(51) International Patent Classification 5:
C07D 235/08, A61K 31/415, C07D 235/12, 235/18

(21) International Application Number: PCT/US96/08353
(22) International Filing Date: 3 June 1996 (03.06.96)
(30) Priority Data: 08/468,482 6 June 1995 (06.06.95) US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION (US/US); Five Giralda Farms, Madison, NJ 07940-0874 (US).
(72) Inventors: ELOKDAH, Hassan, Mahmoud; 432 Chelsea Road, Fairless Hills, PA 19030 (US). SIE-YEARL, Chai; 1 Chatsworth Court, Lawrenceville, NJ 08648 (US). SULKOWSKI, Theodore, Sylvester; 316 Rockland Road, Wayne, PA 19087 (US).

(11) International Publication Number: WO 96/39390
(43) International Publication Date: 12 December 1996 (12.12.96)


Published
With international search report.

(54) Title: BENZIMIDAZOLE DERIVATIVES AS INHIBITORS OF SMOOTH MUSCLE CELL PROLIFERATION

Disclosed herein are compounds and pharmaceutically acceptable salts of compounds of formula (I) or (II), wherein R is alkyl, phenyl or substituted phenyl; R2 is hydrogen, halogen, alkoxy or alkyl; R1 is hydrogen, alkyl, aryl, arylalkyl, or substituted benzyl; which are useful as inhibitors of smooth muscle cell proliferation.

(57) Abstract
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>Armenia</td>
<td>GB</td>
<td>United Kingdom</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>AT</td>
<td>Austria</td>
<td>GE</td>
<td>Georgia</td>
<td>MX</td>
<td>Mexico</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>GN</td>
<td>Guinea</td>
<td>NE</td>
<td>Niger</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GR</td>
<td>Greece</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>HU</td>
<td>Hungary</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>IE</td>
<td>Ireland</td>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>IT</td>
<td>Italy</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>JP</td>
<td>Japan</td>
<td>PT</td>
<td>Portugal</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>KE</td>
<td>Kenya</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>KG</td>
<td>Kyrgyzstan</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>KP</td>
<td>Democratic People’s Republic of Korea</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>CP</td>
<td>Central African Republic</td>
<td>KR</td>
<td>Republic of Korea</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>KZ</td>
<td>Kazakhstan</td>
<td>SG</td>
<td>Singapore</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>LI</td>
<td>Liechtenstein</td>
<td>SI</td>
<td>Slovenia</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d’Ivoire</td>
<td>LK</td>
<td>Sri Lanka</td>
<td>SK</td>
<td>Slovakia</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>LR</td>
<td>Liberia</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>LT</td>
<td>Lithuania</td>
<td>SZ</td>
<td>Swaziland</td>
</tr>
<tr>
<td>CS</td>
<td>Czechoslovakia</td>
<td>LU</td>
<td>Luxembourg</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>LV</td>
<td>Latvia</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>MC</td>
<td>Monaco</td>
<td>TJ</td>
<td>Tajikistan</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>MD</td>
<td>Republic of Moldova</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>EE</td>
<td>Estonia</td>
<td>MG</td>
<td>Madagascar</td>
<td>UA</td>
<td>Ukraine</td>
</tr>
<tr>
<td>ES</td>
<td>Spain</td>
<td>ML</td>
<td>Mali</td>
<td>UG</td>
<td>Uganda</td>
</tr>
<tr>
<td>FI</td>
<td>Finland</td>
<td>MN</td>
<td>Mongolia</td>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>FR</td>
<td>France</td>
<td>MR</td>
<td>Mauritania</td>
<td>UZ</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>GA</td>
<td>Gabon</td>
<td></td>
<td></td>
<td>VN</td>
<td>Viet Nam</td>
</tr>
</tbody>
</table>
BENZIMIDAZOLE DERIVATIVES AS INHIBITORS OF SMOOTH MUSCLE CELL PROLIFERATION

This invention relates to benzimidazole derivatives which are useful as smooth muscle cell proliferation inhibitors and to the use of these compounds and pharmaceutical compositions containing these compounds in the treatment of diseases and conditions associated with excessive smooth muscle cell proliferation, such as restenosis, and to a process for the preparation of such compounds.

Proliferation and directed migration of vascular smooth muscle cells are important vascular occlusive components in such processes as hypertension-induced vascular remodeling, vascular restenosis, and atherosclerosis (Gibbons, G.H.; Dzau, V.J.; NEJM, 1994; 330: 1431). The overall disease process is referred to as hyperproliferative vascular disease based on the etiology of the disease process. Vascular occlusion is preceded by stenosis resulting from intimal smooth muscle cell hyperplasia (Clowes, A.W.; Reidy, M.A.; J. Vasc. Surg., 1991, 13: 885). The underlying cause of intimal smooth muscle cell hyperplasia is vascular smooth muscle cell injury leading to disruption of the endothelium and extracellular matrix (Schwartz, S.M., Human Pathology, 1987; 18: 240; Fingerle, J., Arteriosclerosis, 1990; 10: 1082). Normally, the cells of the arterial wall are under close negative control and in a low basal proliferating state or in a quiescent non-proliferating state. Following vascular injury, the release of growth factors and cytokines result in smooth muscle cell proliferation and migration (Fagin, J.A.; Forrester, J.S., Trends in Cardiovascular Med., 1992; 2; 90.; Shiratani, M.; Yui, Y.; Kawai, C., Endothelium, 1993; 1: 5).


Percutaneous transluminal coronary angioplasty has achieved wide acceptance for the treatment of coronary artery stenosis. In this procedure the endothelium is

DE 4, 129, 603 discloses fused heterocyclic compounds (benzimidazoles) as inhibitors of collagen-induced platelet aggregation and fibrinogen, that may also be useful in the "treatment of transluminal angioplasty". US 5,387,600 discloses 2-thio substituted benzimidazoles for the treatment of atherosclerosis. US 5,026,705 discloses 2-styryl benzimidazolyl pyridazinones as positive inotropic agents useful in the treatment of congestive heart failure.

US 5,200,422 discloses a family of 1-(substituted phenyl or naphthyl)-2H-benzimidazole-2-ones as potassium channel openers. US 4,814,329 discloses 5-substituted-2-thiono or substituted-thio benzimidazole derivatives for treatment of hyperlipoproteinemic diseases and inhibition of atherosclerosis and thrombus formation. US 5,376,665 discloses a group of 4-(benzimidazol-2-yl and benzthiazol-2-yl)-carbamoyl or sulfamoyl-benzyl phosphonate derivatives for the treatment of diabetes and hyperlipidemia. US 4,859,684 discloses a group of 1H-imidazol-1-ylmethyl substituted benzimidazoles for the treatment of androgen dependent disorders. Certain intermediate compounds disclosed therein are benzoyl benzimidazoles of the present invention, however no biological or therapeutic activity is disclosed for these compounds.
In accordance with this invention, there is provided a group of benzoyl benzimidazoles (formula I) and reduction products thereof (formula II) as well as pharmaceutical compositions containing those compounds and the method of using the compounds in the treatment of conditions involving excessive smooth muscle cell proliferation such as restenosis.

