was extracted with EtOAc (2X, 100mL) and the organics were combined and washed with a sat'd aqueous NaCl solution, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by SiO$_2$ flash chromatography (heptane to 1:1 heptane/ EtOAc) to give the desired material as a white solid (445 mg, 45%); 'H NMR (DMSO-d$_6$, 300 MHz) $\delta$ 7.64-7.74 (m, 4H), 7.39-7.44 (m, 4H),
7.29-7.34 (m, 1H), 5.20 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.08 (s, 2H), 1.20 (t, J = 7.2 Hz, 3H).

5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-phenyldindole was used instead of 5-chloroindole in part 1: mp 156-159 °C; Rf 0.55 (10% methanol in chloroform); 1H NMR (DMSO-d6, 300 MHz) δ 7.66-7.69 (m, 4H), 7.57-7.60 (m, 1H), 7.39-7.47 (m, 3H), 7.29-7.35 (m, 2H), 5.06 (s, 2H), 4.66 (s, 2H); LRMS calcd for C24H15F3N2O2S: 452.0; found 453.0 (M + 1)+. Anal. Calcd for C24H15F3N2O2S: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.54; H, 3.32; N, 6.13; S, 7.01.

Example 16

Preparation of 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

Part 1: 6-Phenyldindole

A solution of 6-bromoindole (2.0 g, 10.20 mmol) in anhydrous toluene (20mL) under a nitrogen atmosphere was treated with Pd[P(Ph3)]4 (10% mol). After stirring the mixture for 30 min., phenylboronic acid (1.87 g, 15.30 mmol) in anhydrous EtOH (10 mL) was added followed by the addition of sat’d NaHCO3 (6mL). The bi-phasic mixture was heated to reflux for 24 h. After cooling to room temperature, the mixture was
added to a sat'd brine solution and extracted with EtOAc (2X).
The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 CH₂Cl₂/ heptane) to give the desired material as white powder (900 mg, 45%): ¹H NMR (DMSO-d₆, 300 MHz) δ 11.15 (br s, 1H), 7.58-7.66 (m, 4H), 7.41-7.47 (m, 2H), 7.36 (m, 1H), 7.26-7.31 (m, 2H), 6.42 (m, 1H).

Preparation of 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 6-phenylindole was used instead of 5-chloroindole in part 1: mp 156-159°C; R₄ 0.50 (10% methanol in chloroform); ¹H NMR (DMSO-d₆, 300 MHz) δ 7.65-7.75 (m, 4H), 7.57-7.62 (m, 1H), 7.41-7.50 (m, 3H), 7.26-7.38 (m, 2H), 5.12 (s, 2H), 4.68 (s, 2H); LRMS calcd for C₂₄H₁₅F₃N₂O₂S: 452.0; found 453.0 (M + 1)⁺. Anal. Calcd for C₂₄H₁₅F₃N₂O₂S: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.46; H, 3.33; N, 6.10; S, 6.96.

Example 17

Preparation of 5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid
5-Morpholino-2-nitrotoluene

A mixture of 5-fluoro-2-nitrotoluene (5.11 g, 32.9 mmol), morpholine (4.31 mL, 49.4 mmol) and K₂CO₃ (6.83 g, 49.4 mmol) was diluted in anhydrous DMSO (80 mL) at room temperature with stirring. The mixture was heated to 80°C for 24 h. After cooling to room temperature, H₂O was added and the resultant mixture was extracted with EtOAc (3X, 50 mL). The organic layer was washed with sat’d aqueous NaCl (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The remaining solid was triturated in heptane (200 mL) and filtered to give the desired material (7.10 g, 97%) as a yellow powder: Rₖ 0.40 (75% heptane/ 25% ethyl acetate). ¹H NMR (DMSO-d₆, 300 MHz) δ 7.96 (d, J = 9.9 Hz, 1H), 8.85-8.88 (m, 2H), 3.70 (t, J = 5.0 Hz, 4H), 3.35 (t, J = 5.0 Hz, 4H), 2.53 (s, 3H).

Preparation of 5-Morpholinoindole

Under an atmosphere of nitrogen, a solution of 5-morpholiny1-2-nitrotoluene (7.0 g, 31.5 mmol) in DMF (100mL) was treated with dimethylformamide dimethyl acetal (4.81 mL, 36.2 mmol) and pyrrolidine (2.62 mL, 31.5 mL). The mixture was heated to 100°C and maintained for 12 h. After cooling, the
mixture was concentrated in vacuo to give the desired intermediate as a brick-red solid.

The intermediate enamine was dissolved in EtOAc (200 mL) and added to a pre-charged Parr bottle with 10% Pd/C (600 mg) in EtOAc (40 mL). The mixture was hydrogenated on a Parr-shaker at 55 psi for 2.5 h. The catalyst was filtered through a Celite plug with several washings with EtOAc and the remaining filtrate concentrated in vacuo. The residue was purified by SiO₂ flash chromatography (1:1 Hept/EtOAc) to give 2.0 g (31% over 2 parts) of the desired indole as a cream powder: R₅ 0.30 (10% methanol in chloroform); ¹H NMR (DMSO-d₆, 300 MHz) δ 10.77 (br s, 1H), 7.24 (s, 1H), 7.18-7.20 (m, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.81 (dd, J₁ = 8.7 Hz, J₂ = 2.1 Hz, 1H), 6.25 (dd, J₁ = 3.0 Hz, J₂ = 1.8 Hz, 1H), 3.7 (t, J = 4.50 Hz, 4H), 2.96 (t, J = 4.50 Hz, 4H).

