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SUBSTITUTED INDOLEALKANOIC ACIDS

This is a continuation-in-part of application Serial No. 60/080,143, filed March 31, 1998.

Background of Invention:

The use of aldose reductase inhibitors (ARIs) for the treatment of diabetic complications is well know n. The complications arise from elevated levels of glucose in tissues such as the nerve, kidney, retina and lens that enters the polyol pathway and is converted to sorbitol via aldose reductase. Because sorbitol does not easily cross cell membranes, it a ccumulates inside certain cells resulting in changes in osmotic pressure, alterations in the redox state of pyridine nucleotides (i.e. increased NADH/NAD ratio) and depleted intracellular levels of myoinositol. These biochemical changes, which have been linked to diabetic complications, can be controlled by inhibitors of aldose reductase.

The use of aldose reductase inhibitors for the treatment of diabetic complications has been extensively reviewed, see: (a) *Textbook of Diabetes*, 2nd ed.; Pickup, J. C. and Williams, G. (Eds.); Blackwell Science, Boston, MA **1997**.; (b) Larson, E. R.; Lipinski, C. A. and Sarges, R., *Medicinal Research Reviews*, **1988**, *8* (2), 159 -198; (c) Dvornik, D. *Aldose Reductase Inhibition*. Porte, D. (ed), Biomedical Information Corp., Ne w York, NY. Mc Graw Hill **1987**; (d) Petrash, J. M., Tarle, I.,

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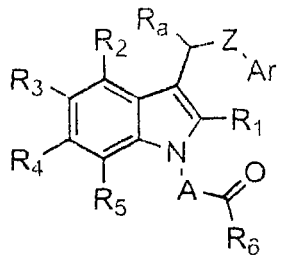
Wilson, D. K. Quiocho. F. A. Perspectives in Diabetes, *Aldose Reductase Catalysis and Crystalography: Insights From Recent Advances in Enzyme Structure and Function* , Diabetes, **1994**, *43*, 955; (e) Aotsuka, T.; Abe, N.; Fukushima, K.; Ashizawa, N.and Yoshida, M., *Bioorg. & Med. Chem . Letters*, **1997**, 7, 1677, (f) , T., Nagaki, Y.; Ishii, A.; Konishi, Y.; Yago, H; Seishi, S.; Okukado, N.; Okamoto, K., *J. Med. Chem .*, **1997**, *40*, 684; (g) Ashizawa, N.; Yoshida, M.; Sugiyama, Y.; Akaike, N.; Ohbayashi, S.; Aotsuka, T.; Abe, N.; Fukushima, K.; Matsuura, A, *Jpn. J. Pharmacol.* **1997**, *73*, 133; (h) Kador, P. F.; Sharpless, N. E., *Molecular Pharmacology* , **1983**, *24*, 521; (I) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E., *J. Med. Chem.* **1985**, 28 (7), 841; (j) Hotta, N., *Biomed. & Pharmacother.* **1995**, *5*, 232; (k) Mylar, B.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, F. D.; Siegel, T. W.; Singleton, D. H., *J. Med. Chem.* **1991**, *34*, 108; (l) Dvornik, D. *Croatica Chemica Acta* **1996**, *69* (2), 613.

Previously described aldose reductase inhibitors most closely related to the present invention include those sighted in: (a) U.S Pat. No. 5,700,819 : *2-Substituted benzothiazole derivatives useful in the treatment of diabetic complications* , (b) U.S Pat. No. 4,868,301: *Processes and intermediates for the preparation of oxophthalazinyl acetic acids having benzothiazole or other heterocyclic side chains* , (c) U.S Pat. No. 5,330,997: *1H-indazole-3-acetic acids as aldose reductase inhibitors*, and (d) U.S Pat. No. 5,236,945 : *1H -indazole-3-*

acetic acids as aldose reductase inhibitors . Although many aldose reductase inhibitors have been extensively developed, none have demonstrated sufficient efficacy in human clinical trials without significant undesirable side effects. Thus no aldose reductase inhibitors are currently available as approved therapeutic agents in the United States; and consequently, there is still a significant need for new, efficacious and safe medications for the treatment of diabetic complications.

Summary of the Invention:

This invention provides compounds that interact with and inhibit aldose reductase. Thus, in a broad aspect, the invention provides compounds of Formula I:



I

or pharmaceutically acceptable salts thereof wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl or mono - or disubstituted with halogen, preferably fluoro or chloro;

Z is a bond, O, S, C(O)NH, or C_1-C_3 alkyl ene optionally substituted with C_1-C_2 alkyl;

R_1 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, C_1-C_6 alkoxy, C_1-C_6 alkyl, nitro, amino, or mono- or di(C_1-C_6)alkylamino;

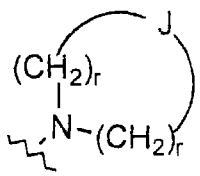
R_2, R_3, R_4 and R_5 are each independently

hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

OR_7, SR_7, $S(O)R_7$, $S(O)_2(R_7)_2$, $C(O)N(R_7)_2$, or $N(R_7)_2$, wherein each R_7 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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy 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



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, $S(O)R_7$, $S(O)_2R_7$ 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)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (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)alkylthio, 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 nit rogen 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, trifluoromethyl thio, 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.

The invention also provide for a compound concerning the aforesaid formula where 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.

In another aspect, the invention provides methods for preparing such compounds.

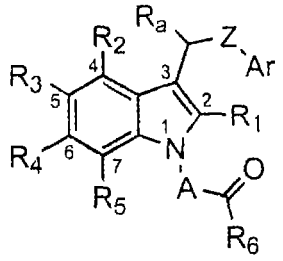
The compounds of the invention inhibit aldose reductase. Since aldose reductase is critical to the production of high levels of sorbitol in individuals with diabetes, inhibitors of aldose reductase are useful in preventing and/or treating various complications associated with diabetes. The compounds of the invention are therefore effective for the treatment of diabetic complications as a result of their ability to inhibit aldose reductase.

Thus, in another aspect, the invention provides methods for treating and/or preventing chronic complications associated with diabetes mellitus, including, for example, diabetic cataracts, retinopathy, nephropathy, and neuropathy.

In still another aspect, the invention provides pharmaceutical compositions containing compounds of Formula I.

Detailed Description of the Invention

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



I

As noted above, the invention provides novel substituted indole alkanoic acids useful in treating and/or preventing complications associated with or arising from elevated levels

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of glucose in individuals suffering from diabetes mellitus.

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_7, SR_7, $S(O)R_7$, $S(O)_2R_7$ 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)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (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)alkylthio, 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 (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.

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 R_4 is trifluoromethyl, Z is a covalent bond or CH_2, R_6 is hydroxy, and each of R_2-R_5 are independently hydrogen, halogen, more preferably bromo or chloro, C_1-C_2 alkyl, phenoxy, benzyloxy, or C_1-C_2 alkoxy, and R_1 is hydrogen or methyl.

Preferred compounds of the invention are those wherein Z is a covalent bond, R_6 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

thazolo[4,5-pyridine-2-y, 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_6) alkylamino R_a is hydrogen,fluro or C_1-C_2 alkyl, and R_1 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 benzoxazol-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 benzo -substituted benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, or indolyl, or Ar is 2-benzothiazolyl substituted on benzo by one trifluoroacetyl or trifluoromethylthio, or one or two of fluoro chloro, bromo, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or one or two, 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 R_2 and R_3 is hydrogen, fluoro, chloro, bromo or methyl, and one of R_4 and R_5 is hydrogen, or

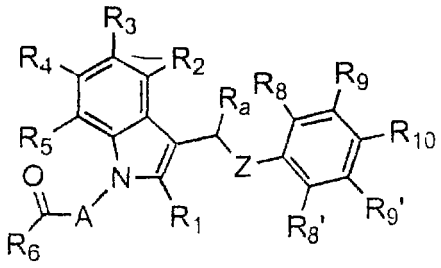
chloro, bromo, methyl, isopropyl, methoxy, nitro or trifluoromethyl; or R_3 and R_4 is 5, 6-difluoro, R_a is hydrogen; and those wherein Ar is optionally substituted benzothiazol-2-yl or quinoxalyl and R_3 and R_4 are each chloro, and R_1 is hydrogen or methyl.