Accordingly, there is provided a pharmaceutically acceptable salt of a compound of formula I or II:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\begin{array}{c}
\text{R}_{2} \quad \text{C} \quad \text{N} \\
\text{R}_{1}
\end{array} \\
\end{array}
\end{align*}
\]

wherein \( R \) is alkyl of 1 to 6 carbon atoms, phenyl, phenyl or benzyl substituted with halogen, hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms; \( R_{2} \) is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms; \( R_{1} \) is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxycarbonyl of 2 to 6 carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms, provided that the pharmaceutically acceptable salt of the compound of formula II is not \( \alpha-(3-\text{fluorophenyl})-2\text{-methyl}-1\text{H}-\text{benzimidazole-5-methanol monohydrochloride or 2-methyl-}\alpha-\text{phenyl-1H-benzimidazole-5-methanol hydrochloride.} \)

In a further aspect of the present invention there is provided a compound of formula I or II:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\begin{array}{c}
\text{R}_{2} \quad \text{C} \quad \text{N} \\
\text{R}_{1}
\end{array} \\
\end{array}
\end{align*}
\]

wherein \( R \) is alkyl of 1 to 6 carbon atoms, substituted phenyl or substituted benzyl in which the substituents are one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, trifluoromethoxy, or alkyl of 1 to 6 carbon atoms; \( R_{2} \) is hydrogen; \( R_{1} \) is hydrogen, benzyl or benzyl substituted with one or more of halogen, carboxyl, alkoxycarbonyl of 2 to 6
carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms, or a pharmaceutically acceptable salt thereof; provided that in formula I when R₁ and R₂ are hydrogen, R is not p-methoxyphenyl.

In another aspect of the present invention there is provided a compound of

\[
\text{I} \quad \begin{array}{c}
\text{C} \\
\text{N} \\
R_1 \\
\text{R} \\
\end{array}
\]

wherein R is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms; R₂ is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms; R₁ is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxycarbonyl of 2 to 6 carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms, or a pharmaceutically acceptable salt thereof; provided that when R₁ and R₂ are hydrogen, R is not phenyl or p-methoxy-phenyl.

Preferred compounds are those of formula I or II wherein R is alkyl of 1 to 6 carbon atoms, phenyl or phenyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms; R₂ is hydrogen; R₁ is hydrogen, or benzyl substituted with one or more of halogen, carboxyl or alkoxycarbonyl of 2 to 6 carbon atoms, or a pharmaceutically acceptable salt thereof.

When R is alkyl it is preferably methyl, ethyl, propyl or butyl. When R is phenyl or benzyl it is preferably substituted with methoxy, trifluoromethoxy, hexyl or hydroxy. When R₁ is benzyl, preferred substituents are halogen, carboxyl or alkoxycarbonyl. When R₁ is substituted with alkoxycarbonyl, it is preferably methoxycarbonyl or ethoxycarbonyl. When halogen is a substituent on any R, R₁ or R₂ group, it is preferably fluorine or chlorine. R₂ is preferably hydrogen.

Particularly preferred compounds are:

- (phenyl-(2-propyl-1H-benzoimidazol-5-yl)-methanone or a pharmaceutically acceptable salt thereof.
- 5 -

- 4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester or a pharmaceutically acceptable salt thereof.

- 4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester or a pharmaceutically acceptable salt thereof.

5 - 4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl) benzoic acid or a pharmaceutically acceptable salt thereof.

- 4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid or a pharmaceutically acceptable salt thereof.

- 4-[5-(hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid or a pharmaceutically acceptable salt thereof.

- 1-(3,4-dichloro-benzyl)-2-propyl-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof.

- 2-[4-hydroxy-3-methoxy-phenyl]-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof.

10 - 2-[4-hexyloxy-3-methoxy-phenyl]-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof.

- (phenyl-[2-[4-trifluoromethoxy-phenyl]-1H-benzoimidazol-5-yl]-methanone or a pharmaceutically acceptable salt thereof.

- [2-(3,4-dimethoxybenzyl)-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof.

The compounds of this invention are prepared according to the general sequence of reactions outlined in the following scheme:
The iminoether hydrochloride (1) is prepared by reacting an appropriate nitrile with an alcohol and hydrogen chloride at around 0°C. Reaction of (1) and a 3,4-diaminobenzophenone in refluxing ethanol affords the corresponding benzoyl benzimidazole (2) where R₁ is hydrogen, substituted in the 2-position. Alkylation of (2) with an alkyl, aryl or arylalkyl halide in dimethyl formamide using sodium hydride as base affords the regioisomers (3a, 3b). The isomers can be separated by recrystallization and chromatography. The benzoylbenzimidazoles further can be reduced with sodium borohydride in ethanol to obtain the corresponding alcohols (4a, 4b).

Thus, according to a further aspect of the present invention there is provided a process for the preparation of a compound of formula I or II as previously defined herein which comprises (a) reacting a nitrile of formula RCN with an alcohol and hydrogen chloride to form a compound of formula (1) in which R is as previously defined (b) reacting the compound of formula 1 and a 3,4-diaminobenzophenone of formula

in which R₂ is as previously defined, in refluxing alcohol to give the corresponding compound of formula (2), (c) optionally alkylating the compound of formula (2) with an alkyl, aryl or arylalkyl halide in the presence of a base affords the isomers (3a, 3b), (d) and optionally separating the isomers by recrystallization and chromatography, (e)
and optionally further reacting the compounds of formula (I) with a reducing agent to obtain the corresponding compound of formula (II).

The pharmaceutically acceptable acid addition salts are those derived from such organic and inorganic acids as: acetic, lactic, citric, fumaric, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, methylbenzene sulfonic, and similarly known acceptable acids. With those compounds possessing an acidic substituent such as the carboxylic acids, the pharmaceutically acceptable salts include the alkali metal salts (sodium or potassium), the alkaline earth metal salts (calcium or magnesium) and ammonium salts.

This invention includes pharmaceutical compositions comprised of the benzimidazoles of the invention either alone or in combination with excipients (i.e. pharmaceutically acceptable materials with no pharmacological effect). Such compositions are useful in treating diseases which are characterized by excessive smooth muscle cell proliferation most frequently arising from vascular reconstructive surgery and transplantation, for example, balloon angioplasty, vascular graft surgery, coronary artery bypass surgery, and heart transplantation. Other disease states in which there is unwanted vascular proliferation include hypertension, asthma, and congestive heart failure. The compounds of this invention are thus useful for treating these diseases and states.