Preparation of 5-morpholino-3(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-morpholinindoIndole was used instead of 5-chloroindole. ¹H NMR (DMSO-d₆, 300 MHz) δ 7.64-7.72 (m, 1H), 7.34 (s, 1H), 7.26 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.91 (dd, J₁ = 9.0 Hz, J₂ = 2.4 Hz, 1H), 4.95 (s, 2H), 4.60 (s, 2H), 3.70-3.73 (m, 4H), 2.97-3.00 (m, 4H).
4H); LRMS calcd for C_{22}H_{18}F_{3}N_{3}O_{3}S: 461.0; found 462 (M + 1)⁺.
Anal. Calcd for C_{22}H_{18}F_{3}N_{3}O_{3}S·H_{2}O: C, 55.11; H, 4.20; N, 8.76; S, 6.69. Found: C, 55.11; H, 4.05; N, 8.57; S, 6.50.

5

Example 18

Preparation of 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid

Preparation of 4-Morpholino-2-nitrotoluene

A mixture of 4-fluoro-2-nitrotoluene (15.34 g, 98.9 mmol), morpholine (12.94 mL, 49.4 mmol) and K₂CO₃ (6.83 g, 148.3 mmol) were diluted in anhydrous DMSO (250 mL) at room temperature with stirring. The mixture was heated to 120°C for 24 h. After cooling to room temperature, H₂O was added and the resultant mixture was extracted with EtOAc (3X, 75 mL). The organic layer was washed with sat'd brine (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The remaining solid was triturated in heptane (200 mL) and filtered to give the desired material (8.00 g, 36.4%) as a yellow powder: R₉ 0.40 (25% ethyl acetate in heptane). ¹H NMR (DMSO-d₆, 300 MHz) δ 7.40 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.20 (dd, J₁ = 8.7 Hz, J₂ = 2.7 Hz, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.35 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H).

25 Preparation of 6-Morpholinoindole

Under an atmosphere of nitrogen, a solution of 4-morpholino-2-nitrotoluene (7.1 g, 31.9 mmol) in DMF (100 mL)
was treated with dimethylformamide dimethyl acetal (4.92 mL, 37.1 mmol) and pyrrolidine (2.67 mL, 31.9 mL). The mixture was heated to 100°C and maintained for 12 h. After cooling, the mixture was concentrated in vacuo to give the desired intermediate as a brick-red solid. The crude intermediate was dissolved in glacial HOAc (250 mL) and warmed to 85°C. Zn (18.17 g, 0.278 mol) was added to the solution portionwise over 30 min. The mixture was heated for 4 h. After cooling to room temperature, the mixture was neutralized with sat'd NaHCO₃ and extracted with Et₂O (3X, 300 mL). The combined organics were washed with sat'd brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by SiO₂ flash chromatography (heptane to 2:1 heptane/EtOAc) to give the desired material as a white crystalline powder (1.0 g, 11% over 2 parts): Rₜ 0.50 (2:1 Heptane/EtOAc); ¹H NMR (DMSO)-d₆, 300 MHz) δ 10.73 (br s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.80 (s, 1H), 6.73 (dd, J₁ = 8.4 Hz, J₂ = 2.4 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 3.72 (t, J = 4.8 Hz, 4H), 3.02 (t, J = 4.8 Hz, 1H).

Preparation of 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that
set forth in Example 2, except that 6-morpholinoindole was used instead of 5-chloroindole in part 1: mp 178-180°C; \(^1\)H NMR (DMSO-d\(_6\), 300 MHz) \(\delta\) 7.66-7.72 (m, 1H), 7.37 (d, \(J = 8.4\) Hz, 1H), 7.29 (s, 1H), 7.06 (d, \(J = 2.4\) Hz, 1H), 6.84 (d, \(J = 8.4\) Hz, 1H), 4.96 (s, 2H), 4.58 (s, 2H), 3.37-3.75 (m, 4H), 3.09-3.13 (m, 4H); LRMS calcd for \(C_{22}H_{14}F_3N_3O_3S\): 461.0; found 462 (M+1)\(^+\). Anal. Calcd for \(C_{22}H_{14}F_3N_3O_3S\) CH\(_2\)Cl\(_2\) 0.50H\(_2\)O: C, 49.74; H, 3.72; N, 7.57; S, 5.77 Found C, 49.73; H, 3.36; N, 7.69; S, 5.58

Example 19

**Preparation of 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-y1)methyl-indole-N-acetic acid**

\[-\]

5-Phenoxy-2-nitrotoluene

A solution of phenol (12.16 g, 0.129 mol) in anhydrous DMSO was treated with \(K_2CO_3\) (17.88 g, 0.129 mol) and stirred at room temperature for 15 min. 5-Fluoro-2-nitrotoluene (13.38 g, 0.086 mol) was added to the solution via syringe. The resultant mixture was heated to 80°C for 12 h. After cooling to room temperature, the mixture was poured into H\(_2\)O (100mL). After
and washed with a sat’d brine solution, dried over MgSO₄,
filtered and concentrated in vacuo. The residue was purified by
flash column chromatography (heptane to 8:1 heptane/ EtOAc) to
give the desired material as a yellow crystalline solid (12.50
5 g, 63%): Rf 0.60 (85% heptane/ 15% EtOAc); ¹H NMR (DMSO-d₆, 300
MHz) δ 8.05 (d, J = 9.0 Hz, 1H), 7.44-7.47 (m, 2H), 7.23-7.29
(m, 1H), 7.12-7.16 (m, 2H), 7.04 (d, J = 2.7 Hz, 1H), 6.90 (dd,
J₁ = 9.0 Hz, J₂ = 2.7 Hz, 1H), 2.51 (s, 3H).