Further more specific compounds are those wherein Z is a covalent bond, R_6 is hydroxy, Ar is optionally substituted benzothiazol-2-yl, R_3 and R_4 are hydrogen, and R_5 is methyl; those wherein Z is a covalent bond, R_6 is hydroxy, R_3, R_4 and R_5 are hydrogen, chloro, fluoro, bromo or C_1-C_2 alkyl, R_a is hydrogen, and Ar is optionally 4,5,6 or 7 benzosubstituted benzothiazolyl-2-trifluoromethyl, benzoxazolyl-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 CH_2, R_6 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, or thiazolo[4,5-b]pyridine-2-yl, or substituted 1,2,4-oxadiazol3-yl, 1,2,4-oxadiazol-5-yl, isothiazol-5-yl, isothiazol4-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_a 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 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:



II

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_a 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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono - or di(C_1-C_6)alkylamino;

R_2, R_3, R_4 and R_5 are each independently

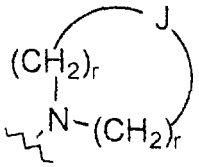
hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$, $C(O)N(R_7)_2$, or

$N(R_7)_2$, wherein each R_7 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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy 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



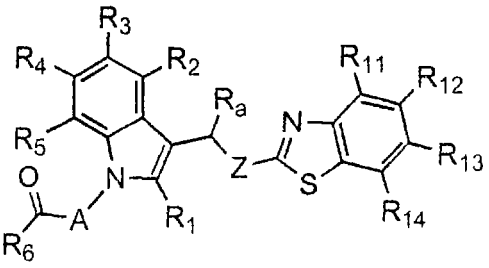
where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2, or 3;

R_6 is hydrogen, an alkoxy group of 1 -6 carbon atoms, or $-O^-M^+$ where M^+ is a cation forming a pharmaceutically acceptable salt; and

R_8, R_9, and R_{10} 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 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_a is hydrogen, C_1-C_6 alkyl, chloro, bromo, fluoro, or trifluoromethyl;

R_1 is hydrogen, C_1-C_6 alkyl, halogen, preferably chloro or fluoro, or phenyl optionally substituted with 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;

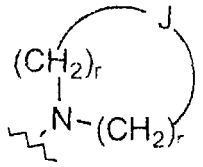
R_2, R_3, R_4 and R_5 are each independently hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$ $C(O)N(R_7)_2$ or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1-6 carbon 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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy 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



where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2 or 3;

R_6 is hydroxy, C_1-C_6 alkoxy, or $-O^-M^+$ where M^+ is a cation forming a pharmaceutically acceptable salt; and

R_{11}, R_{12}, R_{13} and R_{14} are independently hydrogen, halogen, nitro, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkylsulfinyl, or C_1-C_6 alkylsulfonyl.

In preferred compounds of Formula III, the R_2, R_3, R_4 and R_5 substituents, 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. Particularly preferred R_2, R_3, R_4 and R_5 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 R_8 is fluorine, R_9 is hydrogen and R_{10} is bromine or those wherein R_8 and R_{10} are hydrogens and R_9 is nitro.

Preferred compounds of Formula III above are thosewherein 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, R_1 is hydrogen or methyl, Z is a bond, and R_6 is hydroxy or C_1-C_6 alkoxy.

Still more preferred compounds of Formula II are those wherein R_{11}, R_{12} and R_{14} are fluorines and R_{13} is hydrogen. Other more preferred compounds of Formula II are those where R_a is methyl or hydrogen, Z is methylene or, more preferably, a bond, A is CHF or C_1 or C_2 alkylene, preferably methylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are halogens or C_1-C_3 alkyl. Still other more preferred compounds of Formula III are

those where R_a is methyl or hydrogen, Z is methyle ne or, more preferably, a bond, A is CHF or C_1 or C_2 alkylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are fluorines or chlorines.

Particularly preferred compounds of Formula I are those where R_3 and R_4 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen, and R_a is methyl or hydrogen, Z is a bond, A is methylene, methyl substituted methylene, or ethylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are fluorines or chlorines.

The term "prodrug group" denotes a moiety that is converted in vivo into the active compound of formula I wherein R_6 is hydroxy. Such groups are generally known in the art and include ester forming groups, to form an ester prodrug, such as benzyloxy, di(C_1-C_6)alkylaminoethyloxy, 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, C_1-C_6 alkoxy, and O^-M^+ where M^+ represents a cation. Preferred cations include sodium, potassium, and ammonium. Other cations include magnesium and calcium. Further preferred prodrug grops 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

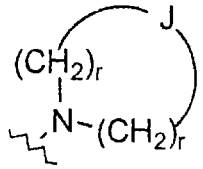
situations, the si ngle enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a r esolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention include the pharmaceutically acceptable acid addition salts of compounds where R_6 includes 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, pa rticularly 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, alkanoic such as acetic , HOOC-(CH_2)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 -benzothiazolyl and benzothiazol-2-yl are synonymous.

Representative groups of the formula



include those where J is oxygen and each r is 2 (morpholinyl), J is nitrogen and each r is 2 (piperazinyl) or one r is 2 and the other 3 (homopiperazinyl), or J is CH_2 and each r is 2 (piperidinyl) or one r is 2 and the other 3 (homopiperidinyl). 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 benzoxazolyl, 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 provide d to give the reader an understanding of the compounds encompassed by the invention:

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-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 general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations contain ing 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 ca rriers 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 com positions 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 un coated 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 capsul es 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 suspensi ons 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.

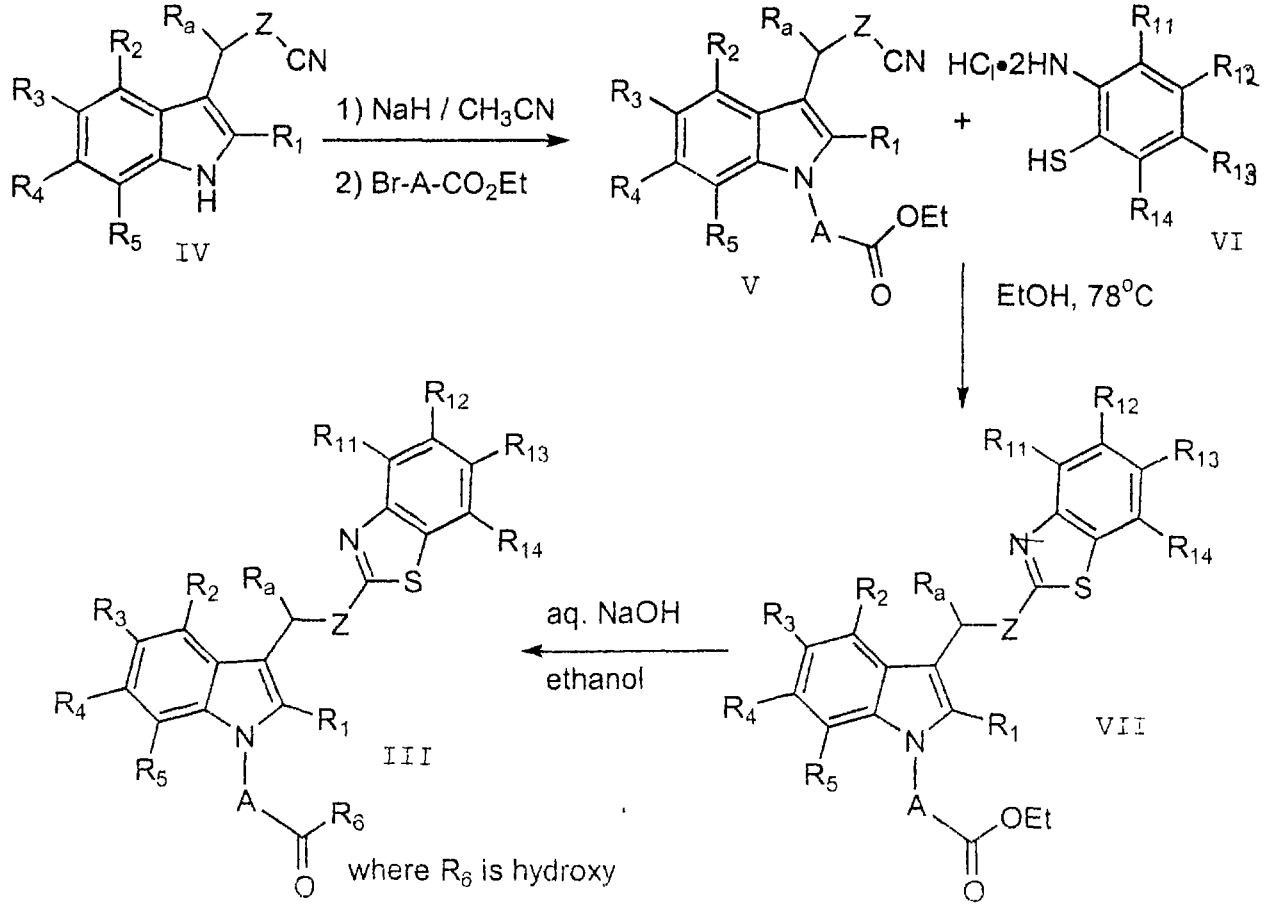
The compounds of the present invention may be prepared by use of known chemical reactions and procedures. General methods for synthesizing the compounds are presented below. It

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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 descri ption 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 benzothiazolyl can be conveniently prep ared from a substituted indole moiety using general Scheme A set forth below.