The compounds of this invention may be administered systemically, for example by intravenous injection, typically ranging from 0.1 to 10 mg/kg/h over 5-30 days, by subcutaneous injection at lower dose or by oral administration at higher dose than intravenous injection. Localized delivery of the compounds of this invention may also be achieved by transmembrane, transdermal or other topical administrative routes using appropriate continuous release devices such as a supporting matrix, where applicable. The compositions of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent and the like. These are formulated in a conventional manner.

The compounds may be administered neat or with a solid or liquid pharmaceutical carrier to a patient in need of such treatment. Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely
divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form. Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.
Thus, according to a further aspect of the present invention there is provided a 
pharmaceutical composition comprising a compound of formula I or II as defined 
herein and a pharmaceutically acceptable carrier.

The dosage to be used in the treatment of a specific patient suffering from a 
disease involving smooth muscle cell proliferation must be subjectively determined by 
the attending physician. The variables involved include the specific disease state and 
the size, age and response pattern of the patient.

The compounds are useful for preventing smooth muscle cell proliferation in a 
mammal. Thus, according to the present invention there is provided a method of 
treatment of a mammal, in particular, for preventing smooth muscle cell proliferation in 
a mammal which comprises administering to that mammal, orally or parenterally, a 
compound of formula I or II as defined herein. There is also provided the use of the 
compounds of formula I or II as defined herein for treatment of a mammal, in 
particular, for preventing smooth muscle cell proliferation in a mammal which 
comprises administering to that mammal, orally or parenterally, a compound of 
formula I or II as defined herein.

The ability of the compounds of the present invention to inhibit smooth muscle 
cell proliferation was established using isolated porcine aortic smooth muscle cells in a 
modification of the procedure of Castellot et al. J. Biol. Chem 257(19) 11256 (1982), 
as follows:

Fresh porcine aortas, scrupulously cleansed of fatty tissue, are rinsed in sterile 
phosphate-buffered saline with 2% antibiotic-antimycotic (100x) liquid (10,000 units 
of penicillin (base), 10,000 μg of streptomycin (base), and 25 μg of amphotericin 
B/mL utilizing penicillin G (sodium salt), streptomycin sulfate, and amphotericin B as 
Fungizone® in 0.85% saline, available from Gibco Laboratories, Grand Island 
Biological Co., Grand Island, NY). The tissue is then digested in 10-15 mL of an 
enzyme solution containing collagenase type I, 165 U/mL; elastase type III, 15 U/mL; 
BSA, 2 mg/mL; and soybean trypsin inhibitor, 0.375 mg/mL, followed by incubation 
at 37°C under 5% CO₂ atmosphere for 10 to 15 minutes. After this treatment, the outer 
surface adventitia is removed by peeling with a forceps. The aorta is then 
longitudinally cut and laid open and the endothelial layer is removed by scraping.
The medial layer of cells is rinsed in the enzyme solution, and placed in a new 100 mm dish with 10 mL of enzyme solution. The medial layer of cells is minced using a fine pair of scissors and digested for 2-3 hours at 37°C in 30 mL of fresh enzyme solution. After digestion, the medial tissue is homogenized using a sterile Pasteur pipette with a fire polished tip or an Eppendorf pipette with a 200-1000 μL sterile pipette tip. The suspension is then centrifuged for 10 minutes at 8000 rpm and the pellet is suspended in 4-6 mL of fresh enzyme solution and plated onto 4-6 100 mm flasks with vented caps. The cells are then allowed to grow to confluence and split using 0.25% trypsin. The cells are evaluated for purity and overall quality using antibody to SMC actin.

The cells are assayed in early passage (generally passage 3-7) at sub-confluent conditions. Cultures are grown in 16 mm (24 well) multi-well culture dishes in media 199 supplemented with 10% fetal bovine serum and 2% antibiotic/antimycotic. At subconfluence, the cells are placed in a defined serum free, lymphocyte medium (AIM-V; Gibco) for 24-48 hours prior to initiating the experimental protocol.

The standard test procedure is initiated by addition of the test compound, ³H thymidine and serum or a specific growth factor to the serum deprived synchronized cells. Growth factor and serum stimulations are optimized for each cell type. The test compounds are added to each well at 50 fold dilution (20 μL/well) and the plates are incubated for 24-36 hours at 37°C in 5% CO₂ atmosphere. Test compounds are dissolved in 50% ethanol and assayed at 1, 10, and 100 μM. As a control, RG 50872 (Bilder, G.A.; et al., Am. J. Cell Physiol., 1991; 260: C721) is routinely assayed under the conditions of each cell preparation at a concentration of 5 μM.

At the completion of the experiment, the plates are placed on ice, washed three times with ice cold PBS and incubated in ice cold 10% trichloroacetic acid (TCA) for 30 minutes to remove acid soluble proteins. Each solution is transferred to a scintillation vial containing 0.4N HCl (500 μL/vial to neutralize NaOH) and each well is rinsed two times with water (500 μL) for a total volume of 2 mL/vial.

Data is quantitated by subjecting the vials to a scintillation counter, in triplicate, for both control and experimental samples. Control (100%) data is obtained from maximally stimulated cells, as the result of growth factor or serum stimulation. Experimental data is obtained from cells maximally stimulated with growth factor or serum and treated with a test compound. (The platelet-derived growth factor used in
the assay was human recombinant PDGF-AB purchased from Upstate Biotechnology Inc., Lake Placid, NY). Data is expressed as a percent of control from which IC50s are determined.

To distinguish cytotoxicity from the ability of a compound to prevent proliferation, the test compounds were examined using a commercial modification of the MTT assay. Briefly, cells were grown in 24 well plates to 70-80% confluency. The cells were serum deprived for 24-48 hours prior to initiation of the experimental protocol. To insure that the MTT assay monitored toxicity rather than proliferation, the cells were incubated with 50 mM test compound in fresh medium without serum for 24 hours at 37°C in a humidified CO2 incubator. Upon completion of the compound treatment, MTT indicator dye was added for 4 hours at 37°C. Cells were then solubilized and aliquots from each well were transferred to a 96-well plate for analysis. Absorbance at 570 nm wavelength with a reference wavelength of 630 nm was recorded using an ELISA plate reader. Results are reported as percent viable using no drug (100% viable) and pre-solubilization (0% viable) standards.