5-Phenoxyindole

A solution of 5-phenoxy-2-nitrotoluene (10.03 g, 0.0428
10 mol) in anhydrous DMF was treated with N,N-dimethylformamide
dimethyl diacetal (6.73 mL, 0.0508 mol) and pyrrolidine (3.63
mL, 0.0438 mol) and heated to 110 °C for 2.5 h. After cooling to
room temperature, the mixture was diluted with EtOAc (500 mL)
and washed H₂O (500 mL). The organics were dried over MgSO₄,
filtered and concentrated in vacuo. The crude intermediate was
dissolved in glacial HOAc (250 mL) and warmed to 85°C. Zn
15 (24.62 g, 0.377 mol) was added to the solution portion wise
over 30 min. The mixture was heated for 4h. After cooling to
room temperature, the mixture was neutralized with sat’d NaHCO₃
and extracted with Et₂O (3X, 300 mL). The combined organics
were washed with sat’d brine, dried over MgSO₄, filtered and
concentrated in vacuo. The residue was purified by SiO₂ flash
chromatography (heptane to 2:1 heptane/ EtOAc) to give the
desired material as a white crystalline powder (3.1 g, 34% over 2 parts): R₂ 0.50 (2:1 Heptane/ EtOAc); ¹H NMR (DMSO-d₆, 300 MHz) δ 11.12 (br s, 1H), 7.48 (s, 1H), 7.30-7.38 (m, 1H), 7.25-7.29 (m, 2H), 7.17 (d, J = 2.7 Hz, 1H), 6.89-7.02 (m, 1H), 6.86-6.88 (m, 2H), 6.80 (dd, J₁ = 8.7 Hz, J₂ = 2.4 Hz, 1H), 6.37 (m, 1H).

Preparation of 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-N-acetic acid

5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-phenoxyindole was used instead of 5-chloroindole in part 1: mp 128-130°C; R₂ 0.45 (10% methanol in chloroform); ¹H NMR (DMSO-d₆, 300 MHz) δ 7.65-7.70 (m, 1H), 7.47 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.21-7.27 (m, 3H), 6.98 (m, 1H), 6.83-6.90 (m, 3H), 5.02 (s, 2H), 4.60 (s, 2H); LRMS calcd for C₂₄H₁₅F₃N₂O₅S: 468.0; found 467.0 (M - 1)⁻. Anal. Calcd for C₂₄H₁₅F₃N₂O₅S: C, 55.11; H, 4.20; N, 8.76; S, 6.69. Found: C, 55.11; H, 4.05; N, 8.57; S, 6.50.

Example 20

Preparation of 7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-Fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 7-fluoroindole was
used instead of 5-chloroindole in part 1: mp 194-196°C; Rf 0.60
(10% methanol in chloroform); ¹H NMR (DMSO-d₆, 300 MHz) δ
7.67-7.73 (m, 1H), 7.46 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H),
6.89-6.99 (m, 2H), 5.06 (s, 2H), 4.64 (s, 2H); LRMS calcd for
C₁₈H₁₉F₄N₂O₂S·H₂O: C, 50.23; H, 3.28; N, 6.51; S, 7.45. Found C,
50.70; H, 2.52; N, 6.60; S, 7.57. 394.0; found 395.0 (M + 1)⁺.
Anal. Calcd for C₁₈H₁₀F₄N₂O₂S

Example 21

Preparation of 7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid was prepared in a manner analogous to that
set forth in Example 2, except that 7-bromoindole was used
instead of 5-chloroindole in part 1: mp 228-230°C; Rf 0.40 (10%
methanol in chloroform); ¹H NMR (DMSO-d₆, 300 MHz) δ 7.65-7.74
(m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.32 (d, J =
7.8 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 5.29 (s, 2H), 4.65 (s,
2H); LRMS calcd for C₁₈H₁₀F₃N₂O₂SBr: 454.0 for (¹¹Br and 456.0 for
¹⁹Br); found 453.0 (M - 1)⁺ and 455.0 (M - 1)⁺. Anal Calcd for
C₁₈H₁₀F₃N₂O₂SBr: C, 47.49; H, 2.21; N, 6.15; S, 7.04. Found: C,
47.65; H, 2.27; N, 6.15; S, 6.98.

Example 22
Preparation of 7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 7-chloroindole was used instead of 5-chloroindole in part 1: mp 228-230°C; R_2 0.38 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.62-7.73 (m, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 5.25 (s, 2H), 4.65 (s, 2H); LRMS calcd for C_{16}H_10F_3N_2O_2SCl: 410.0; found 409.0 (M - 1)^-. Anal. Calcd for C_{16}H_10F_3N_2O_2SCl: C, 52.63; H, 2.45; N, 6.82; S, 7.81. Found: C, 52.60; H, 2.54; N, 6.66; S, 7.59.

Example 23

3-[5-Fluorbenzothiazole-2-yl]methyl-indole-N-acetic Acid

![Chemical Structure]

3-[5-fluorobenzothiazole-2-yl]methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 3, except 2-amino-4-fluorothiophenol hydrochloride was used instead of 2-amino-4,5,7-trifluorothiophenol hydrochloride in part 6: mp 208°C (decomp); R_2 0.10 (10% methanol in dichloromethane); ^1H NMR (DMSO-d_6, 300 MHz) δ 12.91 (s, 1 H), 7.98
Example 24

3-[6-Fluorobenzothiazole-2-yl]methyl-indole-N-acetic Acid

3-[6-fluorobenzothiazole-2-yl]methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 3, except 2-amino-5-fluorothiophenol hydrochloride was used instead of 2-amino-4,5,7-trifluorothiophenol hydrochloride in part 6: mp 203°C (decomp) Rf 0.13 (10% methanol in diehloromethane); 1H NMR (DMSO-d6, 300 MHz) δ 12.91 (s, 1 H), 7.95 (dd, J = 8.9, 5.0 Hz: 1 H), 7.86 (dd, J = 8.8, 2.8 Hz, 1 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.40-7.35 (m, 2 H), 7.32 (dt, J = 8.9, 2.7 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.00 (t, J = 7.6 Hz, 1 H), 5.01 (s, 2 H), 4.54 (s, 2 H); LRMS m/z 341.0 (M + 1)′, 339.0 (M-1). Anal. Calcd for C18H13FN2O2S: C, 63.52; H, 3.85; N, 8.23; S, 9.42; Found: C, 63.40; H, 3.80; N, 8.37; S, 9.43.