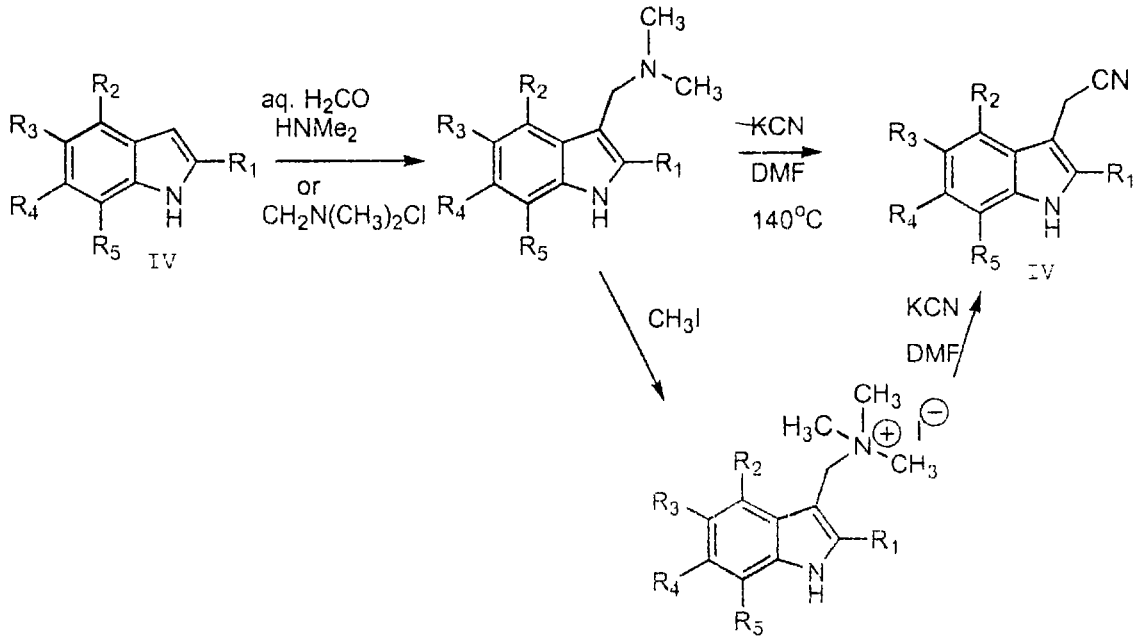
Scheme A

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. Alternativly, phase transfer c atalysis 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, Ney 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.

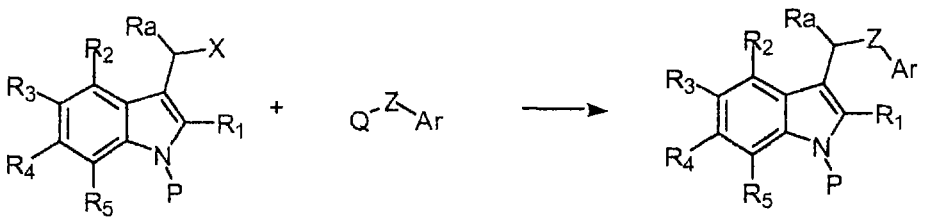


Scheme B

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.

Alternatively, other compounds, such as those where Z -Ar represents a wide variety of substituted hetercycles, may be prepared using the general method outlined in Scheme C. Here, substituted indole intermediates where X is an activating group like hydroxyl, halogen, dialkyl amino, trialkyl ammonium or benzotriazole are coupled with Q -Z-Ar groups using methods well-established in indole chemistry. Examples of these methods where Q is Na or H and Z is sulfur, oxygen, nitrogen carbon or a bond are described in (A) Tidwell, J.H.; Peat, A.J.; Buchwald, S.L. *J. Org. Chem.* **1994**, *59*, 7164; (B) Bruneau, P.; Delvare, C.; Edwards, M.P.; McMillan, R.M. *J. Med. Chem.* **1991**, *34*, 1028; (C) Gan, T.; Cook, J.M. *Tetrahedron Lett.* **1997**, *38*, 1301; (D) Cerreto,F.; Villa, A.; Retico, A.; Scalzo, M. *Eur. J. Med. Chem* . 1992, 27 701; (E) Majchrzak, M.W.; Zobel, J.N.; Obradovich, D.J.; *Synth. Commun.* **1997**, *27*, 3201; (F) DeLeon, C.Y.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 8730; (G) Katritzky, A.R.; Toader, D; Xie, L. *J. Org. Chem.* **1996**, *61*, 7571.

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, a lkyl, sulfonyl or A-COOR. The use of these general methods is illustrated in *Protective Groups in Organic Synthesis*, Second Edition, T. W. Green and P. G. M. Wuts, John Wiley and Sons, Ney York, **1991**.



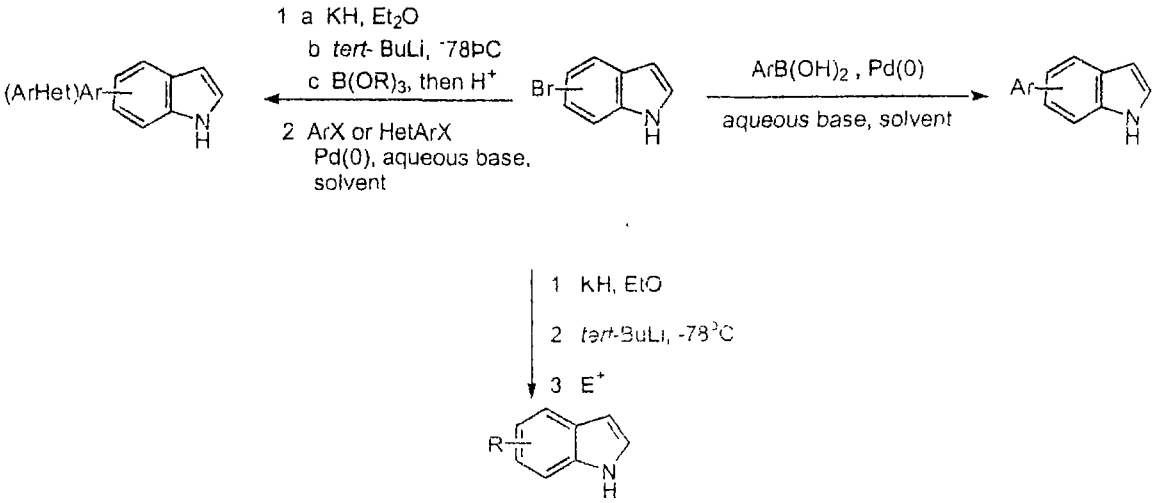
Scheme C

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 *Biorg. 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

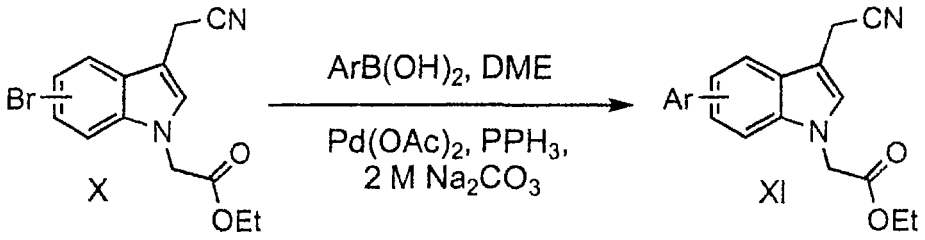
Tetrahedron Lett. **1998**, *39*, 4467, *J. Org. Chem.* **1999**, *64*, 1372 and *Heterocycles* **1992**, *34*, 1395.

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 betwee n boronic acids and aryl halides can be found in Miyaura, N; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.



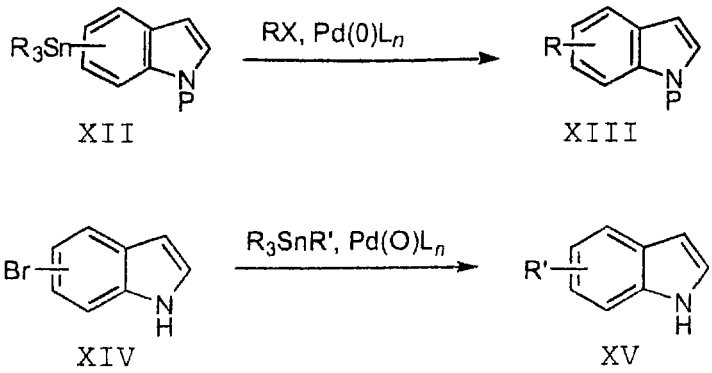
Scheme D

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.

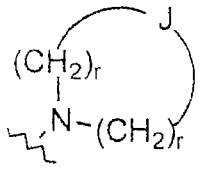


Scheme E

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 $Pd(0)L_n$ 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).