The compounds of the present invention are effective inhibitors of smooth muscle cell proliferation as shown by the data presented in Table 1.
Table I

<table>
<thead>
<tr>
<th>Compound of Example Number</th>
<th>Porcine Smooth Muscle Cell Antiproliferation IC50 or % Inhibition at x Concentration</th>
<th>Cytotoxicity % Viable Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>PDGF</td>
</tr>
<tr>
<td>1</td>
<td>39.4%/20μM</td>
<td>12.9 μM</td>
</tr>
<tr>
<td>2</td>
<td>1.04 μM</td>
<td>1.17 μM</td>
</tr>
<tr>
<td>3</td>
<td>1.58 μM</td>
<td>1.23 μM</td>
</tr>
<tr>
<td>4</td>
<td>61.8%/20μM</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>41%/20μM</td>
<td>15.9 μM</td>
</tr>
<tr>
<td>6</td>
<td>45.9%/20μM</td>
<td>11.2 μM</td>
</tr>
<tr>
<td>7</td>
<td>36%/10μM</td>
<td>17.6 μM</td>
</tr>
<tr>
<td>8</td>
<td>90%/20μM</td>
<td>0.096-0.465 μM</td>
</tr>
<tr>
<td>9</td>
<td>8.03-11.42 μM</td>
<td>3.74-4.14 μM</td>
</tr>
<tr>
<td>10</td>
<td>13.5 μM</td>
<td>0.762 μM</td>
</tr>
<tr>
<td>11</td>
<td>1.82 μM</td>
<td>7.7 μM</td>
</tr>
<tr>
<td>12</td>
<td>7.74 μM</td>
<td>0.081-0.140 μM</td>
</tr>
</tbody>
</table>

The following examples are presented by way of illustration rather than limitation for representative compounds of the invention and methods for their production.

EXAMPLE 1

Step 1
Ethyl butyridimide hydrochloride

A solution of butyronitrile (34.5 g; 0.5 mol) in ethanol (25 g; 0.54 mol) was cooled in an ice bath. The cold solution was then saturated with hydrogen chloride gas. The reaction mixture was refrigerated for 18 hours. The excess ethanol was evaporated under vacuum. The residual oil was then treated with a small amount of diethyl ether. Collection of the colorless solid provided the title compound (23 g, 30% yield) which was used in the reaction described in step 2 of this example. 1H-NMR (DMSO-d6; 200 MHz): δ 12.22 (br s, 1H), 11.33 (br s, 1H), 4.46 (q, 2H), 2.62 (t, 2H), 1.65 (m, 2H), 1.32 (t, 3H), and 0.92 ppm (t, 3H).
Step 2
Phenyl-(2-propyl-1H-benzoimidazol-5-yl)-methanone

A mixture of 3,4 diaminobenzophenone (21.2 g; 0.1 mol) and ethyl butyrimidate hydrochloride (22.7 g; 0.15 mol) in ethanol (500 mL) was heated at reflux for a period of 6 hours. The mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/Hexane; 1:1). Crystallization from ethyl acetate provided 12 g (45% yield) of the title compound as an off-white solid, m.p. 131-132°C. Anal. Calcd. for C_{17}H_{16}N_{2}O: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.20; H, 6.06; N, 10.72.

Mass spectrum (EI; M^+) m/z 264. \textsuperscript{1}H-NMR (DMSO-d\textsubscript{6}; 400 MHz) \( \delta \) 12.56 (br s, 1H), 7.84 (s, 1H), 7.73 (m, 2H), 7.65 (m, 1H), 7.60 (s, 2H), 7.56 (t, 2H), 2.82 (t, 2H), 1.80 (m, 2H), and 0.95 ppm (t, 3H).

EXAMPLE 2

Step 1
4-(5-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester (A) and 4-(6-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester (B)

Phenyl-(2-propyl-1H-benzoimidazol-5-yl)methanone (12.1 g; 45.8 mmol) was dissolved in DMF (300 mL) under an atmosphere of nitrogen. Sodium hydride (60% dispersion in oil, 3.7 g; 92.0 mmol) was then added portionwise. The mixture was then stirred at ambient temperature for 0.5 hour. Methyl 4-bromomethyl benzoate (10.5 g; 45.8 mmol) was then added. The reaction mixture was stirred for a period of 4 hours, then water (50 mL) was added. The mixture was concentrated under vacuum. The residue was then subjected to flash chromatography on silica gel (EtOAc/Hexane; 1:1) affording the title compounds.

Compound (A) eluted first giving 8.3 g (44% yield) as a white solid, m.p. 115-117°C. Anal. Calcd. for C_{26}H_{24}N_{2}O_{3}: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.77; H, 5.98; N, 6.61. Mass spectrum (PBEI; M^+) m/z 412. \textsuperscript{1}H-NMR (DMSO-d\textsubscript{6}; 400 MHz): \( \delta \) 7.95 (t, 3H), 7.73 (d, 2H), 7.59-7.68 (m, 3H), 7.56 (t, 2H), 7.23 (d, 2H), 5.67 (s, 2H), 3.82 (s, 2H), 2.82 (t, 2H), 1.74 (m, 2H), and 0.92 ppm (t, 3H). Assignment of the regiochemistry was based on \textsuperscript{1}H-NMR (NOE) experiments.

Compound (B) eluted next giving 3.8 g (20%) as a white solid, m.p. 142-144°C. Anal. Calcd. for C_{26}H_{24}N_{4}O_{3}: C, 75.71; H, 5.86; N, 6.79. Found: C,
75.72; H, 6.00; N, 6.63. Mass spectrum (PBEI; M+) m/z 412. 1H-NMR (DMSO-d6; 400 MHz): δ 7.92 (d, 2H), 7.82 (s, 1H), 7.73 (d, 1H), 7.58-7.64 (m, 4H), 7.48 (t, 2H), 7.20 (d, 2H), 5.68 (s, 2H), 3.83 (s, 2H), 2.87 (t, 2H), 1.77 (m, 2H), AND 0.94 PPM (T, 3H). Assignment of the regiochemistry was based on 1H-NMR (NOE) experiments.

Step 2

4-(5-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester

4-(5-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester (2.0 g) was heated to reflux in ethanolic hydrogen chloride (100 mL) for a period of 24 hours. The solvent was evaporated. The residue was dissolved in fresh ethanol (100 mL). The resulting solution was decolorized with carbon. The mixture was filtered and evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution, then with water. The organic phase was evaporated. The residue was crystallized from EtOAc/Hexane to give 1.2 g (57% yield) of the title compound as a white solid, m.p. 126-128°C. Anal. Calcd. for C27H26N2O3: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.04; H, 6.12; N, 6.56. Mass spectrum (EI; M+) m/z 426. 1H-NMR (DMSO-d6; 400 MHz): δ 7.95 (s, 1H), 7.92 (d, 2H), 7.73 (d, 2H), 7.62-7.68 (m, 3H), 7.53-7.59 (m, 2H), 7.22 (d, 2H), 5.67 (s, 2H), 4.28 (q, 2H), 2.82 (t, 2H), 1.74 (m, 2H), 1.28 (t, 3H), and 0.92 ppm (t, 3H).