The compounds of Examples 25-32 were prepared essentially according to the procedures set forth above in examples 1 and/or 2 with appropriate substitution of starting materials.
Example 25

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid

\( \text{mp 176-177°C; Rf 0.34 (20% methanol in dichlormethane); } ^1H \text{ NMR (DMSO-d}_6, \text{ 300 MHz) } \delta 7.60-7.73 \text{ (m, 1H), 7.60 } (s, \text{ 1H}), 7.52 \text{ (d, J = 8.1 Hz, 1H), 7.44 } (d, J = 8.1 Hz, \text{ 1H}), t, J = 7.5 \text{ Hz, 1H), 7.02 } (t, J = 7.5 \text{ Hz, 1H), 5.35 } (q, J = 8.1 \text{ Hz, 1H), 4.64 } (s, \text{ 2H), 1.72 } (d, J = 8.1 \text{ Hz, 3H); LRMS calcd for C}_{19}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{S: 390.0; Found 391.0 (M } + 1)^{+}. \text{ Anal. Calcd for C}_{19}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{SH}_2\text{O: C, 55.88; H, 3.70; N, 6.86; S, 7.85 Found: } \text{C, 56.09; H, 3.31; N, 6.89; S, 7.99.}

Example 26

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-3-propionic acid

-75-
mp 200-201°C; Rf 0.50 (20% methanol in dichloromethane); 1H NMR (DMSO-d$_6$, 300 MHz) δ 7.63-7.71 (m, 1H), 7.51 (s, 1H), 7.47 (d, J = 3.0 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 4.61 (s, 2H), 4.39 (t, J = 6.6 Hz, 2H), 2.75 (t, J = 6.6 Hz, 2H); LRMS calcd for C$_{19}$H$_{13}$F$_3$N$_2$O$_2$S: 390.0; Found 391.0 (M +1)$^+$. Anal Calcd for C$_{19}$H$_{13}$F$_3$N$_2$O$_2$S: C, 58.46; H, 3.36; N, 7.18; S, 8.21 Found: C, 58.63; H, 3.40; N, 7.20; S, 8.30.

Example 27

Preparation of 6-Bromo-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid: mp 265-267°C; Rf 0.19 (20% methanol in dichloromethane); 1H NMR (DMSO-d$_6$, 300 MHz) δ 8.28 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.67-7.69 (m, 2H), 7.43-7.47 (m, 2H), 7.14 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 4.61 (s, 2H); LRMS calcd for C$_{19}$H$_{12}$F$_3$N$_2$O$_2$SBr:469.0; Found 469.0 (M + 1)$^+$. for Br = 79. Anal. Calcd for C$_{19}$H$_{12}$F$_3$N$_2$O$_2$SBr: C, 48.63; H, 2.58; N, 5.97; S, 6.83. Found: C, 48.60; H, 2.63; N, 5.88; S, 6.91.

Example 28

6-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid: mp 118-120°C; Rf 0.27 (20% methanol in dichloromethane); 1H NMR (DMSO-d$_6$, 300 MHz) δ 7.63-7.73 (m, 1H), 7.39 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.97 (s, 2H), 4.61 (s, 2H); 3.07 (s, 3H); LRMS calcd for C$_{19}$H$_{13}$F$_3$N$_2$O$_2$S: 406.0; Found 407.0 (M + )$^+$. Anal. Calcd
for C_{19}H_{18}F_{3}N_{3}O_{3}SH_{2}O: C, 53.77; H, 3.56; N, 6.60; S, 7.56 Found:
C, 53.87; H, 3.56; N, 6.67; S, 7.67.

**Example 29**

4-Chloro-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid

mp 203-206 °C; R_f 0.24 (20% methanol in dichloromethane); H NMR (DMSO-d_6, 300 MHz) δ 7.63-7.71 (m, 1H), 7.57 (s, 1H), 7.33 (d, J' = 9.0 Hz, 1H), 7.12 (dd, J (1) = 9.0, J (2) = 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 5.08 (s, 2H), 4.78 (s, 2H); LRMS calcd for C_{19}H_{18}F_{3}N_{3}O_{3}SCl: 410.0; Found 411.0 (M+1)^+ and 409.0 (M-1)^-.

**Example 30**

5-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid
mp 165-167 °C; \( R_f \) 0.37 (20% methanol in dichloromethane); \(^1\text{H} \) NMR (DMSO-\( d_6 \), 300 MHz) \( \delta \) 7.61-7.70 (m, 1H), 7.35 (d, \( J = 9.0 \) Hz, 1H), 7.26 (s, 1H), 6.90 (s, 1H), 6.64 (d, \( J = 9.0 \) Hz, 1H), 4.79 (s, 2H); 4.56 (s, 2H), 3.72 (s, 3H); LRMS calcd for \( \text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{S} \): 406.0; Found 407.0 (M+1)^+ and 405.0 (M-1)^-.