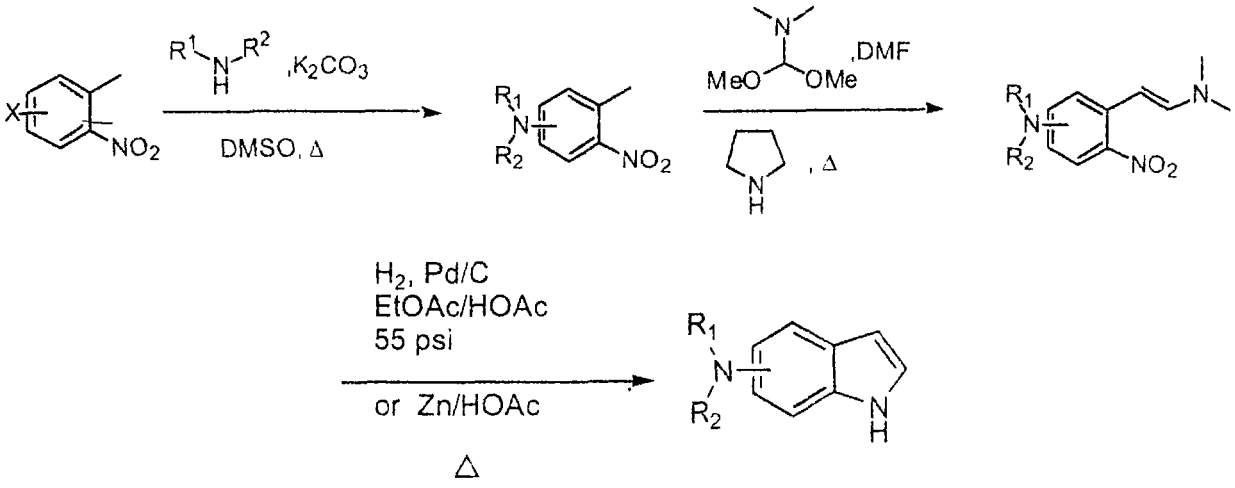
A general procedure for the synthesis of intermediate compounds using amines of the formula NR_xR_{x2} (NR_1R_2 in the scheme below) is given in scheme F below. In Scheme F, R_x and R_{x2} are the same or different and represent hydrogen, C_1-C_6 alkyl, or R_x and R_{x2} together represent a group of the formula:



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 rin gs 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_2CO_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

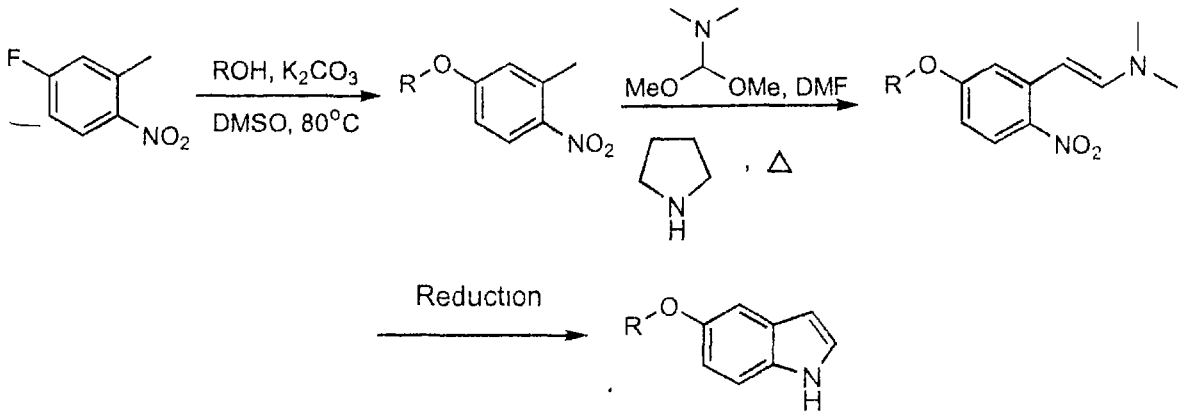
o-nitrotoluene with *N,N*-dimethylformamide dimethyl acetal followed by a reductive cyclization under suitable conditions such as hydrogen over a palladium catalyst or Zn/HOAc as described in Sundberg, R.J. *Indoles*; Chapter 2, Academic Press Inc., San Diego, CA, 1996. A representative description of the process can also be found in *Organic Synthesis*, **1984**, *63*, 214.



Scheme F

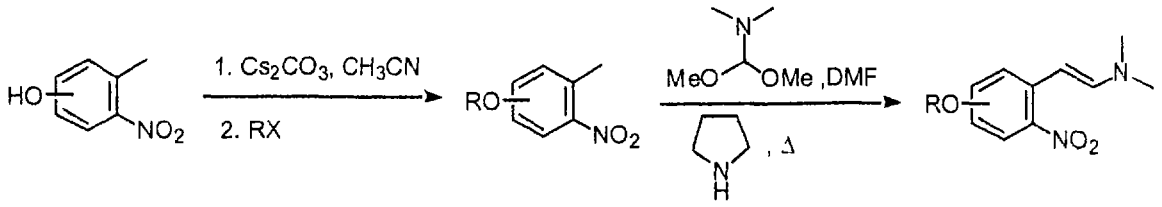
A general procedure for the synthesis of intermediate compounds wherein R is an aromatic, heteroaromatic or alkyl group is indicated in Scheme G below. As previously described, nucleophilic substitution of halogen, preferably fluorine, in an aromatic system is a method often used to substitute aromatic 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 K_2CO_3 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

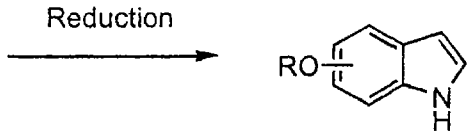
transfer c atalysis (PTC) methods have been used to prepare intermediate ethers of this type as described in *Synth. Comm.* **1990**, *20*, 2855. The appropriately substituted o-nitrotoluene can then be converted to the appropriate indole by the Leimgruber-Batcho method previously desribed.



Scheme G

The preparation of intermediate alkoxy indole compounds wherein R is C_1-C_5 alkyl is outlined in Scheme H below. Commercially available nitrophenols can be alkylated under mild conditions with a base such as, for example, K_2CO_3 or Cs_2CO_3, in a polar aprotic solvent, e.g. CH_3CN, with a variety of suitable alkyl halides. See *Synth. Comm.* **1995**, *25*, 1367. The alkoxy o-nitrotoluene can then be converted to the de sired indole as described above.

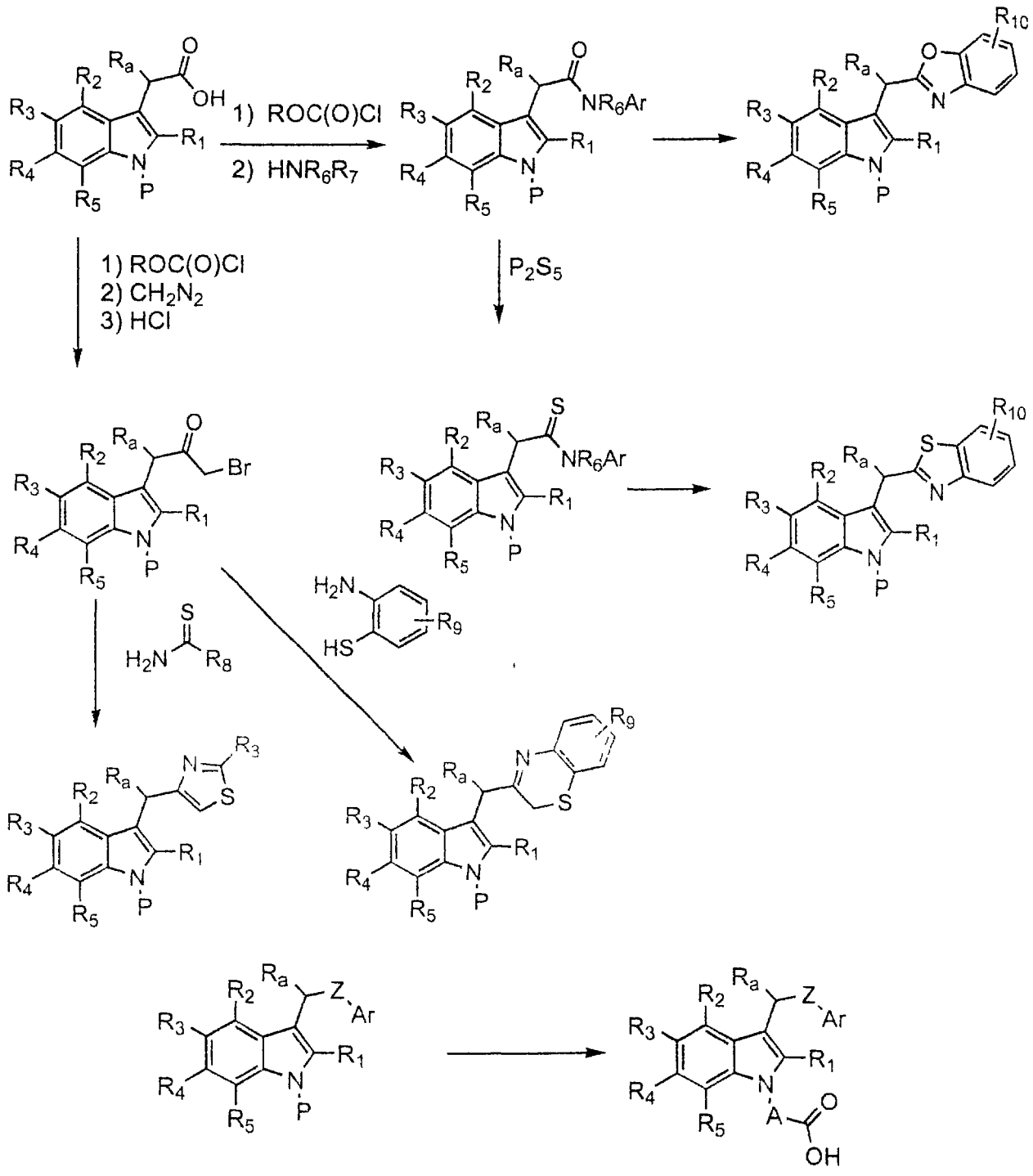




Scheme H

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 con veniently 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 -dicyclohexylcarbodiinide (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 hetercycle 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 thicamides or 2 -aminothiophenols to produce thiazole or benzothiazine derivatives. Examples of methods to prepare th e chloro- and bromomethyl ketones are illustrated in Rotella, D.P.; *Tetrahedron Lett.* **1995**, *36*, 5453 and Albeck, A.; Persky,

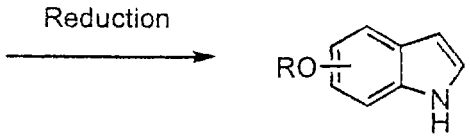
R.; *Tetrahedron* **1994**, *50*, 6333. Depending on the reaction conditions in a given synthetic sequence a protecting group may be required. It is also understood that the specific order of steps used in the synthesis depends on the particular example being prepared. P may represent H, A -COOH, A-COO-lower 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.