EXAMPLE 3

4-(6-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester

The title compound was prepared by the procedure described in step 2 of example 2 using 1.5 g of 4-(6-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester. Crystallization from EtOAc/Hexane afforded the title compound (0.9 g, 57% yield) as a white solid, m.p. 124-126°C. Anal. Calcd. for C27H26N2O3: C, 76.03; H, 6.14; N, 6.57. Found: C, 75.94; H, 6.08; N, 6.54. Mass spectrum (EI; M+) m/z 426. 1H-NMR (DMSO-d6; 400 MHz): δ 7.92 (d, 2H), 7.81 (s, 1H), 7.72 (d, 1H), 7.58-7.65 (m, 4H), 7.49 (t, 2H), 7.20 (d, 2H), 5.68 (s, 2H), 4.29 (q, 2H), 2.88 (t, 2H), 1.77 (m, 2H), 1.29 (t, 3H), and 0.94 ppm (t, 3H).
EXAMPLE 4

4-(6-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl) benzoic acid

A solution of potassium hydroxide (1.0 g in 10 mL of water) was added to a solution of 4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester (1.0 g) in methanol (25 mL). The mixture was heated at reflux for a period of 3 hours. The reaction mixture was cooled to ambient temperature. The methanol was evaporated under vacuum. The residue was diluted with water (30 mL), then extracted with ethyl acetate (24 mL). The aqueous phase was acidified with 1N HCl. The precipitated solid was collected and air dried to afford the title compound (0.6 g, 63% yield) as a white solid m.p. 295–296°C. Anal. Calcd. for C_{25}H_{22}N_{2}O_{3}: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.03; H, 5.65; N, 6.86. Mass spectrum (PBEI; M⁺) m/z 398. ¹H-NMR (DMSO-d₆; 400 MHz): δ 13.0 (br s, 1H), 7.91 (d, 2H), 7.82 (s, 1H), 7.72 (d, 1H), 7.58-7.64 (m, 4H), 7.47 (t, 2H), 7.18 (d, 2H), 5.67 (s, 2H), 2.88 (t, 2H), 1.78 (m, 2H), and 0.94 ppm (t, 3H).

EXAMPLE 5

4-(5-Benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid

The title compound was prepared by the procedure described in step 1 of example 4 using 1.0 g of 4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid methyl ester. The title compound was obtained (0.65 g, 67% yield) as a white solid, m.p. 125-128°C. Anal. Calcd. for C_{25}H_{22}N_{2}O_{3}: C, 75.36; H, 5.57; N, 7.03. Found: C, 74.96; H, 5.79; N, 6.72. Mass spectrum (PBCl⁺; [M+H] m/z 399. ¹H-NMR (DMSO-d₆; 400 MHz): δ 12.96 (br s, 1H), 7.95 (s, 1H), 7.90 (d, 2H), 7.73 (dd, 2H), 7.60-7.68 (m, 3H), 7.56 (t, 2H), 7.20 (d, 2H), 5.67 (s, 2H), 2.83 (dd, 2H), 1.75 (m, 2H), and 0.93 ppm (t, 3H).

EXAMPLE 6

Step 1

4-[6-(Hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid ethyl ester

To a solution of 4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester (1.5 g; 3.5 mmol) in ethanol (50 mL) was added sodium borohydride (1.0 g:
29.4 mmol). After stirring at ambient temperature for 4 hours, acetone (20 mL) was added. The solvent was evaporated. The residue was dissolved in ethyl acetate and washed with water. The organic phase was evaporated to give the title compound (0.9 g, 60% yield) as a white solid which was used without further purification in step 2.

Step 2

4-[5-(Hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid

A solution of potassium hydroxide (1.0 g in 10 mL of water) was added to a solution of 4-[6-(hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid ethyl ester (0.5 g) in ethanol (40 mL). The mixture was heated at reflux for a period of 4 hours. The solvent was evaporated. The residue was dissolved in water and neutralized with 1N HCl. The solid was collected by filtration and dried to give the title compound as a mono hydrate (0.3 g, 60% yield), m.p. 146-149°C. Anal. Calcd. for C25H24N2O3+H2O: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.78; H, 5.86; N, 6.39. Mass spectrum (DCI+M+H)+ m/z 401. 1H-NMR (DMSO-d6; 400 MHz): δ 12.96 (br s, 1H), 7.89 (d, 2H), 7.50 (m, 2H), 7.31 (d, 2H), 7.23 (t, 2H), 7.16 (t, 4H), 5.86 (br s, 1H), 5.74 (s, 1H), 5.58 (s, 2H), 2.81 (t, 2H), 1.73 (m, 2H), and 0.91 (t, 3H).

EXAMPLE 7

Step 1

4-[5-(Hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid ethyl ester

The title compound was prepared by the procedure described in step 1 of example 6 using 1.5 g of 4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester. The title compound was obtained (1.0 g, 67% yield) and was used without further purification in step 2.

Step 2

4-[5-(Hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid hydrochloride

A solution of potassium hydroxide (1.0 g in 10 mL of water) was added to a solution of 4-[5-(hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid ethyl ester (0.5 g) in ethanol (30 mL). The mixture was heated at reflux
for a period of 4 hours. The solvent was evaporated. The residue was dissolved in warm water (50 mL). The resulting solution was acidified with concentrated HCl. The precipitated solid was collected by filtration and dried to give the title compound as the monohydrochloride, monohydrate (0.4 g, 75% yield) as a white solid, m.p. 209-212°C.

Anal. Calcd. for C_{25}H_{24}N_{2}O_{3}·HCl·H_{2}O: C, 66.00; H, 5.98; N, 6.16; Cl, 7.81.

Found: C, 65.90; H, 5.82; N, 6.15; Cl, 8.20. Mass spectrum (EI; M⁺) m/z 400. ¹H-NMR (DMSO-d₆; 400 MHz) δ 13.0 (br s, 1H), 7.90 (d, 2H), 7.82 (s, 1H), 7.64 (d, 1H), 7.47 (d, 1H), 7.39 (d, 2H), 7.28-7.34 (q, 4H), 7.19 (t, 1H), 6.12 (br s, 1H), 5.89 (s, 1H), 5.81 (s, 2H), 3.14 (t, 2H), 1.77 (m, 2H), and 0.92 ppm (t, 3H).

EXAMPLE 8

[1-(3,4-Dichloro-benzyl)-2-propyl-1H-benzoimidazol-5-yl]-phenyl-methanone

A solution of phenyl-(2-propyl-1H-benzoimidazol-5-yl)methanone (5.28 g; 0.02 mol) in DMF (80 mL) was stirred under an atmosphere of nitrogen. Sodium hydride (60% dispersion in oil, 0.8 g; 0.02 mol) was added. The mixture was then stirred for 0.5 hour at ambient temperature. 3,4-dichlorobenzyl bromide (4.8 g; 0.02 mol) was then added in portions. The mixture was stirred at 80-90°C for 3.5 hours, then at ambient temperature for 18 hours. The solvent was evaporated under vacuum.

The residue was extracted with ethyl acetate (300 mL) and washed with water (2x200 mL). The organic phase was evaporated. Purification was achieved by flash chromatography on silica gel (EtOAc/Hexane; 1:9 to 1:3). Recrystallization from ethyl acetate affords the title compound (4.2 g; 50% yield) as a white solid, m.p. 168-169°C.