**Example 31**

5-Bromo-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid: mp 209-294 °C; \( R_f \) 0.18 (20% methanol in dichloromethane); \(^1\text{H} \) NMR (DMSO-\( d_6 \), 300 MHz) \( \delta \) 7.78 (d, \( J = 1.8 \) Hz, 1H), 7.65-7.73 (m, 1H), 7.49 (s, 1H), 7.61 (d, \( J = 9.0 \) Hz, 1H), 7.25 (dd, \( J_{i} = 9.0 \) Hz, \( J_{j} = 1.8 \) Hz, 1H), 5.04 (s, 2H); 4.64 (s, 2H); LRMS calcd for \( \text{C}_{21}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2\text{SBr} \): 455.0; Found 455.0 (M+1)^+ for Br 79 and 457 (M+1)^+ for Br 81.

**Example 32**

3-(6-chlorobenzothiazol-2-yl) methyl-indole-N-acetic acid

![Chemical Structure](image)
Example 33

The uric acid lowering activity of the test compounds of this invention is demonstrated using the following experiments with normal human test subjects.

Thirty six healthy human subjects are administered either a tablet or a suspension containing the noted amount of the compound of Example 3 after fasting for at least 8 hours. Twelve subjects are administered 200 mg of compound; twelve subjects are administered 400 mg of compound; and twelve subjects are administered 600 mg of compound. Blood was collected before subjects are given the compound (Day -1) and again the day following administration (Day 2). Serum uric acid levels may be measured using standard automated procedures based on a uricase peroxidase method. The results are listed below in Tables 1, 2, and 3. Serum uric acid levels are presented in mg/dL.

<table>
<thead>
<tr>
<th>Uric Acid Subject</th>
<th>Tablet</th>
<th>Day -1</th>
<th>Day 2</th>
<th>% reduction</th>
<th>Suspension</th>
<th>Day -1</th>
<th>Day 2</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (200 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>-41%</td>
<td>3.3</td>
<td>2.1</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>4.9</td>
<td>5.7</td>
<td>-16%</td>
<td>6.3</td>
<td>5.6</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>3.1</td>
<td>39%</td>
<td>4.5</td>
<td>2.9</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>5.0</td>
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<td>5.0</td>
<td>3.2</td>
<td>36%</td>
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</tr>
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<td>6.0</td>
<td>4.4</td>
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</tr>
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<td>4.3</td>
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<td>23%</td>
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<tr>
<td>12</td>
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<td>4.0</td>
<td>20%</td>
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<td></td>
</tr>
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Table 2

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<th>% reduction</th>
</tr>
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<td>-13%</td>
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<td>18</td>
<td>4.6</td>
<td>3.5</td>
<td>24%</td>
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<td>19</td>
<td>4.5</td>
<td>2.4</td>
<td>47%</td>
</tr>
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</tr>
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</tr>
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<td>9%</td>
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</tr>
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Table 3

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<th>% reduction</th>
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<td>28</td>
<td>3.0</td>
<td>1.9</td>
<td>37%</td>
</tr>
<tr>
<td>29</td>
<td>3.9</td>
<td>1.7</td>
<td>58%</td>
</tr>
<tr>
<td>30</td>
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<td>-6%</td>
</tr>
<tr>
<td>32</td>
<td>nd*</td>
<td>3.3</td>
<td>nd</td>
</tr>
<tr>
<td>33</td>
<td>4.3</td>
<td>6.2</td>
<td>-44%</td>
</tr>
<tr>
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<td>5.5</td>
<td>3.0</td>
<td>45%</td>
</tr>
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<td>35</td>
<td>4.4</td>
<td>2.0</td>
<td>55%</td>
</tr>
<tr>
<td>36</td>
<td>5.9</td>
<td>3.4</td>
<td>42%</td>
</tr>
</tbody>
</table>

*Not determined

The results demonstrate that the compounds of the invention lower blood uric acid levels. Such compounds are therefore useful in the treatment of diseases associated with elevated levels of uric acid, e.g., gout. Accordingly, an aspect of the invention is treatment of gout with the inventive compounds; treatment includes both prevention and alleviation.

Example 34

In another study, 48 subjects were divided into four groups, A, B, C and D, and administered the noted amount of the
compound of Example 3. Each group was composed of 12 subjects of whom 9 received the compound and 3 received placebo. The non-placebo members of group A received 50 mg of compound, administered orally once a day for 28 days as a single 50 mg tablet. The non-placebo members of group B received 200 mg of compound administered orally once a day for 28 days as a single 200 mg tablet. The non-placebo members of group C received 500 mg of compound administered orally once a day for 28 days as two 50 mg tablets and two 200 mg tablets. The non-placebo members of group D received 800 mg of compound administered orally once a day for 28 days as four 200 mg tablets. The 3 placebo members of each group, received an amount of placebo, as a tablet, equivalent to the amount of test compound - 50 mg placebo for group A, 200 mg placebo for group B, 500 mg placebo for group C and 800 mg placebo for group D. Each subject received a single dose of either compound or placebo for 28 days. The subjects were confined at the clinical site beginning the day before dose administration until 72 hours after the final dose administration on Day 28 and returned for an outpatient visit on Day 35.