Scheme I

Another strategy involves the synthesis of substituted indoles via an intramolecular cyclization of an aniline nitrogen onto a substituted alkyne as shown in Scheme J. 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. Fur ther 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 a cetylenic 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.



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

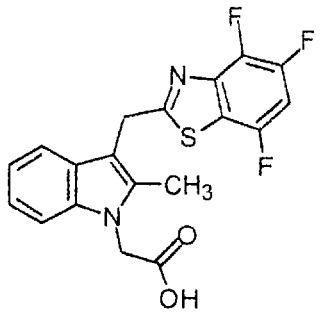
skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

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

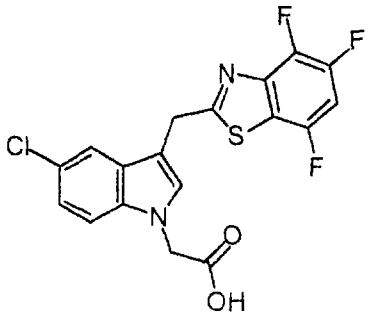


2-Methyl-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 2 -methylindole was used instead of 5-chloroindole in step 1: 178-180°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75-7.62 (m, 1 H), 7.45 (d, *J* = 9.0 Hz, 1 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 7.08 (t, *J* = 9 Hz, 1 H), 6.99 (t, *J* = 9.0 Hz, 1 H), 5.00 (s, 2 H), 4.60 (s, 2 H), 2.38 (s, 3 H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for

$C_{19}H_{13}F_3N_2O_2S$: C, 58.46; H, 3.36; N, 7.18; S, 8.21. F ound: 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



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 al lowed to warm to room temperature and stir overnight. The mixture was added to a sat'd solution of $NaHCO_3$. 1 N NaOH was added until the pH was between 9 -10. The resulting mixture was extracted with CH_2Cl_2 (3X). The organics were combined and washed with a sat'd aq. NaCl, dried over $MgSO_4$, 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

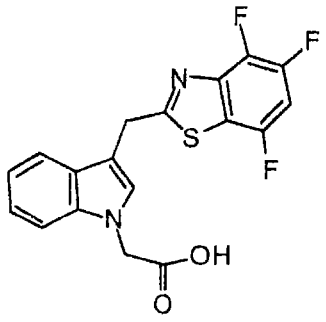
stirring. To this was added KCN (2.18 g, 33.5 mmol) in H_2O (10 mL). The mixture was warmed to 140 °C and stirred for 14 h. H_2O was added and the mixture was extracted with EtOAc (2X). The organics were combined and washed with sat'd brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (3:2, Heptane: EtOAc) to give 2.65 g (63%) of 5 -chloroindole-3-acetonitrile. ^1H NMR (DMSO-d_6, 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 (steps 1 -7), except 5 -chloroindole-3-acetonitrile was used instead of 3-indolyl acetonitrile in step 5: mp 188 -189 °C; ^1H NMR (DMSO-d_6, 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, J_1 = 9.0, J_2 = 2.4 Hz, 1 H), 5.04 (s, 2 H), 4.65 (s, 2 H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 410.0; found 411.0 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 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 -tetrofluoroaniline (200 g, 1.21 mol) in anhydrous pyridine (103 mL, 1.27 mol) wa s 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 $MgSO_4$, 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; R_f 0.48 (50% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 10.10 (s, 1 H), 7.87 -7.74 (m, 1 H), 2.09 (s, 3 H). Anal. Calcd for $C_8H_5F_4NO$: 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 ph osphorous 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 °C 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 °C, 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 disolved in ethyl acetate (1,000 mL), dried over $MgSO_4$ 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: 103-104°C; R_f 0.67 (50% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 11.20 (s, 1 H), 8.00-7.88 (m, 1 H), 2.66 (s, 3 H). Anal. Calcd for $C_8H_5F_4NS$: 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 °C, 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 $MgSO_4$, filtered and concentrated to give 4,5,7 -trifluoro-2-methylbenzothiazole (116.8 g, 96%) as a light brown solid: mp: 91-92 °C; R_f 0.56 (30% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.76-7.67 (m, 1 H), 2.87 (s, 3 H); . Anal. Calcd for $C_8H_4F_3NS$: 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 (appox. 200 mL). The solution was extracted with ether (750 mL) and washed with water (200 mL). The organic layer was dried over Na_2SO_4, 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; R_f 0.43 (30% ethyl acetate in heptane); Anal. Calcd for $C_6H_5ClF_3NS$: 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 $MgSO_4$, filtered and concentrated. The crude product was recrystalized from heptane and ethyl acetate to give the target compound as a white crystalline solid (19 g, 49%): mp 98-99 °C; R_f 0.29 (30% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.59 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1 H), 7.40 (dd, J_1 = 8.1 Hz, J_2 = 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 calc d for $C_{14}H_{14}N_2O_2$: 242.3; found 243.0 $(M + 1)^+$. Anal. Calcd for $C_{14}H_{14}N_2O_2$: 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); ^1H 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 $C_{20}H_{15}F_3N_2O_2S$: 404.4; found 405.0 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{15}F_3N_2O_2S$; 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.

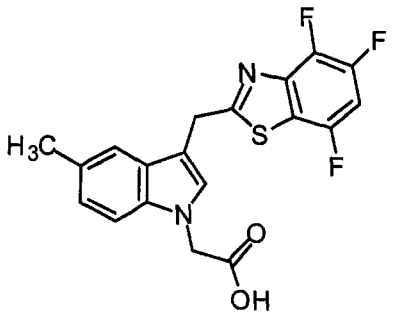
3-(4,5,7-trifluorobenzothiazol-2yl) methyl -indole-*N*-acetic acid:

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 Na_2SO_4, filtered and concentrated. The resulting material was stirred as a supension 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; R_f 0.44 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 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 $C_{18}H_{11}F_3N_2O_2S$: 376.4; found 375.0 $(M - 1)^-$. Anal. Calcd for $C_{18}H_{11}F_3N_2O_2S$: 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 step 1: mp 131 -133 °C; ^{1}H NMR (DMSO-d_6, 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, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 4.98 (s, 2 H), 4.60 (s, 2 H), 2.32 (s, 3 H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for

$C_{19}H_{13}F_3N_2O_2S$: 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 step 1: mp 216 -218 °C; ^{1}H NMR (DMSO-d_6, 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 $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2S$: 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:

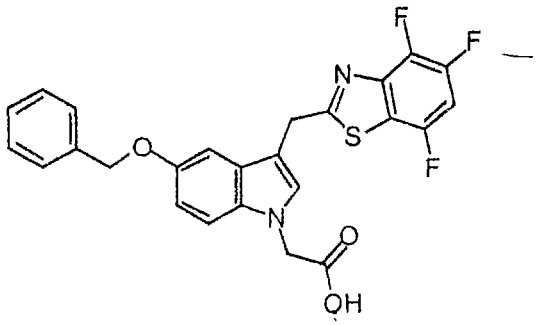
Preparation of 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

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-chlorolindole was used instead of 5-chloroindole in step 1: mp 194 -195°C; ^{1}H NMR (DMSO-d_6, 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_1 = 8.4 Hz, J_2 = 2.1 Hz, 1 H), 4.76 (s, 2 H), 4.62 (s, 2 H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 410.0;

found 411.0 (M + 1) $^{+}$. Analysis calculated for C $_{18}H_{10}F_3N_2O_2SCl$: 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)methyl-indole-*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 step 1: mp 165 -168°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 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 $C_{25}H_{17}F_3N_2O_2S$: 482.0; found 483.0 (M + 1)$^{+}$.