Anal. Calcd. for C_{24}H_{20}Cl_{2}N_{2}O: C, 68.09; H, 4.76; N, 6.62. Found: C, 67.70; H, 4.46; N, 6.49. Mass spectrum (DEI; M⁺) m/z 422, 424, 426. ¹H-NMR (DMSO-d₆; 400 MHz) δ 7.94 (d, 1H), 7.73 (d, 2H), 7.64-7.72 (m, 3H), 7.59 (m, 1H), 7.56 (t, 2H), 7.47 (d, 1H), 6.98 (dd, 1H), 5.59 (s, 2H), 2.84 (t, 2H), 1.76 (m, 2H) and 0.94 ppm (t, 3H).

EXAMPLE 9

Step 1

Ethyl-(4-Hydroxy-3-methoxy)-benzoimide hydrochloride

A solution of 4-hydroxy-3-methoxybenzonitrile (10 g, 67 mmol) in 60 mL of ethyl alcohol was cooled in an ice bath. The cold solution was then saturated with
hydrogen chloride gas. The reaction mixture was kept refrigerated for 18 hours. The precipitate was collected by filtration. The colorless solid gave 7.2 g (47% yield) of the title compound which was used in the next reaction, m.p. 151-154°C. ¹H-NMR (DMSO-d₆; 200 MHz) δ 11.78 (s, 1H), 10.9 (s, 1H), 7.8 (s, 1H), 7.6 (d, 1H), 6.98 (d, 1H), 4.5 (q, 2H), 3.8 (s, 3H), and 1.4 ppm (t, 3H).

Step 2

[2-(4-Hydroxy-3-methoxy-phenyl)-1H-benzoimidazol-5-yl]-phenyl-methanone

A mixture of 3,4-diaminobenzophenone (2.12 g; 10 mmol) and ethyl-(4-hydroxy-3-methoxy)-benzoinidate hydrochloride (2.31 g; 10 mmol) in ethanol (70 mL) was stirred at ambient temperature for 18 hours. Yellow solid formed was separated by filtration. Recrystallization from ethanol gave 862 mg (26% yield) of the title compound as a creamy solid, hydrochloride, m.p. 261°C dec. Anal. Calcd. for C₂₁H₁₆N₂O₃.HCl: C, 66.23 H, 4.50; N, 7.35. Found: C, 65.69; H, 4.37; N, 7.18.

¹H-NMR (DMSO-d₆; 400 MHz) δ 8.08 (s, 1H), 8.02 (s, 1H), 7.85-7.92 (m, 3H), 7.8 (d, 2H), 7.7 (t, 1H), 7.6 (t, 2H), 7.08 (d, 1H), 3.9 (s, 3H), 3.8 ppm (s, 1H).

EXAMPLE 10

Step 1

4-Hexyloxy-3-methoxybenzonitrile

To a suspension of sodium hydride, 60% dispersion in oil, (4.8 g; 0.11 mol) in 40 mL of DMF, a solution of 4-hydroxy-3-methoxy-benzonitrile (14.9 g; 0.1 mol) in DMF (40 mL) was added dropwise over 10 minutes. After addition, the reaction mixture was stirred at ambient temperature for 30 minutes, then bromohexane (16.5 g; 0.1 mol) in DMF (20 mL) was added. The reaction mixture was stirred at ambient temperature for 18 hours. The DMF containing reaction mixture was concentrated to a residue, and H₂O (100 mL) was added to the residue. The solid was collected by filtration to obtain 8.2 g (35% yield) of the title compound as white solid. ¹H-NMR (DMSO-d₆; 200 MHz) δ 7.45 (s, 1H), 7.42 (s, 1H), 7.1 (d, 1H), 4.0 (t, 2H), 3.8 (s, 3H), 1.6-1.8 (m, 2H), 1.2-1.5 (m, 8H), and 0.9 ppm (t, 3H).
Step 2

Methyl-(4-Hexyloxy-3-methoxy)-benzoimidate hydrochloride

The title compound was prepared in 60% yield (3.1 g) by the procedure of step 1 of Example 9 using 4-hexyloxy-3-methoxybenzonitrile (4.0 g; 17 mmol) and methanol. $^1$H-NMR (DMSO-d$_6$; 200 MHz) δ 11.6 (s, 1H), 7.8-7.7 (d, 2H), 7.2 (d, 1H), 4.13 (s, 3H), 4.1 (t, 2H), 3.82 (s, 3H), 1.6-1.8 (m, 2H), 1.2-1.5 (m, 8H), 0.85 ppm (t, 3H).

Step 3

[2-(4-Hexyloxy-3-methoxy-phenyl)-1H-benzoimidazol-5-yl]phenyl-methanone

A mixture of 3,4-diaminobenzenophenone (1.49 g; 6.6 mmol) and methyl-(4-hexyloxy-3-methoxy)-benzoimide hydrochloride (2.0 g; 6.6 mmol) in methanol (50 mL) was stirred at ambient temperature for 72 hours. Precipitate formed was collected by filtration. The creamy solid gave 1.4 g (50% yield) of the title compound, m.p. 150-153°C. Anal. Calcd. for C$_{27}$H$_{28}$N$_2$O$_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.67; H, 6.59; N, 6.54. Mass Spectrum: (EI; M$^+$) m/z 428. $^1$H-NMR (DMSO-d$_6$; 400 MHz) δ 7.85-7.9 (d, 1H), 7.71-7.8 (m, 4H), 7.62-7.7 (dd, 3H), 7.6 (t, 2H), 7.15 (d, 1H), 4.1 (t, 2H), 3.89 (s, 3H), 1.7-1.8 (m, 2H), 1.38-1.46 (m, 2H), 1.26-1.35 (m, 4H), 0.88 ppm (t, 3H).

EXAMPLE 11

Step 1

Methyl-(4-Trifluoromethoxy)-benzoimidate hydrochloride

The title compound was prepared in 59 % yield (4.0 g) from 4-trifluoromethoxybenzonitrile (5.0 g; 26 mmol) and methanol (50 mL) using the procedure described in the step 1 of Example 9, m.p. 148-151°C.

Step 2

Phenyl-[2-(4-trifluoromethoxy-phenyl)-1H-benzoimidazol-5-yl]methanone

The title compound was prepared by the procedure described in step 3 of Example 10 using methyl-(4-trifluoromethoxy)-benzoimidate hydrochloride (2.0 g; 7.8
mmol). Recrystallization from methanol afforded 1.5 g (52%) of off-white solid, m.p. 215-217°C. Anal. Calcd. for C_{21}H_{13}N_{2}O_{2} F_{3} : C, 65.97; H, 3.43; N, 7.33; Found: C, 66.09; H, 3.28; N, 7.34. ¹H-NMR (DMSO-d$_6$; 200MHz) δ 13.5 (d, 1H), 8.3-8.4 (d, 2H), 7.9-8.1 (d, 1H), 7.7-7.9 (m, 5H), 7.5-7.6 ppm (m, 4H).