Uric acid levels were measured prior to beginning the study (screening), on the day immediately prior to commencement of the study (day-1), and then as noted in the table. Hours indicates the time since the last dose was administered. For example, Day 7, 0 hour indicates the time the serum uric acid level at the time the dose was administered and Day 7, 2 hour
indicates the uric acid level two hours after the administration that day. Further, the Day 30, 60 hour level is the serum uric acid level measured 60 hours (on Day 30) after the last dose was administered on Day 28. The uric acid levels are presented in mg/dL as a mean of all subjects in each group. The results of the study are summarized in Table 4.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Screening</th>
<th>Day 1 0 Hour</th>
<th>Day 1 0.5 Hour</th>
<th>Day 1 1 Hour</th>
<th>Day 1 2 Hour</th>
<th>Day 1 3 Hour</th>
<th>Day 1 4 Hour</th>
<th>Day 1 6 Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.52</td>
<td>4.70</td>
<td>4.72</td>
<td>4.64</td>
<td>4.56</td>
<td>4.40</td>
<td>4.26</td>
<td>4.26</td>
</tr>
<tr>
<td>B</td>
<td>5.11</td>
<td>5.16</td>
<td>5.10</td>
<td>5.01</td>
<td>4.91</td>
<td>4.58</td>
<td>4.28</td>
<td>4.04</td>
</tr>
<tr>
<td>C</td>
<td>5.28</td>
<td>5.10</td>
<td>5.16</td>
<td>5.08</td>
<td>4.81</td>
<td>4.27</td>
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<td>3.54</td>
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<tr>
<td>D</td>
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<td>5.64</td>
<td>5.57</td>
<td>5.12</td>
<td>4.46</td>
<td>3.97</td>
<td>3.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.16</td>
<td>5.03</td>
<td>4.78</td>
<td>4.71</td>
<td>4.76</td>
<td>4.74</td>
<td>4.73</td>
<td>4.84</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1 8 Hour</th>
<th>Day 1 10 Hour</th>
<th>Day 1 12 Hour</th>
<th>Day 1 16 Hour</th>
<th>Day 1 24 Hour</th>
<th>Day 3 0 Hour</th>
<th>Day 7 0.5 Hour</th>
<th>Day 7 1 Hour</th>
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</thead>
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<td>3.89</td>
<td>3.98</td>
<td>4.19</td>
<td>3.62</td>
<td>3.36</td>
<td>3.33</td>
</tr>
<tr>
<td>B</td>
<td>3.37</td>
<td>3.16</td>
<td>3.12</td>
<td>3.01</td>
<td>3.64</td>
<td>2.94</td>
<td>2.86</td>
<td>2.79</td>
</tr>
<tr>
<td>C</td>
<td>2.82</td>
<td>2.59</td>
<td>2.56</td>
<td>2.36</td>
<td>2.74</td>
<td>2.21</td>
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<td>2.21</td>
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<tr>
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<td>2.64</td>
<td>2.19</td>
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<td>2.10</td>
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<td>4.59</td>
<td>4.45</td>
<td>4.92</td>
<td>5.04</td>
<td>5.19</td>
<td>5.25</td>
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</table>
### Uric Acid Level
(mean of all subjects in each group, mg/dL)

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<tr>
<th>Treatment</th>
<th>Day 7 2 Hour</th>
<th>Day 7 3 Hour</th>
<th>Day 7 4 Hour</th>
<th>Day 7 6 Hour</th>
<th>Day 7 8 Hour</th>
<th>Day 7 10 Hour</th>
<th>Day 7 12 Hour</th>
<th>Day 7 16 Hour</th>
<th>Day 7 24 Hour</th>
</tr>
</thead>
<tbody>
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<td>2.99</td>
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<td>3.36</td>
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<td>3.07</td>
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</tr>
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<td>2.61</td>
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<td>2.47</td>
<td>2.72</td>
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<td>2.70</td>
</tr>
<tr>
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<td>2.08</td>
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<td>1.90</td>
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<table>
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<th>Day 14 1 Hour</th>
<th>Day 14 2 Hour</th>
<th>Day 14 3 Hour</th>
<th>Day 14 4 Hour</th>
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<th>Day 14 8 Hour</th>
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<td>1.82</td>
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<td>1.91</td>
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<td>5.25</td>
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<table>
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<th>Day 14 24 Hour</th>
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<th>Day 28 0 Hour</th>
<th>Day 28 0.05 Hour</th>
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<th>Day 28 2 Hour</th>
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<td>2.26</td>
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<td>5.50</td>
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<td>4.07</td>
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<td>2.32</td>
<td>2.20</td>
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The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.
What is claimed is:

1. A method for reducing serum uric acid levels, which method comprises administering to a mammal in need of such treatment an effective amount of a compound of the formula:

   ![Chemical Structure]

   or a pharmaceutically acceptable salt thereof wherein

   **A** is a C₁-C₄ alkylene group optionally substituted with C₁-C₂ alkyl or mono- or disubstituted with halogen;

   **Z** is a bond, O, S, C(O)NH, or C₁-C₃ alkylene optionally substituted with C₁-C₂ alkyl;

   **R₁** is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₅ alkoxy, C₁-C₅ alkyl, nitro, amino, or mono- or di(C₁-C₄)alkylamino;

   **R₂, R₃, R₄**, and **R₅** are each independently hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

   OR₆, SR₆, S(O)R₆, S(O)₂N(R₆)₂, C(O)N(R₆)₂, or N(R₆)₂, wherein each **R₆** is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or
more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; or a group of the formula

\[
\begin{align*}
\text{J} & \quad \text{(CH₂)ᵣ} \\
\text{N-} & \quad \text{(CH₂)ᵣ} \\
\text{R}_6 & \quad \text{L}
\end{align*}
\]

where

J is a bond, CH₂, oxygen, or nitrogen; and each r is independently 2 or 3;
R₆ is hydroxy or a prodrug group;
R₄ is hydrogen, C₁-C₆ alkyl, fluoro, or trifluoromethyl;
and Ar represents a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more
halogens), nitro, OR, SR, S(O)R, S(O)₂R, or N(R)₂, wherein R is hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino, or the phenyl group may be condensed with benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl, perfluoroethyl, trifluoroacetyl, or (C₁-C₆) alkanoyl, hydroxy, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) alkythio, trifluoromethoxy, trifluoromethylthio, (C₁-C₆) alkylsulfinyl, (C₁-C₆) alkylsulfonyl; a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, (C₁-C₆) alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thiethyl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or (C₁-C₆) alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) alkythio, trifluoromethoxy, trifluoromethylthio, (C₁-
C₆)alkylsulfinyl, (C₁-C₆)alkylsulfonyl or trifluoromethyl, or two fluoro or two trifluoromethyl with one hydroxy or one (C₁-C₆)alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thiényl optionally substituted in the 3-position by fluoro, chloro, bromo, (C₁-C₆)alkyl or (C₁-C₆)alkoxy;