Example 8:

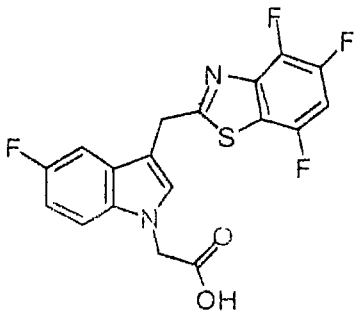
Preparation of 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that

set forth in Example 2, except 6-fluoroindole was used instead of 5-chloroindole in step 1: mp 200-203°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 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 $C_{18}H_{10}F_4N_2O_2S$: 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 step 1: mp 193-195°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 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 $C_{18}H_{10}F_4N_2O_2S$: 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 step 1: mp 211 -213°C, R_f 0.50 (10% methanol in diehloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) □ 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 (steps 5 -7), except 2 -amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2-amino-3,4,6-trifluorothiophenol hydrochloride in step 6: mp 233-234 °C; ^{1}H NMR (DMSO-d_6, 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).

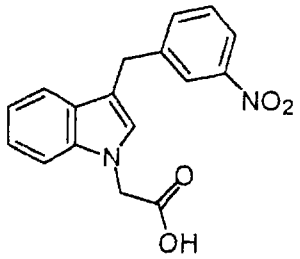
Example 12:

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 step 1 and, 2 -amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2 -amino-3,4,6-trifluorothiophenol hydrochloride in step 2 (Example 3, step 6): mp 248 -249°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.35 (s, 1 H), 7.27 (s, 1 H), 7.25 (d, J = 8.1 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 4.96 (s, 2 H), 4.57 (s, 2 H), 2.31, (s, 3 H); LRMS calcd for $C_{20}H_{15}F_3N_2O_2S$:; found 405 (M + H).

Example 13:

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



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

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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 $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chr omatography (50% ethyl acetate in heptane): Rf0.25 (40% ethyl acetate in heptane) ^1H NMR (DMSO-d_6, 300 MHz) δ 7.53 (d, J = 6.3 Hz, 1 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 th is solution was added Ag_2CO_3/Celite (50% by weight, 0.500 g, 0.9 mmol). The mixture was warmed to 90°C and maintained overnight. H_2O 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 $MgSO_4$, filtered and concentrated *in vacuo* . The residue was purified by SiO_2 flash chromatography (3:2 Heptane: EtOAc) to give 180 mg (22%) as a pale yellow oil. ^1H NMR (DMSO-d_6, 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

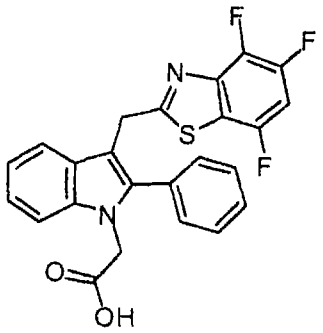
H), 4.19 (s, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 1.18 (t, J = 7.2 Hz, 3 H).

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 mixt ure 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 $MgSO_4$, 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; ^{1}H NMR (DMSO-d_5, 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 $C_{17}H_{14}N_2O_4S$: 310.0; found 311 $(M + 1)^+$.

Example 14

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



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 step 1: mp 238-239°C; R_f 0.60 (10% methanol in chloroform); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 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 $C_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 $(M + 1)^+$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_2S$: 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 atmsophere and treated wit h $Pd(OAc)_2$ (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_2CO_3 (3.11 mL, 6.2 mmol) was added *via* syringe. After 12h, the mixture was cooled to room temperature

and added to H_2O (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%); ^1H NMR (DMSO-d_6, 300 MHz) δ 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-phenylindole was used instead of 5-chloroindole in step 1: mp 156-159 °C; R_f 0.55 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 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 $C_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 $(M+1)^+$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_2S$: 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

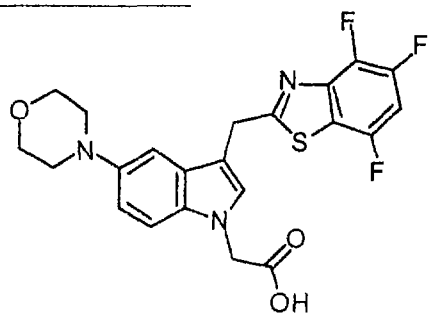
Step 1: 6-Phenylindole

A solution of 6 -bromoindole (2.0 g, 10.20 mmol) in anhydrous toluene (20mL) under a nitrogen atmosphere was treated with $Pd[P(Ph_3)]_4$ (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 addi tion of sat'd $NaHCO_3$ (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 CH_2Cl_2/ heptane) to give the desired material as white powder (900 mg, 45%): ^1H NMR (DMSO-d_6, 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 step 1: mp 156-159°C; R_f 0.50 (10% methanol in chloroform); ^1H NMR (DMSO-d_5, 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 C $_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 $(M+1)^+$. Anal. Calcd for C $_{24}H_{15}F_3N_2O_2S$: 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 K_2CO_3 (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, H_2O 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 $MgSO_4$, 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: R_f 0.40 (75% heptane/ 25% ethyl acetate). ^1H NMR (DMSO-d_6, 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-morpholinyl-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 mixutre 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 hydrogentated 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 SiO_2 flash chromatography (1:1 Hept/EtOAc) to give 2.0 g (31% over 2 steps) of the desired indole as a cream powder: R_f 0.30 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 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, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 6.25 (dd, J_1 = 3.0 Hz, J_2 = 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-morpholinoindole was used instead of 5-chloroindole. ^1H NMR (DMSO-d_6, 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, J_1= 9.0 Hz, J_2= 2.4 Hz, 1H), 4.95 (s, 2H), 4.60 (s, 2H), 3.70-3.73 (m, 4H), 2.97-3.00 (m, 4H); LRMS calcd for $C_{22}H_{18}F_3N_3O_3S$: 461.0; found 462 $(M+1)^+$.

Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S$ $1H_2O$: 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 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 K_2CO_3 (6.83 g, 148.3 mmol) were diluted in anhydrous DMSO (250 mL) at room temperature with stirring. The mi xture was heated to 120 °C for 24 h. After cooling to room temperature, H $_2$O 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 $MgSO_4$, filtered and concentrated *in vacuo*. The remaining solid was triturated in hepatane (200 mL) and filtered to give the desired material (8.00 g, 36.4%) as a yellow powder: R $_f$ 0.40 (25% ethyl acetate in heptane). ^{1}H NMR (DMSO -d_6, 300 MHz) δ 7.40 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.20 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.35 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H).

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 4h. After cooling to room temperature, the mixtu re was neutralized with sat'd $NaHCO_3$ and extracted with Et_2O (3X, 300 mL). The combined organics were washed with sat'd brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by SiO_2 flash chromatography (heptane to 2:1 heptane/EtOAc) to give the desired material as a white crystalline powder (1.0 g, 11% over 2 steps): R_f 0.50 (2:1 Heptane/EtOAc); ^1H NMR (DMSO) -d_6, 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, J_1 = 8.4 Hz, J_2 = 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).

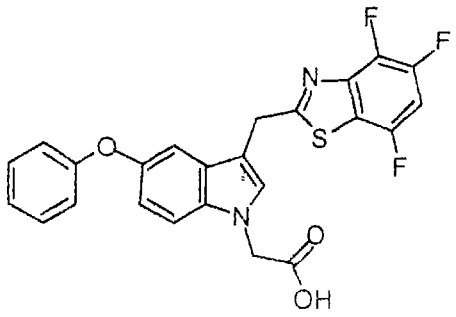
Preparation of 6 -morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-*N*-acetic acid

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 step 1: mp 178 -180°C; ^1H NMR (DMSO-d_5, 300 MHz) δ 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 $C_{22}H_{18}F_3N_3O_3S$: 461.0; found 462 $(M+1)^+$. Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S\ CH_2Cl_2\ 0.50H_2O$: 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-yl)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 p oured into H_2O (100mL). After extraction with EtOAc (2X, 100mL), the organics were combined and washed with a sat'd brine solution, drieds over $MgSO_4$, 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

g, 63%): R_f 0.60 (85% heptane/ 15% EtOAc); ^{1}H NMR (DMSO-d_6, 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, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H), 2.51 (s, 3H).

5-Phenoxyindole

A solution of 5 -phenoxy-2-nitrotoluene (10.03 g, 0.0428 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 H_2O (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 (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 $NaHCO_3$ and extracted with Et_2O (3X, 300 mL). The combined organics were washed with sat'd brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (heptane to 2:1 heptane/ EtOAc) to give the desired material as a white crystalline powder (3.1 g, 34% over 2 steps): R_f 0.50 (2:1 Heptane/ EtOAc); ^{1}H NMR (DMSO -d_6, 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, J_1 = 8. 7 Hz, J_2 = 2.4 Hz, 1H), 6.37 (m, 1H).