**EXAMPLE 12**

**Step 1**

Methyl-(3,4-Dimethoxyphenyl)-acetimidate hydrochloride

The title compound was prepared by the procedure described in step 1 of Example 9 using 3,4-dimethoxyphenylacetanitrile (10 g; 56 mmol) in methanol (150 mL). 7.8 g (54% yield) of the title compound was obtained and used in the next reaction.

**Step 2**

[2-(3,4-Dimethoxybenzyl)-1H-benzoimidazol-5-yl]-phenyl-methanone

A mixture of methyl-(3,4-dimethoxyphenyl)-acetimidate hydrochloride (2.5 g; 10 mmol) and 2,3-diaminobenzophenone (2.1 g; 10 mmol) in methanol (70 mL) was stirred at ambient temperature for 72 hours. The reaction mixture was concentrated to dryness, and H$_2$O was added. The solid (2.3 g) was subjected to flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH; 9:1) to afford a gummy material. This was dissolved in diethyl ether, and Ether-HCl was added to obtain the title compound as a buff solid, hydrochloride, penta-hydrate (250 mg), m.p. 172-175°C. Anal. Calcd. for C$_{23}$H$_{20}$N$_2$O$_3$HCl.5H$_2$O: C, 66.97; H, 5.23; N, 6.79. Found: C, 67.11, H, 4.84; N, 6.77. Mass Spectrum: (EI; M$^+$) m/z 372. ¹H-NMR (DMSO-d$_6$; 400 MHz) δ 8.0 (s, 1H) 7.84-7.9 (m, 2H), 7.68-7.77 (m, 3H), 7.55-7.61 (m, 2H), 7.2 (s, 1H), 6.93-7.01 (m, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.77 ppm (s, 3H)
CLAIMS

(1) A pharmaceutically acceptable salt of a compound of formula I or II:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\end{align*}
\]

wherein

- R is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;
- R₂ is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;
- R₁ is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxy carbonyl of 2 to 6 carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms; provided that the pharmaceutically acceptable salt of the compound of formula II is not \(\alpha-\text{3-fluorophenyl})\)-2-methyl-1H-benzimidazole-5-methanol monohydrochloride or 2-methyl-\(\alpha\)-phenyl-1H-benzimidazole-5-methanol hydrochloride.

(2) A compound of formula I:

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

wherein

- R is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;
- R₂ is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;
- R₁ is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of
halogen, carboxyl, alkoxycarbonyl of 2 to 6 carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms, or a pharmaceutically acceptable salt thereof; provided that when R₁ and R₂ are hydrogen, R is not phenyl or p-methoxy-phenyl.

5 (3) A compound of formula I or II:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\end{array} & \quad \begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\end{array}
\end{align*}
\]

wherein

R is alkyl of 1 to 6 carbon atoms, substituted phenyl or substituted benzyl in which the substituents are one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, trifluoromethoxy, or alkyl of 1 to 6 carbon atoms;

R₂ is hydrogen;

R₁ is hydrogen, benzyl or benzyl substituted with one or more of halogen, carboxyl, alkoxycarbonyl of 2 to 6 carbon atoms or aryloxycarbonyl of 7 to 12 carbon atoms, or a pharmaceutically acceptable salt thereof; provided that in formula I when R₁ and R₂ are hydrogen, R is not p-methoxy-phenyl.

(4) A compound according to claim 1, 2 or 3 wherein R is alkyl of 1 to 6 carbon atoms, phenyl, phenyl or benzyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, or alkyl of 1 to 6 carbon atoms;

R₂ is hydrogen; R₁ is hydrogen or benzyl substituted with one or more of halogen, carboxyl, or alkoxycarbonyl of 2 to 6 carbon atoms.

(5) A compound which is:

25 phenyl-(2-propyl-1H-benzoimidazol-5-yl)-methanone or a pharmaceutically acceptable salt thereof;

4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester or a pharmaceutically acceptable salt thereof;

4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid ethyl ester or a pharmaceutically acceptable salt thereof;
4-(6-benzoyl-2-propyl-benzoimidazol-1-ylmethyl) benzoic acid or a pharmaceutically acceptable salt thereof;

4-(5-benzoyl-2-propyl-benzoimidazol-1-ylmethyl)-benzoic acid or a pharmaceutically acceptable salt thereof;

5 4-[5-(hydroxy-(phenyl)-methyl)-2-propyl-benzoimidazol-1-ylmethyl]-benzoic acid or a pharmaceutically acceptable salt thereof;
[1-(3,4-dichloro-benzyl)-2-propyl-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof;
[2-(4-hydroxy-3-methoxy-phenyl)-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof;
[2-(4-hexyloxy-3-methoxy-phenyl)-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof;
phenyl-[2-(4-trifluoromethoxy-phenyl)-1H-benzoimidazol-5-yl]-methanone or a pharmaceutically acceptable salt thereof;

15 [2-(3,4-dimethoxybenzyl)-1H-benzoimidazol-5-yl]-phenyl-methanone or a pharmaceutically acceptable salt thereof.

(6) A pharmaceutical composition comprising a compound of formula I or II:

![Chemical Structures]

wherein

R is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with one or more of hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;

R₂ is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;

R₁ is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxy carbonyl of 2 to 6 carbon atoms or aryloxy carbonyl of 7 to 12 carbon atoms,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
(7) A method of treatment of a mammal which comprises administering to that mammal, orally or parenterally, a compound of formula I or II:

\[
\begin{align*}
\text{I} & : \text{ } & \text{II} \\
\text{R}_2 & \quad \text{R}_1 & \quad \text{OH} \\
\end{align*}
\]

wherein

- \( \text{R} \) is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;
- \( \text{R}_2 \) is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;
- \( \text{R}_1 \) is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxy carbonyl of 2 to 6 carbon atoms or aryloxy carbonyl of 7 to 12 carbon atoms,

or a pharmaceutically acceptable salt thereof.

(8) A method according to claim 7 in which the method of treatment is for preventing smooth muscle cell proliferation in a mammal.

(9) A method according to Claim 8 wherein said smooth muscle cell proliferation manifests itself as restenosis following angioplasty.

(10) A compound of formula I or II:

\[
\begin{align*}
\text{I} & : \text{ } & \text{II} \\
\text{R}_2 & \quad \text{R}_1 & \quad \text{OH} \\
\end{align*}
\]

wherein

- \( \text{R} \) is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, phenyl or benzyl substituted with hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;
R₂ is hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;
R₁ is hydrogen, alkyl of 1 to 6 carbon atoms, aryl of 6 to 10 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxy carbonyl of 2 to 6 carbon atoms or aryloxy carbonyl of 7 to 12 carbon atoms, or a pharmaceutically acceptable salt thereof, for use in the treatment of mammals.

(11) A compound as claimed in claim 10 for use in the treatment of diseases or conditions related to smooth muscle cell proliferation.

(12) A compound according to claim 3, 4 or 5 for use in the treatment of mammals.