a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by one or two (C₁-C₆)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thiényl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bromo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl, (C₁-C₆)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thiényl optionally substituted in the 3-position by fluoro, chloro, (C₁-C₆)alkyl or (C₁-C₆)alkoxy;

said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bromo, methoxy, or trifluoromethyl;

oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or with furane, each optionally substituted by one of fluoro,
chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;
imidazolopyridine or triazolopyridine optionally substituted by
one of trifluoromethyl, trifluoromethylthio, bromo, or
(C<sub>1</sub>-C<sub>6</sub>)alkoxy, or two of fluoro or chloro;
thienothiophene or thienofuran optionally substituted by one of
fluoro, chloro or trifluoromethyl;
thienotriazole optionally substituted by one of chloro or
trifluoromethyl;
naphthothiazole; naphthoxazole; or thienoisothiazole.

2. A method according to claim 1, wherein Ar is aryl or
heteroaryl, each of which is substituted with up to four groups
independently selected from hydrogen, fluorine, chlorine,
bromine, trifluoromethyl and nitro.

3. A method according to claim 1, wherein Ar is a
substituted phenyl of Formula II or a substituted benzothiazole
of Formula III

\[ R_8 \quad R_9 \quad R_{10} \quad R_{11} \quad R_{12} \quad R_{13} \quad R_{14} \]

\[ \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \]

\[ \text{II} \quad \text{III} \]
wherein R₈, R₉, R₉', R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are independently hydrogen, fluorine, chlorine, bromine, trifluoromethyl or nitro.

4. A method according to claim 3, wherein A is methylene and Z is a bond.

5. A method according to claim 3, wherein Rₙ is hydrogen and Z is a bond.

6. A method according to claim 3, wherein A is methylene, Rₙ is hydrogen, and Z is a bond.

7. A method according to claim 6, wherein Ar is a substituted benzothiazole of Formula III.

8. A method according to claim 7, wherein at least one of R₁₁, R₁₂, R₁₃, and R₁₄ is trifluoromethyl.

9. A method according to claim 8, wherein R₁₂ is trifluoromethyl.

10. A method according to claim 7, wherein R₁₁, R₁₂, and R₁₄ are fluorines and R₁₃ is hydrogen.
11. A method according to claim 10, wherein $R_6$ is hydrogen.

12. A method according to claim 10, wherein $R_6$ is $C_1$-$C_6$ alkyl.

13. A method according to claim 6, wherein $Ar$ is a substituted phenyl of Formula II.

14. A method according to claim 13, wherein at least one of $R_8$, $R_8'$, $R_9$, $R_9'$, $R_{10}$ is trifluoromethyl.

15. A method according to claim 14, wherein $R_6$ is trifluoromethyl.

16. A method according to claim 15, wherein $R_8$, $R_8'$, $R_9$, $R_9'$, $R_{10}$ are fluorines and $R_{13}$ is hydrogen.

17. A method according to claim 16, wherein $R_6$ is hydrogen.

18. A method according to claim 16, wherein $R_6$ is $C_1$-$C_6$ alkyl.
19. A method according to claim 1, which is selected from the group consisting of

5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-chloro-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester;

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;
6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-Methyl-3-(5-Trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid;

3-(3-nitrophenyl)methyl-indole-N-acetic acid;

3-(3-nitrophenyl)methyl-indole-N-acetic acid, ethyl ester;

2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;

7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid;
3-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-
indole-N-acetic acid;

3-[[5-Fluorobenzothiazole-2-yl]methyl]-indole-N-acetic
acid; and

3-[[6-Fluorobenzothiazole-2-yl]methyl]-indole-N-acetic
acid.

20. A method according to claim 3, wherein Ar is a
substituted benzothiazole of Formula III, $R_{12}$ is
trifluoromethyl, A is methylene, methylene substituted with a
methyl group, or ethylene, and $R_2$, $R_3$, $R_4$ and $R_5$, in
combination, represent one of bromo, cyano or nitro, one or two
of fluoro, chloro, hydroxy, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, or
trifluoromethyl, or two fluoro or two methyl with one hydroxy
or one $(C_1-C_6)$alkoxy, or one or, preferably, two fluoro and one
methyl, or three fluoro groups.

21. A method for treating or preventing gout, which
method comprises administering to a mammal an effective amount
of a compound of the formula:

![Chemical Structure](image-url)

or a pharmaceutically acceptable salt thereof wherein
A is a C₁-C₄ alkylene group optionally substituted with C₁-C₂ alkyl or mono- or disubstituted with halogen;

Z is a bond, O, S, C(O)NH, or C₁-C₄ alkylene optionally substituted with C₁-C₂ alkyl;

R₁ is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, nitro, amino, or mono- or di(C₁-C₆)alkylamino;

R₂, R₃, R₄ and R₅ are each independently hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

OR₆, SR₆, S(O)R₆, S(O)₂N(R₆), C(O)N(R₆), or N(R₆), wherein each R₆ is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino;
where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ alkoxy, amino, and mono- or di(C$_1$-C$_6$)alkylamino; or a group of the formula

$$
\begin{align*}
\mathrm{J} & \quad (\mathrm{CH}_2)_r \\
\mathrm{N} & \quad (\mathrm{CH}_2)_r
\end{align*}
$$

where

J is a bond, CH$_2$, oxygen, or nitrogen; and
each r is independently 2 or 3;