Preparation of 5 -phenoxy-3-(4,5,7-triflurobenzothiazol-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 fort h in Example 2, except that 5 -phenoxyindole was used instead of 5 -chloroindole in step 1: mp 128 -130°C; R_f 0.45 (10% methanol in chloroform); ^{1}H NMR (DMSO-d_6, 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 C $_{24}H_{15}F_3N_2O_3S$: 468.0; found 467.0 $(M - 1)^-$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_3S$: 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 step 1: mp 194-196°C; R_f 0.60 (10% methanol in chloroform); ^{1}H NMR (DMSO-d_6, 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 $C_{18}H_{10}F_4N_2O_2S \bullet H_2O$: C, 50.23; H, 3.28; N, 6.51; S, 7.45. Found C,

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50.70; H, 2.52; N, 6.60; S, 7.57. 394.0; found 395.0 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{10}F_4N_2O_2S$

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 step 1: mp 228-230°C; R_f 0.40 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 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 $C_{18}H_{10}F_3N_2O_2SBr$: 454.0 for (^{79}Br and 456.0 for ^{81}Br); found 453.0 $(M - 1)^-$ and 455.0 $(M - 1)^-$. Anal Calcd for $C_{18}H_{10}F_3N_2O_2SBr$: 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

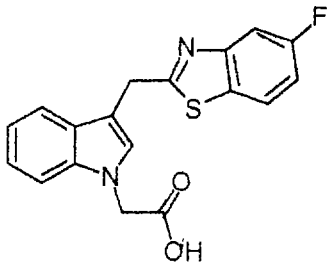
Preparation of 7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

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 step 1: mp 228-230°C; R_f 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 $C_{18}H_{10}F_3N_2O_2SCl$: 410.0; found 409.0 $(M - 1)^-$. Anal. Calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 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



3-[5-fluorbenzothiazole-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 step 6: mp 208°C (decomp); R $_f$0.10 (10% methanol in diehloromethane) ^{1}H NMR (DMSO -d_5, 300 MHz) δ 12.91 (s, 1 H), 7.98 (dd, J = 8.9, 5.6 Hz: 1 H), 7.78 (dd, J = 10.0, 2.6 Hz, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.40 (s, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.26 (dt, J = 8.9, 2.4 Hz, 1 H), 7.13 (t, J = 7.8 Hz, 1 H), 7.01 (t, J = 7.8 Hz, 1 H), 5.01 (s, 2 H), 4.56 (s, 2 H); LRMS *m/z* 341.0 (M + 1) $^+$, 339.0 (M -1). Anal. Calcd for $C_{18}H_{13}FN_2O_2S$: 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.

Example 24

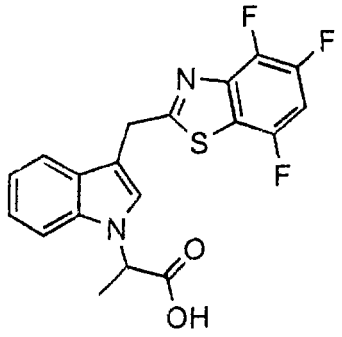
3-[6-Fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic Acid

3-[6-fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic aci d 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 step 6: mp 203°C (decomp) R_f 0.13 (10% methanol in diehloromethane); ^{1}H NMR (DMSO -d_6, 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 $C_{18}H_{13}FN_2O_2S$: C, 63.52; H, 3.85; N, 8.23; S, 9.42. Found: C, 63.52; H, 3.86; N, 8.35: S, 9.53.

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

Example 25

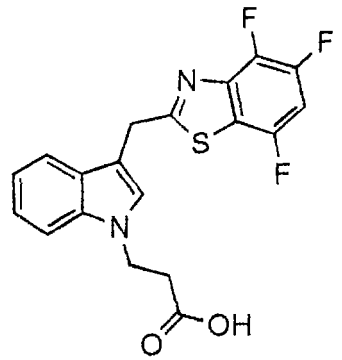
3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid



mp 176-177°C; R_f 0.34 (20% methanol in dichlormeth ane); ^{1}H NMR (DMSO-d_5, 300 MHz) δ 7.60-7.73 (m, 1H), 7.60 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), t, *J*=7.5 Hz, 1H), 7.02 (t, *J*=7.5 Hz, 1H), 5.35 (q, *J*= 8.1 Hz, 1H), 4.64 (s, 2H), 1.72 (d, *J* = 8.1 Hz, 3H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; Found 391.0 $(M^+ 1)^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2SH_2O$: C, 55.88; H, 3.70; N, 6.86; S, 7.85 Found: 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



mp 200-201°C; R_f 0.50 (20% methanol in dichloromethane); ^{1}H 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 $C_{19}H_{13}F_3N_2O_2S$: 390.0; Found 391.0 (M +1)$^+$. Anal Calcd for $C_{19}H_{13}F_3N_2O_2S$: 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

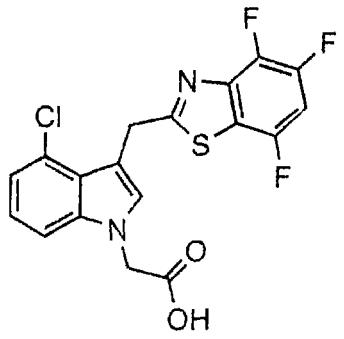
Preparation of 6 -Bromo-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid : mp 265 -267°C; R_f 0.19 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.67-7.69 (m, 2H), 7.43-7.47 (m, 2H), 7.14 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 4.61 (s, 2H); LRMS calcd for $C_{19}H_{12}F_3N_2O_2SBr$:469.0; Found 469.0 (M + 1)$^+$ for Br = 79. Anal. Calcd for $C_{19}H_{12}F_3N_2O_2SBr$: 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 aci d: mp 118 -120°C; R_f 0.27 (20% methanol in dichloromethane); ^{1}H 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 $C_{19}H_{13}F_3N_2O_3S$: 406.0; Found 407.0 (M +)$^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_3SH_2O$: 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

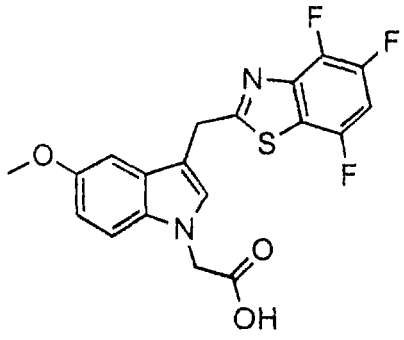
4-Chloro-3-(4,5,7-trifluorobenzothiazol-2yl) methyl-indole-N-acetic acid



mp 203-206 °C; R_f 0.24 (20% methanol in dichloromethane); ^1H 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); L RMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 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); ^1H NMR (DMSO-d_6, 300 MHz) δ 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),

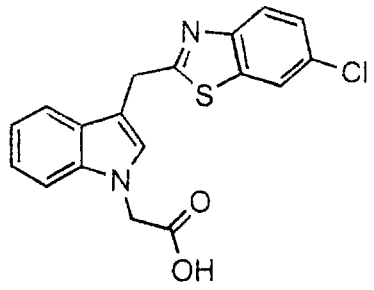
4.79 (s, 2H); 4.56 (s, 2H), 3.72 (s, 3H); LRMS calcd for $C_{10}H_{13}F_3N_2O_2S$: 406.0; Found 407.0 $(M+1)^+$ and 405.0 $(M-1)^-$.

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); ^1H NMR (DMSO-d_6, 300 MHz) δ 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, $J_{(1)}$= 9.0 Hz, $J_{(2)}$= 1.8 Hz, 1H), 5.04 (s, 2H); 4.64 (s, 2H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SBr$: 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



Representative compounds of the invention were tested for their potency, selectivity and efficacy as inhibitors of human aldose reductase. The potency or aldose reductase inhibiting effects of the compounds were tested using methods similar to those described by Butera et al. in *J. Med. Chem.* **1989**, *32*, 757. Using this assay, the concentrations required to inhibit

human aldose reductase (hALR2) activity by 50% (IC50) were determined.

In a second assay, a number of the same compounds were tested for their ability to inhibit aldehyde reductase (hALR1), a structurally related enzyme. The test method employed were essentially those described by Ishii, et al., *J. Med. Chem .* **1996** *39*: 1924. Using this assay, the concentrations required to inhibit human al dehyde reductase activity by 50% (IC50) were determined.

From these data, the hALR1 / hALR2 ratios were determined. Since high potency of test compounds as inhibitors of aldose reductase is desirable, low hALR2 IC50 values are sought. On the other hand, high potency of test compounds as inhibitors of aldehyde reductase is undesirable, and high hALR1 IC50s values are sought. Accordingly, the hALR1 / hALR2 ratio is used to determine the selectivity of the test compounds. The importance of this selectivity is described in Kotani, et al., *J. Med. Chem. 40*: 684, **1997**.

The results of all these tests are combined and illustrated in Table 1.