(13) A compound according to claim 3, 4 or 5 for use in the treatment of diseases or conditions related to smooth muscle cell proliferation.

(14) A compound according to Claim 11 or 13 wherein said smooth muscle cell proliferation manifests itself as restenosis following angioplasty.

(15) A process for the preparation of a compound of formula I or II

\[
\begin{align*}
\text{I} & \quad \text{II} \\
R₂ & \quad R₂ \\
R₁ & \quad (\text{alkyl of 1 to 6 carbon atoms, phenyl, phenyl or benzyl substituted with hydroxyl, alkoxy of 1 to 6 carbon atoms, haloalkoxy of 1 to 6 carbon atoms, trifluoromethyl or alkyl of 1 to 6 carbon atoms;}) \\
R₂ & \quad (\text{hydrogen, halogen, alkoxy of 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;} \\
R₁ & \quad (\text{aryl of 1 to 6 carbon atoms, arylalkyl of 7 to 12 carbon atoms, or benzyl substituted with one or more of halogen, carboxyl, alkoxy carbonyl of 2 to 6 carbon atoms or aryloxy carbonyl of 7 to 12 carbon atoms;})
\end{align*}
\]
which comprises

(a) reacting a nitrile of formula $RCN$ with an alcohol and hydrogen chloride to form a compound of formula (1) in which $R$ is as previously defined:

$$
\begin{align*}
\text{N.HCl} \\
\text{OEt}
\end{align*}
$$

(b) reacting the compound of formula 1 and a 3,4-diaminobenzophenone of formula

in which $R_2$ is as previously defined, in refluxing alcohol to give the corresponding compound of formula (2)

(c) and optionally alkylation the compound of formula (2) with an alkyl, aryl or arylalkyl halide in the presence of a base affords the isomers (3a, 3b)

(d) and optionally separating the isomers by recrystallization and chromatography;
(e) and optionally further reacting the compounds of formula (I) with a reducing agent to obtain the corresponding compound of formula (II).
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC 6 | C07D235/08 | A61K31/415 | C07D235/12 | C07D235/18 |

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

| Minimum documentation searched (classification system followed by classification symbols) |
| IPC 6 | C07D |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CHEMICAL ABSTRACTS, vol. 120, no. 23, 6 June 1994 Columbus, Ohio, US; abstract no. 298542, MASTER H E ET AL: &quot;Action of methyl acetacetate on 3,4-diaminobenzophenone&quot; XP002013573 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX; vol. 120, page 7591CS; the compounds: RN [97375-60-5], [154957-51-4] and [154957-54-7]; &amp; INDIAN J. PHARM. SCI. (IJSIDW,0250474X);93; VOL.55 (6); PP.225-9, ST. XAVIER'S COLL.;NADKARNY-SACASA RES. LAB.; BOMBAY; 400 061; INDIA (IN).</td>
<td>1,2,4</td>
</tr>
</tbody>
</table>

---

Further documents are listed in the continuation of box C.

**T** Patent family members are listed in annex.

**Date of the actual completion of the international search**

18 September 1996

**Date of mailing of the international search report**

27.09.96

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 631 epo nl, Fax (+31-70) 340-3016

**Authorized officer**

Fink, D
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CHEMICAL ABSTRACTS, vol. 119, no. 17, 25 October 1993 Columbus, Ohio, US; abstract no. 180743, RAO P S ET AL: &quot;Reactions of 4-benzoyl-o-phenylenediamine: synthesis of dihydro-1,5-benzodiazepines, quinoxalines and benzimidazoles&quot; XP002013574 see abstract: the compound no. III (R2 = PhCH2) &amp; INDIAN J. CHEM., SECT. B (IJSDBD,03764699);92; VOL.31B (11); PP.733-5, INDIAN INST. CHEM. TECHNOL.;HYDERABAD; 500 007; INDIA (IN), ---</td>
<td>2</td>
</tr>
<tr>
<td>X</td>
<td>CHEMICAL ABSTRACTS, vol. 113, no. 17, 22 October 1990 Columbus, Ohio, US; abstract no. 152325, VENKATARATNAM R V ET AL: &quot;Studies on formation of 1-aralkyl-2-aryl-6-benzoylbenzimidazoles from 4-benzoyl-o-phenylenediamine and aromatic aldehydes&quot; XP002013575 see abstract: the compound no. II (R = H) &amp; INDIAN J. CHEM., SECT. B (IJSDBD,03764699);90; VOL.29B (5); PP.488-90, INDIAN INST. CHEM. TECHNOL.;HYDERABAD; 500 007; INDIA (IN), ---</td>
<td>2,4</td>
</tr>
<tr>
<td>X</td>
<td>EP,A,0 260 744 (JANSSEN PHARMACEUTICA NV) 23 March 1988 cited in the application see page 22, line 27 see page 20, line 25 see page 20, line 17 ---</td>
<td>3,4</td>
</tr>
<tr>
<td>X</td>
<td>CHEMICAL ABSTRACTS, vol. 66, no. 10, 6 March 1967 Columbus, Ohio, US; abstract no. 38863j, A V STETSENKO ET AL: &quot;Imidacyanines containing benzimidazole rings with weakly basic substituents&quot; XP002013576 see abstract &amp; UKR. KHIM. ZH., vol. 32, no. 8, 1966, pages 853-856, ---</td>
<td>1,2</td>
</tr>
</tbody>
</table>

Form PCT/ISA/21B (continuation of second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>CHEMICAL ABSTRACTS, vol. 63, no. 1, 5 July 1965 Columbus, Ohio, US; &quot;Trimethine dyes containing a 5(6)-benzoylbenzimidazole nucleus&quot; column 5797b; XP002013577 see abstract; the compound no. (IV) &amp; BE.A,657 733 (GEVAERT PHOTO-PRODUCTEN N.V.) 16 April 1965 ---</td>
<td>2</td>
</tr>
<tr>
<td>A</td>
<td>GB,A,2 119 790 (MAY &amp; BAKER LTD) 23 November 1983 see page 6; claim 1 see page 1, line 26 - line 27</td>
<td>1-14</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 7 - 9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AU-A- 7838587</td>
<td>14-04-88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA-A- 1323366</td>
<td>19-10-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE-A- 3783107</td>
<td>28-01-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES-T- 2053524</td>
<td>01-08-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK-A- 123694</td>
<td>18-11-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IE-B- 60514</td>
<td>27-07-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-A- 1085975</td>
<td>30-03-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-C- 1875175</td>
<td>26-09-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG-A- 118994</td>
<td>28-04-95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SU-A- 1662350</td>
<td>07-07-91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US-A- 4859684</td>
<td>22-08-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR-A- 2525218</td>
<td>21-10-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-A- 58188865</td>
<td>04-11-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LU-A- 84747</td>
<td>05-12-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL-A- 8301310</td>
<td>01-11-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE-A- 8302084</td>
<td>16-10-83</td>
</tr>
</tbody>
</table>