R$_6$ is hydroxy or a prodrug group;

R$_a$ is hydrogen, C$_1$-C$_6$ alkyl, fluoro, or trifluoromethyl;

and Ar represents a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR$_7$, SR$_7$, S(O)R$_7$, S(O)$_2$R$_7$, or N(R$_7$)$_2$ wherein R$_7$ is hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C$_1$-C$_6$ alkyl, C$_1$-C$_6$ alkoxy, amino, and mono- or di(C$_1$-C$_6$)alkylamino, or the phenyl group may be condensed with benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl,
perfluoroethyl, trifluoroacetyl, or \((C_1-C_6)\) alkanoyl, hydroxy, \((C_1-C_6)\) alkyl, \((C_1-C_6)\) alkoxy, \((C_1-C_6)\) alkythio, trifluoromethoxy, trifluoromethylthio, \((C_1-C_6)\) alkylsulfanyl, \((C_1-C_6)\) alkylsulfonyl;

a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, \((C_1-C_6)\) alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or \((C_1-C_6)\) alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, \((C_1-C_6)\) alkyl, \((C_1-C_6)\) alkoxy, \((C_1-C_6)\) alkythio, trifluoromethoxy, trifluoromethylthio, \((C_1-C_6)\) alkylsulfanyl, \((C_1-C_6)\) alkylsulfonyl or trifluoromethyl, or two fluoro or two trifluoromethyl with one hydroxy or one \((C_1-C_6)\) alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, bromo, \((C_1-C_6)\) alkyl or \((C_1-C_6)\) alkoxy;

a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by
one or two \((C_1-C_6)\)alkyl or phenyl, or condensed with benzoy, or substituted by one of pyridyl, furyl or thiethyl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bomo, \((C_1-C_6)\)alkyl, \((C_1-C_6)\)alkoxy, \((C_1-C_6)\)alkylthio, \((C_1-C_6)\)alkylsulfinyl, \((C_1-C_6)\)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thiethyl optionally substituted in the 3-position by fluoro, chloro, \((C_1-C_6)\)alkyl or \((C_1-C_6)\)alkoxy;

said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bomo, methoxy, or trifluoromethyl;

oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;

imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or \((C_1-C_6)\)alkoxy, or two of fluoro or chloro;
thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl;
thienotriazole optionally substituted by one of chloro or trifluoromethyl;
naphthothiazole; naphthoxazole; or thienoisothiazole.

22. The use of a compound according to Formula I in the preparation of a medicament for use in lowering serum uric acid levels, where Formula I is

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof wherein

A is a C₁-C₄ alkylene group optionally substituted with C₁-C₂ alkyl or mono- or disubstituted with halogen;

Z is a bond, O, S, C(=O)NH, or C₁-C₃ alkylene optionally substituted with C₁-C₂ alkyl;

R₁ is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, nitro, amino, or mono- or di(C₁-C₆)alkylamino;

R₂, R₃, R₄ and R₅ are each independently hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

OR₇, SR₇, S(O)R₇, S(O)₂N(R₇)₂, C(=O)N(R₇)₂, or N(R₇)₂, wherein each R₇ is independently hydrogen, an alkyl group of 1-
6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, and mono- or di(C₁-C₆)alkylamino; or a group of the formula

\[
\begin{array}{c}
\text{J} \\
\text{N} - (\text{CH}_2)_{\text{r}} \\
\text{CH}_2
\end{array}
\]

where

J is a bond, CH₂, oxygen, or nitrogen; and each r is independently 2 or 3;

20 R₆ is hydroxy or a prodrug group;

R₄ is hydrogen, C₁-C₆ alkyl, fluoro, or trifluoromethyl;

and Ar represents a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6
carbon atoms (which may be substituted with one or more halogens), nitro, OR, SR, S(O)R, S(O)₂R, or N(R)₂ wherein R is hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C₁₋C₆ alkyl, C₁₋C₆ alkoxy, amino, and mono- or di(C₁₋C₆)alkylamino, or the phenyl group may be condensed with benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl, perfluoroethyl, trifluoroacetyl, or (C₁₋C₆)alkanoyl, hydroxy, (C₁₋C₆)alkyl, (C₁₋C₆)alkoxy, (C₁₋C₆)alkythio, trifluoromethoxy, trifluoromethylthio, (C₁₋C₆)alkylsulfinyl, (C₁₋C₆)alkylsulfonyl;

a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, (C₁₋C₆)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or (C₁₋C₆)alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, (C₁₋C₆)alkyl, (C₁₋C₆)alkoxy, (C₁₋C₆)alkythio,
trifluoromethoxy, trifluoromethylthio, \((C_1-C_6)\)alkylsulfinyl, \((C_1-C_6)\)alkylsulfonyl or trifluoromethyl, or two fluoro or two trifluoromethyl with one hydroxy or one \((C_1-C_6)\)alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, bromo, \((C_1-C_6)\)alkyl or \((C_1-C_6)\)alkoxy; a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by one or two \((C_1-C_6)\)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bromo, \((C_1-C_6)\)alkyl, \((C_1-C_6)\)alkoxy, \((C_1-C_6)\)alkylthio, \((C_1-C_6)\)alkylsulfinyl, \((C_1-C_6)\)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, \((C_1-C_6)\)alkyl or \((C_1-C_6)\)alkoxy; said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bromo, methoxy, or trifluoromethyl; oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or
with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;
imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or (C₁-C₅)alkoxy, or two of fluoro or chloro;
thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl;
thienotriazole optionally substituted by one of chloro or trifluoromethyl;
naphthothiazole; naphthoxazole; or thienoisothiazole.