Example #	hALR2 (IC50)	HALR1 (IC50)	HALR1 / hALR2
1	8 nM	13,000 nM	1,200
2	10nM	11,000nM	1,100
3	5 nM	27,000 nM	5,400
4	8 nM	34,000 nM	4,250
5	6 nM	21,000 nM	3,500

6	8 nM	2,700 nM	340
7	12 nM	4,800 nM	400
8	7 nM	7,500 nM	1,100
9	11 nM	21,000 nM	1,900
10	5nM	13,000 nM	2,600
11	99 nM	5,600 nM	57
12	102 nM	10,000 nM	98
13	73 nM	13,000 nM	178
14	101 nM	16,000	160
15	53 nM	10,000	190
16	25 nM	6,200 nM	248
17	8 nM	41,000 nM	5,100
18	15 nM	>100 μM	>6,700
19	30 nM	11,000 nM	370
20	7 nM	7,000 nM	1,000
21	14 nM	18,000 nM	1,300
22	9.1 nM	19,000 nM	2,100
23	9 nM	6,500 nM	720
24	1,040 nM	4,500 nM	4
25	160 nM	6,500 nM	41
26	17 nM	88,000 nM	5,200
27	52 nM	<5,000 nM	<96
28	5 nM	12,000 nM	2,400
29	11 nM	14,000	1,270
30	7.7 nM	21,000 nM	2,700
31	13 nM	9,700	746
32	660 nM	Not Tested	Not Tested
Tolrestat	13 nM	1,940 nM	149

The results show the superior potency, selectivity and efficacy of representative compounds of the invention. Such

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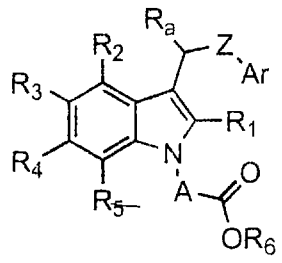
compounds are useful in the treatment of chronic complications arising from diabetes mellitus, such as diabetic cataracts, retinopathy and neuropathy. Accordingly, an as pect of the invention is treatment of such complications with the inventive compounds; treatment includes both prevention and alleviation. The compounds are useful in the treatment of, for example, diabetic cataracts, retinopathy, nephropathy and neuropathy.

In a third, optional, set of experiments, the compounds can be assayed for their ability to normalize or reduce sorbitol accumulation in the sciatic nerve of streptozotocin - induced diabetic rats. The test methods employed to determine the efficacy are essentially those of Mylari, et al., *J. Med. Chem.* *34*: 108, **1991**.

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 for th in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

We claim:

1. A compound of the formula:



wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl or mono- or disubstituted with halogen;

Z is a bond, O, S, C(O)NH, or C_1-C_3 alkylene optionally substituted with C_1-C_2 alkyl;

R_1 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, C_1-C_6 alkoxy, C_1-C_6 alkyl, nitro, amino, or mono- or di(C_1-C_6)alkylamino;

R_2, R_3, R_4 and R_5 are each independently

hydrogen, halogen, nitro, or an alkyl group of 1 -6 carbon atoms (which may be substituted with one or more halogens);

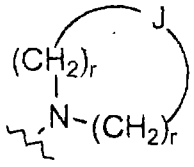
OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$, $C(O)N(R_7)_2$, or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1 -6

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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)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, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy 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



where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2 or 3;

R_6 is hydrogen 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, $S(O)R_7$, $S(O)_2R_7$ 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_5 alkyl, C_1-C_5 alkoxy, amino, and mono- or di(C_1-C_5)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)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (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)alkylthio, 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 t hiophene or with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;

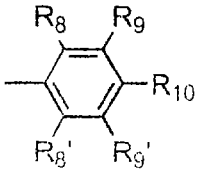
imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or (C_1-C_6)alkoxy, or two of fluoro or chloro;

thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl;

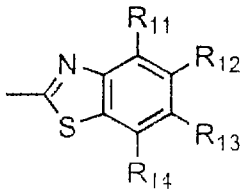
thienotriazole optionally substituted by one of chloro or trifluoromethyl; naphthothiazole; naphthoxazole; or thienoisothiazole.

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



II



III

wherein R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are independently hydrogen, fluorine, chlorine, bromine, trifluoromethyl or nitro.

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

5. A compound according to claim 3, wherein R_a is hydrogen and Z is a bond.

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

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

8. A compound according to claim 7, wherein at least one of R_{11}, R_{12}, R_{13}, and R_{14} is trifluoromethyl.

9. A compound according to claim 8, wherein R_{12} is trifluoromethyl.

10. A compound according to claim 7, wherein R_{11}, R_{12}, and R_{14} are fluorines and R_{13} is hydrogen.

11. A compound according to claim 10, wherein R_6 is hydrogen.

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

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

14. A compound according to claim 13, wherein at least one of R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10} is trifluoromethyl.

15. A compound according to claim 14, wherein R_9 is trifluoromethyl.

16. A compound according to claim 15, wherein R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10} are fluorines and R_1 is hydrogen.

17. A compound according to claim 16, wherein R_5 is hydrogen.

18. A compound according to claim 16, wherein R_5 is C_1-C_5 alkyl.

19. A compound according to claim 1, which is 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester.

20. A compound according to claim 1, which is 3 -(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-*N*-acetic acid.

21. A compound according to claim 1, which is 5-chloro-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

22. A compound according to claim 1, which is 5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester.

23. A compound according to claim 1, which is 2 -methyl-3-(4,5,7 trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

24. A compound according to claim 1, which is 5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

25. A compound according to claim 1, which is 7 -methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

26. A compound according to claim 1, which is 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

27. A compound according to claim 1, which is 5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

28. A compound according to claim 1, which is 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

29. A compound according to claim 1, which is 5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

30. A compound according to claim 1, which is 6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

31. A compound according to claim 1, which is 3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

32. A compound according to claim 1, which is 5-Methyl-3-(5-Trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

33. A compound according to claim 1, which is 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid.

34. A compound according to claim 1, which is 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid, ethyl ester.

36. A compound according to claim 1, which is 2 -phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

37. A compound according to claim 1, which is 5 -phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

38. A compound according to claim 1, which is 6 -phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

39. A compound according to claim 1, which is 5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

40. A compound according to claim 1, which is 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

41. A compound according to claim 1, which is 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

42. A compound according to claim 1, which is 7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

43. A compound according to claim 1, which is 7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

44. A compound according to claim 1, which is 7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

45. A compound according to claim 1, which is 3-(5-fluorobenzothiazole-2-yl) methyl-indole-*N*-acetic acid.

46. A compound according to claim 1, which is 3-(6-fluorobenzothiazole-2-yl) methyl-indole-*N*-acetic acid.

47. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1.

48. A method of preventing or alleviating chronic complications arising from diabetes mellitus, which comprises

administering to a mammal in need of such treatment an effective amount of a compound according to claim 47.

49. A method according to claim 48 wherein the complications are selected from the group consisting of diabetic cataracts, retinopathy, nephropathy and neuropathy.

50. A compound 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.

51. A compound according to claim 1, which is 2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

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52. A compound according to claim 1, which is 5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

53. A compound according to claim 1, which is 7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

54. A compound according to claim 1, which is 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

55. A compound according to claim 1, which is 5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

56. A compound according to claim 1, which is 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

57. A compound according to claim 1, which is 5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

58. A compound according to claim 1, which is 6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

59. A compound according to claim 1, which is 3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic Acid, ethyl ester

60. A compound according to claim 1, which is 5-Methyl-3-(5-Trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester

61. A compound according to claim 1, which is 2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

62. A compound according to claim 1, which is 5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

63. A compound according to claim 1, which is 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

64. A compound according to claim 1, which is 5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

65. A compound according to claim 1, which is 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

66. A compound according to claim 1, which is 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

67. A compound according to claim 1, which is 7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

68. A compound according to claim 1, which is 7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

69. A compound according to claim 1, which is 7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

70. A compound according to claim 1, which is 3-[5-fluorobenzothiazole-2-yl]methyl-indole-*N*-acetic Acid, ethyl ester

71. A compound according to claim 1, which is 3-[6-fluorobenzothiazole-2-yl]methyl-indole-*N*-acetic Acid, ethyl ester

72. A compound according to claim 1, which is 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid

73. A compound according to claim 1, which is 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid, ethyl ester

74. A compound according to claim 1, which is 3-(4-5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-3-propionic acid

75. A compound according to claim 1, which is 3-(4-5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-3-propionic acid, ethyl ester

76. A compound according to claim 1, which is 6-Bromo-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid

77. A compound according to claim 1, which is 6-Bromo-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

78. A compound according to claim 1, which is 6-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

79. A compound according to claim 1, which is 6-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

80. A compound according to claim 1, which is 4-Chloro-3-(4,5,7-trifluorobenzothiazol-2yl)methyl-indole-N-acetic acid

81. A compound according to claim 1, which is 4-Chloro-3-(4,5,7-trifluorobenzothiazol-2yl)methyl-indole-N-acetic acid, ethyl ester

82. A compound according to claim 1, which is 5-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

83. A compound according to claim 1, which is 5-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

84. A compound according to claim 1, which is 5-Bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

85. A compound according to claim 1, which is 5-Bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester

86. A compound according to claim 1, which is 3-(6-chlorobenzothiazol-2-yl)methyl-indole-N-acetic acid

87. A compound according to claim 1, which is 3-(6-chlorobenzothiazol-2-yl)methyl-indole-N-acetic acid, ethyl ester.

88. A pharmaceutical composition comprising an effective amount of a compound according to claim 20.

89. A pharmaceutical composition compris ing an effective amount of a compound according to claim 21.

90. A pharmaceutical composition comprising an effective amount of a compound according to claim 23.

91. A pharmaceutical composition comprising an effective amount of a compound according to claim 31.